**Australian Government**

**Department of Health and Ageing**
**Therapeutic Goods Administration**

# Australian Public Assessment Report
# for
# Pandemic influenza vaccine

**Proprietary Product Name: Pandemic Influenza Vaccine H5N1 Baxter**

**Submission No: PM-2008-1961-2**

**Sponsor: Baxter Healthcare Pty Ltd**

*December 2010*

# Contents

*AusPAR Pandemic Influenza Vaccine H1N1 Baxter Pandemic influenza vaccine*
*Baxter Healthcare Pty Ltd PM-2009-1961-2 Final 9 December 2010*

*Page 2 of 58*

# I.    *Introduction to Product Submission*

## Submission Details

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|---|---|
| *Type of Submission* | New Biological Entity |
| *Decision:* | Approved |
| *Date of Decision:* | 23 August 2010 |
| | |
| *Active ingredient(s):* | Pandemic influenza vaccine |
| *Product Name(s):* | Pandemic Influenza Vaccine H5N1 Baxter |
| *Sponsor's Name and Address:* | Baxter Healthcare Pty Ltd<br>1 Baxter Drive<br>Toongabbie NSW 2146 |
| *Dose form(s):* | Suspension for injection |
| *Strength(s):* | 7.5 µg Haemagglutinin per 0.5 mL dose |
| *Container(s):* | Multi-dose glass vial containing 5.85 mL of vaccine; stoppered with latex-free rubber stopper and aluminium crimp seal |
| *Pack size(s):* | 20 x 10 mL glass vials |
| *Approved Therapeutic use:* | Pandemic Influenza Vaccine H5N1 Baxter is indicated for prophylaxis of influenza in an officially declared pandemic situation. Pandemic influenza vaccine should be used in accordance with official recommendations. |
| *Route(s) of administration:* | Intramuscular Injection into the deltoid muscle |
| *Dosage:* | 0.5 mL. A second dose of vaccine should be given after an interval of at least 3 weeks. |
| *ARTG Number (s)* | 153381 |

## Product Background

At the time this application was submitted there were no currently available licensed vaccines in Australia for pandemic influenza viruses. There were several inter-pandemic influenza vaccines in Australia. The one available for the longest period of time is a non-adjuvanted vaccine grown in embryonated eggs from seed virus generally obtained through the WHO Collaborating Centre for Influenza Reference and Research (located at the Victorian Infectious Diseases Reference Laboratory [VIDRL] in Melbourne), usually with virus obtained from clinical isolates supplied by virology laboratories around Australia. This vaccine is trivalent – in 2009 and for many years prior, consisting of an A/H3 strain, A/H1 strain and B strain influenza virus. The current human influenza vaccines are grown in the allantoic cavity of embryonated eggs, killed, then split virion or purified antigen prepared, detergent/solvent disrupted, inactivated with beta-propiolactone or formaldehyde, and purified by zonal centrifugation [NHMRC 2008].[1] The vaccine is currently distributed as single doses of 0.5 mL given by IMI or deep SCI (see for example http://www.influenzaspecialistgroup.org.au/content/view/30/43/). More recently, inter-pandemic

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[1] NHMRC (National Health and Medical Research Council), 2008, Australian Immunisation Handbook, 9th ed., pp184-194.

*AusPAR Pandemic Influenza Vaccine H1N1 Baxter Pandemic influenza vaccine*
*Baxter Healthcare Pty Ltd PM-2009-1961-2 Final 9 December 2010*

*Page 3 of 58*

influenza vaccines that are adjuvanted, vaccines administered intranasally, and vaccines administered intradermally have become available. Some of these are licensed (particularly the adjuvanted and intradermal). The sponsor of Pandemic Vaccine H5N1 Baxter specifically indicated the use of non-adjuvanted vaccine was designed to model the current major inter-pandemic vaccines used, in order to simplify regulatory issues.

This application differs in the following ways from some other vaccine proposals:

- The vaccine tested is not necessarily that proposed for use. Due to the antigenic variability in avian influenza strains (classified into clades on the basis of antigens), the actual vaccine used in a pandemic will depend upon the circulating strain/s at the time.[2]
- The use of vaccine grown in Vero cells differs from all currently available human influenza vaccines.
- The use of whole virion vaccine differs from all currently used human inter-pandemic vaccines, and resembles the vaccine types used previously for human inter-pandemic influenza [Bernstein 1982, Carle 1988] and more recently for potential pandemic strains [Lin 2006].[3,4,5]
- The vaccine needs to be available at any time of year, as compared with the usual inter-pandemic or epidemic influenza vaccines that are typically available in Australia from autumn, through winter and usually not available after that until the following autumn. This is because pandemic strains may arise in the northern hemisphere (most frequently in mainland Asia) resulting in different epidemiological patterns.
- Critical issues for the development of the vaccine itself are the necessity for speed - time between the beginning of the pandemic and the peak may be measured in weeks to months and is less predictable than inter-pandemic human influenza, and the need for matching of the vaccine to the circulating (wild type) strains as these vary significantly.
- Technically there are significant differences between avian-derived pandemic viruses and inter-pandemic strains. Particularly, avian strains kill embryonated eggs and so culture in cell lines (such as MDCK or Vero cells) is often used, or reverse genetics with the placing of immunogenic proteins (such as haemagglutinin and neuraminidase) within a laboratory "backbone" strain virus such as A/PR/8/34 means that the technologies can be developed prior to actual vaccine creation. In this application, the use of cell-grown virus is used. There are still significant concerns regarding the clinical protection offered by cell-grown vaccines. The sponsor has used a whole virion vaccine to attempt to reduce some of the issues relating to cell grown virus, and the issues relating to low antibody response to avian split virus vaccines.
- Genetically engineered strains (for example, on a A/PR/8/34 "backbone") require mammalian cells, which have additional parameters required to be met for pandemic vaccines including, according to the TGA-adopted European Union guideline:[6]
    ii    use of a cell substrate approved for human vaccine production,

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[2] A clade is a group of related organisms (in this case avian influenza viruses) that share features inherited from a common ancestor.

[3] Bernstein DI, Zahradnik JM, DeAngelis CJ, Cherry JD: Influenza immunization in children and young adults: clinical reactions and total and IgM antibody responses after immunization with whole-virus or split-product influenza vaccines. Am J Dis  Child 1982, 136:513-517.

[4] Carle F, Bolgiani M, Zanon P, Moiraghi Ruggenini A, Zotti C: Immunoprophylaxis for influenza: comparison of a subunit and a whole virion vaccine. *Bollettino dell Istituto Sieroterapico Milanese* 1988, 67:105-115.

[5] Lin J, Zhang J, Dong X, et al. Safety and immunogenicity of an inactivated adjuvanted whole-virion influenza A (H5N1) vaccine: a Phase I randomised controlled trial. Lancet 2006; 368: 991–97.

[6] EMEA (18 December 2008). EMEA/CHMP/166042/2007. Committee for Medicinal Products for Human Use (CHMP). Guideline on dossier structure and content for pandemic influenza vaccine marketing authorisation application (revision). (EMEA/CHMP/VEG/4717/2003-Rev.1).

iii  cells used to generate the virus are compliant with the "TSE note for guidance", in order to reduce the risk of transmission of agents such as new variant CJD,

iv  records are maintained which include documentation of other influenzas viruses or viral nucleic acid handled at the same time as rescue work, thereby reducing the risk of cross contamination,

v  the reference virus must have been assessed as suitable by a collaborating laboratory with respect to antigenic, genetic and phenotypic characteristics, and

vi  a clear protocol for production of the virus in this manner must be available.

- Some authorities recommend additional challenge studies in animals (for influenza vaccines the models are usually ferrets or mice) if possible to provide further evidence of efficacy.

The indication sought by the applicant is:

*Prophylaxis of influenza in an officially declared pandemic situation. Pandemic influenza vaccine should be used in accordance with official guidance.*

## Regulatory Status

The same submission for the vaccine has been submitted for registration in Australia, New Zealand, Switzerland and Europe:

It was approved by the European Medicines Agency (EMA) for licensure in the European Union (EU) on 4 March 2009, in Switzerland in 2010 and in New Zealand in August 2010. The indication is the same in all countries:

*Prophylaxis of influenza in an officially declared pandemic situation.*

## Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

# II.  Quality Findings

## Drug Substance (active ingredient)

### Structure and Physicochemical Properties

The drug substance is an aqueous solution containing Vero cell-derived, formaldehyde- and UV-inactivated, sucrose gradient purified whole virions of influenza virus type A (mock-up strains: A/Vietnam/1203/2004 or A/Indonesia/05/2005). Additional components of the drug substance are Tween 80, Sodium Chloride and Tris-buffer (trometamol).

The product does not contain egg or chicken protein and is free of preservatives. Except for preparation of the Master Cell Bank, no animal or human serum components are used in the production of the vaccine.

### Manufacture

This substance is manufactured by four main steps; Vero cell propagation, Virus propagation and harvest, Inactivation, and Purification and sterile filtration

Cell banking processes are satisfactory.

All viral/prion safety issues have been addressed, including use of animal-derived excipients, supplements in the fermentation process and in cell banking.

Production Vero Cells (PVC) are produced and then infected with Production Virus Seed (PVS) of respective influenza virus (that is, H5N1). Then the virus is harvested and inactivated by sequential formaldehyde and UV irradiation inactivation steps. The final stage of Drug Substance manufacture

*AusPAR Pandemic Influenza Vaccine H1N1 Baxter Pandemic influenza vaccine*
*Baxter Healthcare Pty Ltd PM-2009-1961-2 Final 9 December 2010*

*Page 5 of 58*

is the sterile filtration of the Monovalent Bulk (MVB).  Finally the MVB is store at +2 to +8°C and then transported to the formulation/filling facility in bags at +2 to +8°C.

## Specifications

The proposed specifications, which control identity, content, potency, purity and other biological and physical properties of the drug substance relevant to the dose form and its intended clinical use were reviewed and found satisfactory.

Appropriate validation data have been submitted in support of the test procedures.

## Stability

Stability data have been generated under real time/stressed conditions to characterise the stability/degradation profile of the substance and to establish a shelf life.

The following production stages/intermediates; Seed Virus bank  (SVB) for strain A/Vietnam/1194/2004 only, Purified Monovalent Virus Harvest (PMVH), and Monovalent Bulk (MVB), were included in the stability studies

The stability test results on SVB Lot. No. PI/H5/VN04/05/01 (strain A/Vietnam/1194/2004) for 0, 1, 2 years time points have been provided.

Three PMVH and MVB batches of Vietnam-strain produced in years 2006 and 2007 and one batch of Indonesia strain produced in year 2007 were tested for stability. The stability test results for 0 and 6 months time points have been provided for both PMVH and MVB. Stability testing is planned over a 36 month period. The results available so far demonstrate that the antigen content of the PMVH and MVB preparations were generally not affected during storage at ≤ -60°C in the dark and at 2 to 8°C, respectively.

The quality evaluator requested that the sponsor should submit further stability data once available for both strains.

The shelf life of the SVB is not set yet but the stability study is planned for twenty years. Based on the data currently available on the Pandemic Influenza Vaccine for Clinical batches and conformance batches and previous experience with seasonal Vero cell derived influenza vaccine, the following maximum storage durations are planned; 2 years at ≤ -60°C for PMVH, and 2 years at +2 to +8°C for MVB.

## Drug Product

### Formulation(s)

Pandemic Vaccine H5N1 Baxter pandemic influenza vaccine is a monovalent, non-adjuvanted inactivated whole virus vaccine containing 7.5 μg/dose of haemagglutinin (HA) and is supplied in a 5.85 mL volume in a 10 mL glass vial with rubber stopper and flip off cap.  The product is intended for multi-dose use (10 x 0.5 mL dose) and does not contain a preservative. One vaccine dose of 0.5 mL contains 7.5 μg haemagglutinin antigen in a non-adjuvanted formulation.  The pH of the final vaccine formulation is in the range of 7.3 to 7.6.

Pandemic Vaccine H5N1 Baxter is administered intramuscularly in a 2-dose schedule, introduced to those 18 years of age and older with a subsequent dose delivered after a 3-week interval. The vaccine has a proposed shelf-life of 24 months at +2 to +8°C. An open shelf life of 3 hours following first withdrawal of a dose, or one vaccination session is proposed, whichever is the less.

### Manufacture

In summary, the MVB is sterilised by filtration then the sterile MVBs are transported by truck at +2 to +8°C from the Bohumil facility in the Czech Republic to Vienna/Austria for formulation and filling in the Baxter facility Lange Allee 51. Excipients (Tris-buffer and Tween 80 solution) are

*AusPAR Pandemic Influenza Vaccine H1N1 Baxter Pandemic influenza vaccine*
*Baxter Healthcare Pty Ltd PM-2009-1961-2 Final 9 December 2010*

*Page 6 of 58*

sterilised by filtration and added aseptically to the sterile MVB. The sterile bulk drug is then aseptically filled into the containers.

### Specifications

The proposed specifications, which control identity, potency, purity, dose delivery and other physical, chemical and microbiological properties relevant to the clinical use of the product were reviewed and found satisfactory.

The single radial immunodiffusion potency (SRD) test is used to determine antigen content when reagents are available. As can be expected, during a pandemic, reagents may not be available immediately. If this were to occur, alternative methods will be used to test antigen until reagents become available, at which time, the SRD test will then be used.

Appropriate validation data have been submitted in support of the test procedures.

### Stability

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product. The proposed shelf life of final container in multi-dose vial is 2 years when stored at +2 to +8°C. Five batches of Vietnam strain vaccine and three batches of Indonesia strain are used for the studies. The available stability test results demonstrate a good stability of the vaccine. The antigen contents of the Final Container Product were generally not affected during storage at 2 to 8$^{o}$C and at 23 to 27$^{o}$C (temperature excursion) for one week. The HA content met the release criterion.

A statistical evaluation of stability data was not performed due to the limited number of time points available.

During the actual use in case of pandemic or pre-pandemic, it is anticipated that the actual duration of "one vaccination session" for one vial will be less than 2-3 hours. Therefore, the open shelf life following first withdrawal of a dose: "vial to be used within one vaccination session or within 3 hours, whichever is less". The following instructions on the label of multi-dose vial will be included "Contains no preservative – vial to be used within one vaccination session or within 3 hours, whichever is less". The homogeneity of the vaccine in the vial during withdrawal of the 10 doses (up to 8 hrs) as well as absence of antigen adsorption during use of the vaccine in two different syringes has been evaluated.

The quality evaluator noted that real time stability studies on the Final Container Product vaccine at regular storage conditions and temperature excursion are incomplete; the sponsor will provide the TGA with real-time results of stability studies (for at least three batches) supported with statistical evaluation once available.

## Bioavailability

Biopharmaceutic data are not required for this product because product is indicated for immediate use in an officially declared pandemic situation.

## Quality Summary and Conclusions

The administrative, product usage, chemical, pharmaceutical, microbiological and biopharmaceutic data (as applicable) submitted in support of this application have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA.

### Issues of concern

A number of deficiencies and other issues requiring resolution before the product can be recommended for approval were identified during the evaluation and were referred to the sponsor

for comment or resolution. These issues are summarised below under *Pharmaceutical Subcommittee Consideration*.

## Pharmaceutical Subcommittee Consideration

The application was reviewed by the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM) at its 126th meeting.

The PSC resolved to recommend to the Australian Drug Evaluation Committee (ADEC) (which preceded ACPM) that:

There should be no objection on quality and pharmaceutic grounds to approval of the application by Baxter Healthcare Pty Ltd to register Pandemic Vaccine H5N1 Baxter suspension for injection containing 7.5 µg of influenza virus haemagglutinin in 0.5 mL, provided all outstanding issues are addressed to the satisfaction of the TGA.

*The sponsor responded to all issues raised in the area of manufacture/quality control including those concerning viral safety, endotoxins and sterility and therefore, there are no outstanding issues regarding these aspects. However, the sponsor has been asked to provide the TGA with any further results generated from ongoing stability studies at $\leq$ - 60$^o$C for purified monovalent virus harvest (PMVH), and at regular storage conditions (+2 to +8$^o$C) and temperature excursion (+23 to +27$^o$C) for monovalent bulk and the final product to support the proposed shelf-life when available.*

The PSC endorsed all the questions raised by the TGA in relation to quality and pharmaceutic issues. In addition, the Committee considered that the sponsor should be asked to include monovalent bulk lots from each manufacturing site in the stability testing protocol.

*The sponsor responded that overview stability studies were provided in the original submission. However, the sponsor claimed that the Orth facility was used to manufacture the MVBs for the first clinical study, Phase I/II 810501 in small scale. Stability studies on the monovalent bulk were not performed for the Phase I/II study material, it was only included in a stability study on the final Product stage and therefore stability results are not available on the monovalent bulk.*

*All future productions of MVBs as well as any commercial production of Pandemic Vaccine H5N1 Baxter will take place in the Bohumil facility in large scale. The material produced there, for clinical studies, was included in stability studies as provided in a response to a TGA question. The Seed Virus Bank (SVB) produced in the Orth facility was also included in the stability studies program.*

The PSC considered the use of multi-dose vials for this product unacceptable.

*The sponsor responded that the product will likely be used during large vaccination campaigns in the case of a pandemic and therefore, the in-use period of one vial is low. The sponsor justified that the storage as well as the distribution of large quantities of this vaccine for vaccination campaigns is highly facilitated due to the multi-dose representation. Furthermore supply of a tenfold larger number of single-dose syringes or vials in a pandemic scenario could not be guaranteed.*

*The technical aspects of the multi-dose final container closure system reduce the risk of microbiological contamination. The ten doses contained in the multi-dose vial will each be withdrawn with different sterile syringes. At each withdrawal the needle of the syringe penetrates the stopper, which is qualified by the supplier for 10 withdrawals. The stopper is kept on the vial via the crimping cap and will not be removed at any time during the vaccination session.*

*The sponsor commented that other pandemic influenza vaccines registered in the ARTG are also supplied in a multi-dose vial.*

## III. Nonclinical Findings

### Introduction

Baxter Healthcare Pty Ltd has applied to register Pandemic Vaccine H5N1 Baxter, a monovalent, inactivated, whole virion (influenza subtype A/H5N1), non-adjuvanted, Vero cell-derived 'mock-up' pandemic influenza vaccine for the prophylaxis of influenza infection in an officially declared pandemic situation, in patients 18 years or older. The vaccine is supplied as multi-dose glass vials containing suspension for IM injection. The recommended dose is two injections (dose volume of 0.5 mL) containing 7.5 µg/dose of haemagglutinin (HA) antigen, at least three weeks apart.

Although other mock-up pandemic influenza vaccines are registered in Australia (for example, Panvax and Prepandemrix), this represents the first cell culture-derived pandemic influenza vaccine to be considered for registration. The use of cell culture, rather than eggs to cultivate virus offers several advantages, namely reduced production times, the ability to safely use whole, wild-type virus (without reassortment) and potential problems with egg supply during an avian derived pandemic situation.

The data submitted in support of the application were generally adequate, and relevant studies were compliant with Good Laboratory Practice (GLP). The use of a non-adjuvanted vaccine is supported by the nonclinical data which indicated that the presence of an adjuvant impacted the immunogenicity and seroconversion in a mouse, and showed increased toxicity in rats.

### Pharmacology

#### Primary pharmacodynamics

Two different reference virus strains were used in the mock-up monovalent pandemic influenza vaccine, namely A/Vietnam/1203/2004 (Clade 1) and /Indonesia/05/2005 (Clade 2.1) virus. These strains are suitable for a mock-up pandemic influenza vaccine, as they represent highly pathogenic strains not in current circulation. All antibody titres listed in the text below represent a dilution factor (1:$x$), but are expressed as whole numbers ($x$) for simplicity.

#### *Immunogenicity*

Several studies were submitted that investigated the immunogenicity of mock-up vaccine (for both reference virus strains) in mice, rats, guinea pigs (subcutaneous [SC] administration) and ferrets (intramuscular [IM] administration). The studies were generally adequate, and most studies investigated the effects of inclusion of an aluminium hydroxide [Al(OH)$_3$] adjuvant (no adjuvant is proposed in the clinical formulation; findings for treatments including adjuvant are thus not discussed in detail in this assessment). A wide range of antigen doses were tested in mice and guinea pigs (0.00024 – 3.75 µg haemagglutinin antigen [HA] in both species; exposure comparisons based on body surface area were not possible, due to the different routes of administration). Limited dose-ranging was conducted in studies in rats and ferrets. Individual data were not available in many studies, and it was thus not possible to fully evaluate the rate of seroconversion in different species. The dosing regimen in all studies (two injections, three weeks apart) was similar to the proposed clinical regimen.

Immunogenicity in mice and guinea pigs was quantified by combinations of three different validated *in vitro* assays (enzyme-linked immunosorbent assay [ELISA]-based, HA inhibition (HAI) and microneutralisation (µN) assays). ELISA assays appeared to be the most sensitive, although the other two assays are considered to quantify functional activity of virus-specific antibodies. Either chicken or horse erythrocytes were used in HAI assays in mice. Horse erythrocytes were found to be more sensitive, thus comparisons between studies were difficult. µN assays were used in studies in ferrets.

*AusPAR Pandemic Influenza Vaccine H1N1 Baxter Pandemic influenza vaccine*
*Baxter Healthcare Pty Ltd PM-2009-1961-2 Final 9 December 2010*

*Page 9 of 58*

Mock-up vaccines based on both viral strains were highly immunogenic in mice and guinea pigs, often with positive ELISA titres at the lowest administered dose. Functional antibodies (HAI and µN assays) were generally detected at five-fold higher doses than ELISA titres. Antibody titres increased with antigen dose, but were generally less than dose-proportional. Specific antibodies were detected by ELISA in both species three weeks after the first dose, and were markedly increased after the second dose. The effect of addition of adjuvant was variable in different studies, although immunogenicity was generally reduced in the presence of adjuvant in mice, and increased in guinea pigs. Immunogenicity was generally consistent amongst different batches and manufacturing scales of the mock-up vaccine. In the key dose-ranging immunogenicity study in mice (A/Vietnam/1203/2004 virus), an $ED_{50}$[7] of 1 ng HA was obtained (similar results were obtained in another study comparing different manufacturing scales). Seroconversion of 100% of mice was generally documented at doses ≥0.15 µg HA. An $ED_{50}$ of < 0.2 ng was obtained in a study in guinea pigs (A/Vietnam/1203/2004 virus), although the dose-response was poor. A clear immune response in rats (100% seroconversion and high antibody titres) at a dose of 45 µg HA validated the use of this species in toxicity studies.

Both mock-up vaccines (without adjuvant) were immunogenic in ferrets, with homologous seroconversion (measured by µN assay) of 55-86% of vaccinated ferrets two weeks after the second dose (doses of 7.5 µg HA for treatment with A/Vietnam/1203/2004-based vaccine and 3.5 and 7.5 µg HA for A/Indonesia/05/2005-based vaccine in ferrets; this was approximately 8 and 15 times the proposed clinical exposure, based on $mg/m^2$, respectively). $ED_{50}$ values were not calculated in ferrets, due to the limited range of doses tested.

The TGA-adopted EU guidelines for pandemic vaccines states that a candidate vaccine should at least be able to elicit sufficient immunological responses to meet all three of the current standards set for existing vaccines in adults or older adults > 60 years.[6,8] According to the sponsor's *Clinical Overview*, all three criteria were met in adults 18-59 years (two separate clinical studies were conducted) after the second dose. In elderly subjects (≥60 years old), the criteria for seroprotection rate and seroconversion factor were met after the second dose. The seroconversion rate in elderly subjects (26.7%; µN titre was used as a surrogate for HI titre) was slightly lower than the Committee for Medicinal Products for Human Use (CPMP) of the EU criteria (> 30%); the sponsor attributed this to the relatively high proportion of subjects with a pre-existing H5N1 antibody titre. This issue was referred to the clinical evaluator/Delegate.

### Lethal challenge

Lethal challenge studies were conducted as a part of some of the above immunogenicity studies in mice and seronegative ferrets with vaccine for both reference viruses. Mice and ferrets were challenged three weeks after the second vaccine dose with $1 \times 10^5$ median tissue culture infective dose ($TCID_{50}$) of the homologous virus, intranasally. Protection by the vaccine was measured in terms of survival of treated animals after two weeks; the sponsor stated that animals were observed for clinical signs, although no data were provided for mice.

Survival of 100% of immunised mice generally occurred at doses ≥0.03 µg HA. In the key dose-ranging immunogenicity study in mice (A/Vietnam/1203/2004 virus), a $PD_{50}$[9] of 3 ng HA was obtained, and full protection was associated with a positive µN assay titre. Survival was generally reduced when the vaccine was adjuvanted.

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[7] Dose capable of seroconverting half the treated animals.

[8] EMEA (12 March 1997). Committee for Proprietary Medicinal Products (CPMP). Note for guidance on harmonisation of requirements for influenza vaccines. (CPMP/BWP/214/96).

[9] Dose associated with protection of 50% of treated animals.

*AusPAR Pandemic Influenza Vaccine H1N1 Baxter Pandemic influenza vaccine*
*Baxter Healthcare Pty Ltd PM-2009-1961-2 Final 9 December 2010*

*Page 10 of 58*

All immunised ferrets survived homologous lethal challenge at doses ≥3.75 µg HA (compared with 100% mortality in control groups). Seroconversion was not predictive of survival in ferrets (that is, the rate of survival following homologous challenge was greater than the rate of seroconversion, although different results may have been obtained with a more sensitive serological assay). Ferrets in all groups exhibited clinical signs consistent with viral infection (sneezing, coughing, not eating, faecal alterations) following challenge; vaccinated ferrets generally recovered within 3-11 days, whereas the untreated ferrets steadily worsened and generally died within a week of challenge. Similar viral load was detected in nasal wash of all ferrets (both reference viruses), irrespective of immunisation status. Viral titre was detected in the lungs, liver, brain and olfactory bulb of most ferrets, irrespective of treatment, following homologous or heterologous challenge with A/Vietnam/1203/2004, and in the same organs from unvaccinated ferrets only following homologous challenge with A/Indonesia/05/2005.

Immunisation and homologous or heterologous challenge with A/Indonesia/05/2005 was associated with increased white blood cells (WBC) and neutrophil counts at the end of the observation period. Blood urea and creatinine levels were increased in immunised ferrets in this study; the significance of this finding was unclear in the absence of histopathology data from relevant tissues. Any histopathology findings (inflammation; only the brain, olfactory bulb, liver and lungs were analysed) were generally consistent with viral infection. Ferrets vaccinated with A/Vietnam/1203/2004 also had histopathology changes consistent with chronic adaptive responses, for example, fibrosis in the lung and gliosis in the brain. The two antigen doses administered to ferrets were 8 - 15 times (mg/m²-based) greater than the proposed clinical dose; the study therefore provided limited evidence of efficacy in this species.

Passive immunisation of mice and guinea pigs (that is, immunisation with sera from animals administered two doses of mock-up vaccine [A/Vietnam/1203/2004 virus]) was associated with detection of functional antibodies (µN assay) following administration of neutralising antibody titres ≥20 in mice, and ≥10 in guinea pigs. Survival following passive immunisation and subsequent homologous challenge ($1x10^4$ $TCID_{50}$) was greater in mice than guinea pigs, with 100% survival following administration of neutralising antibody titres ≥20 in mice, and ≥40 in guinea pigs. $PD_{50}$ values were 5.17 for mice, and 7.13 for guinea pigs.

There was no evidence of enhanced influenza disease following challenge in immunised mice and ferrets, although this is generally of greater concern in aluminium-adjuvanted vaccines.

*Cross-protection*

The cross-protective immunogenicity of mock-up vaccines for both reference virus strains was investigated in studies in mice, guinea pigs and ferrets. This generally involved quantification of antibody titres specific for the heterologous reference virus following immunisation. Survival following lethal challenge with heterologous reference virus was also investigated in mice and ferrets.

Immunogenicity to heterologous virus was generally lower than to homologous virus, although immune responses were nevertheless detected in all species. Positive antibody titres to heterologous reference virus were detected by ELISA at doses ≥1.2 ng HA in mice and ≥0.24 ng HA in guinea pigs. Immunisation of ferrets with A/Vietnam/1203/2004 virus appeared to provide good cross-protection against A/Indonesia/05/2005 virus, with similar seroconversion rates and antibody titres compared with homologous virus (refer to *Immunogenicity* above). Limited cross-protection against the heterologous reference virus was observed following treatment with A/Vietnam/1203/2004-based vaccine, with only 2/22 treated ferrets with detectable antibody titre.

Following immunisation of mice with A/Vietnam/1203/2004, $PD_{50}$ values of 7-11 ng HA and 5-10 ng HA were obtained after lethal challenge ($1x10^5$ $TCID_{50}$) with A/Indonesia/05/2005 or A/Hong Kong/156/1997, respectively. A dose-related increase in survival occurred in ferrets immunised

*AusPAR Pandemic Influenza Vaccine H1N1 Baxter Pandemic influenza vaccine*
*Baxter Healthcare Pty Ltd PM-2009-1961-2 Final 9 December 2010*

*Page 11 of 58*

with A/Indonesia/05/2005 virus and subsequently challenged with A/Vietnam/1203/2004 virus ($1.5 \times 10^5$ $TCID_{50}$), with survival of 3/8 ferrets at the highest dose of 7.5 µg HA (15 times greater than the clinical exposure, based on mg/m$^2$). Limited cross-protection from heterologous challenge was observed in this species following vaccination with A/Indonesia/05/2005, with up to 63% survival.

One study in guinea pigs investigated the cross-protective immunogenicity afforded by A/Vietnam/1203/2004 virus-based vaccine containing adjuvant against several H5N1 strains (Clades 1, 2.1, 2.2 and 3), and one H5N3 and one H7N1 strain. Similar µN assay titres were observed for other Clade 1 strains (Vietnam/1194/2004 and Thailand/83/2004) as for the homologous strain. Immunogenicity towards an H5N3 strain, and Clade 2.1 and 2.2 strains was slightly reduced compared with the homologous strain (although still strong), and increased immunogenicity compared with the homologous strain was observed for a Clade 3 strain (Hong Kong/156/1997). Vaccination with the mock-up vaccine offered no immunogenicity to an H7N1 strain. This study also investigated the cross-protective immunogenicity offered by a vaccine containing recombinant HA protein derived from A/Vietnam/1203/2004 isolate. Antibodies specific for most strains were detected, although titres were markedly reduced compared with the whole-virion vaccine. Although the vaccine administered in this study contained adjuvant, a similar pattern of results may be predicted for non-adjuvanted vaccine, based on other heterologous studies in guinea pigs.

## Pharmacokinetics, Safety Pharmacology and Relative Exposure

### Safety pharmacology and pharmacokinetics

No safety pharmacology or pharmacokinetic studies were submitted, in accordance with the relevant TGA-adopted EU guidelines.[6,10]

### Relative exposure

Exposure levels (mg/m$^2$-based) of the mock-up vaccine, with respect to the HA antigen dose from an immunogenicity study in ferrets and toxicity studies in rats were compared with the proposed clinical dose, and are presented in Table 1(studies with representative doses are shown, the list is not exhaustive). The vaccine was administered by the SC route in immunogenicity studies in mice, rats and guinea pigs, compared with the proposed clinical route (IM). It is therefore not possible to make exposure comparisons based on body surface area for the submitted SC studies. The recommended dose and schedule of administration for the vaccine is two IM injections of 7.5 µg HA, at least three weeks apart. Although data were also obtained for vaccines containing Al(OH)$_3$ adjuvant, exposure margins were only calculated for doses without adjuvant, as this is the proposed clinical formulation. Doses resulting in exposure markedly greater than that of the proposed clinical dose were generally well-tolerated, as discussed under *General toxicity* below.

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[10] EMEA (17 December 1997). Committee for Proprietary Medicinal Products (CPMP). Note for guidance on preclinical and pharmacological testing of vaccines. (CPMP/SWP/465/95).

*AusPAR Pandemic Influenza Vaccine H1N1 Baxter Pandemic influenza vaccine*
*Baxter Healthcare Pty Ltd PM-2009-1961-2 Final 9 December 2010*

*Page 12 of 58*

Table 1: Relative exposure in key lethal challenge and toxicity studies by the IM route

| Study no. | Species | HA dose (µg) | HA dose (µg/kg)[a] | HA dose (µg/m²)[b] | Exposure multiples[c] |
|---|---|---|---|---|---|
| **Lethal challenge studies** | | | | | |
| 706-G005803 | Ferret | 3.75, 7.5 | 3.75, 7.5 | 38, 75 | 8, 15 |
| **Toxicity studies** | | | | | |
| PAN0001L01 | Rat | 45 | 225 | 1350 | 270 |
| BAX0005 | | 36 | 180 | 1080 | 216 |
| **Reproductive toxicity studies** | | | | | |
| BAX0012 | Rat | 6 | 30 | 150 | 30 |
| **Clinical dose** | | | | | |
| NA | Human | 7.5 | 0.15 | 5 | NA |

[a]Body weights: rats 0.2 kg, ferrets 1.0 kg and human 50 kg.
[b]Body surface area conversion factors: rat 6, ferret 10 and human 33.
[c]Obtained by comparing the value in the study with the corresponding value in humans.
NA = not applicable

## Toxicology

### General toxicity

As the proposed vaccine is derived from a new manufacturing process, the relevant TGA-adopted EU guideline recommends local tolerance testing in an appropriate small animal model.[6] The sponsor submitted one single-dose and one repeat dose toxicity study in rats, in which A/Vietnam/1203/2005 virus-based vaccine were administered by the clinical (IM) route. A total of three consecutive doses (one extra than that proposed in humans) was administered in the repeat dose study, with a recovery period of up to 17 days. The studies were GLP compliant and generally adequate, and both included analysis of local toxicity.

In the single dose study, the HA antigen dose was 45 µg, and 36 µg in the repeat dose study. Reduced HA doses were also administered in the presence of Al(OH)$_3$ adjuvant; as no adjuvant is proposed in the clinical formulation, such treatment will not be discussed in detail in this report. The HA dose in rats was markedly greater (> 200 times) than the human dose, based on body surface area (refer to *Relative exposure* above). Total dose volumes in both studies were similar to the proposed clinical dose volume.

The vaccine was generally well-tolerated, with no deaths, clinical signs or effects on body weight. Findings were restricted to local toxicity (macrophage infiltration after one or three doses, and myofibre necrosis and inflammation after repeated administration) and lymphoid changes consistent with an immune response (follicular hyperplasia of the popliteal lymph node in the single dose study). Additional toxicity was documented in rats administered vaccine with adjuvant, such as histiocytosis of the injection sites and inguinal lymph nodes in the repeat dose study, and a low incidence of bleeding of the thymus in the single dose study.

### Genotoxicity and carcinogenicity

No genotoxicity or carcinogenicity studies were submitted, in accordance with the relevant guidelines.[6,8]

### Reproductive toxicity

The sponsor submitted a rat embryofetal and postnatal development study, in which females were administered three IM doses of the mock-up vaccine (A/Indonesia/05/2005 virus) in the proposed

clinical formulation, containing 6 µg HA, in a dose volume of 400 µL (80% the adult human dose)[11]. This was approximately 30 times greater than the proposed clinical dose, based on body surface area (refer to Table 1). The first two doses were administered 42 and 14 days prior to mating, and the third dose on gestation day (GD) 7 (the vaccine was not administered during lactation). Half the rats were sacrificed on GD 20 for fetal examinations, and the remainder raised their pups to post-natal day (PND) 21, and pup development was assessed. Offspring (1/sex from 20 litters) were subsequently observed until seven weeks of age.

The study was GLP-compliant and the data were generally adequate, although only one dose was administered during gestation. The vaccine was well-tolerated, with no overt toxicity to treated females, fetuses or live offspring. Fetal weights were increased in treated rats, particularly in males; this finding was not considered to be adverse, as there were no similar effects in live offspring. Several findings occurred in fetuses from treated females (for example, offset alignment of the pelvic girdle and variation in lens size) at an incidence greater than historical control ranges. However, these were not considered treatment-related, as they occurred at low incidence (< 2%), and related findings were not documented in live offspring.

All treated dams had relatively high levels of specific antibodies (HAI assay) after two doses. Specific antibodies were detected in sera from all fetuses, with enhanced seroconversion (i.e. greater antibody titres) in pups, indicative of antibody transfer from dams *in utero* and in milk. Antibody titres declined following weaning.

Embryofetal development studies are usually required in 2 species, according to the TGA-adopted EU guideline.[10] However, FDA Guidelines state that in most cases, it is sufficient to conduct developmental toxicity studies using only one species[12]. Clinical comment was sought regarding use in pregnancy.

### Pyrogenicity

One study in rabbits investigated the pyrogenicity of the mock-up vaccine, by determining changes in body temperature six hours after IV administration of several batches of vaccine (dose volume was 5 times greater than the proposed clinical dose). Doses of up to 30 µg HA (without adjuvant) were administered. The assay was validated with the use of appropriate positive and negative controls. No significant change in body temperature was documented with any batch of the mock-up vaccine, compared with a seasonal influenza vaccine with a good safety and pyrogenicity profile, or with negative control groups.

### Excipient: polysorbate 80

The sponsor submitted a literature-based risk assessment in support of the use of polysorbate 80 in the proposed vaccine formulation. Polysorbate 80 is present in other ARTG-registered products indicated for IM administration at levels similar or greater than the proposed vaccine formulation; thus the safety of polysorbate 80 is considered to be established, and will not be discussed further in this report.

## Nonclinical Summary and Conclusions

The mock-up vaccine was highly immunogenic in mice and guinea pigs after SC administration of two doses, with positive ELISA titres following doses of 0.00024 – 3.75 µg HA (it was not possible to calculate exposure margins due to the different route of administration). Specific antibodies were detected after the first dose, and were markedly increased after the second dose. Seroconversion of

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[11] In response to a question, the sponsor stated that a second reproductive toxicity of the same design, using the other reference virus mock-up vaccine was underway, but data were not yet available.

[12] Guidance for Industry: Considerations for developmental toxicity studies for preventive and therapeutic vaccines for infectious disease indications (www.fda.gov/cber/guidelines.htm).

all treated mice occurred at doses ≥0.15 µg HA, and $ED_{50}$ values were approximately 1 ng HA in mice, and < 0.2 ng HA in guinea pigs. Protective efficacy was demonstrated in mice following homologous lethal challenge ($1x10^5$ $TCID_{50}$), with 100% survival at doses ≥0.03 µg HA ($PD_{50}$ values were 3 ng HA). The mock-up whole-virion vaccine was more immunogenic in guinea pigs than a recombinant HA-based vaccine from the same strain (both containing $Al(OH)_3$ adjuvant).

Efficacy was demonstrated in ferrets, with high exposure margins. Seroconversion of 55-86% of ferrets (µN assay) occurred two weeks after the second dose. $ED_{50}$ values were not calculated, due to limited dose-ranging in this species. Ferrets showed 100% survival following homologous lethal challenge ($1x10^5$ $TCID_{50}$) at doses 8 - 15 times the proposed clinical exposure.

Cross-protection from other H5N1 viruses (usually the heterologous reference virus) was demonstrated in mice, guinea pigs and ferrets, although immunogenicity was lower than with homologous virus. Positive antibody titres to heterologous reference virus were detected at doses ≥1.2 ng HA in mice and ≥0.24 ng HA in guinea pigs. $PD_{50}$ values of 7-11 ng HA and 5-10 ng HA were obtained in mice after heterologous lethal challenge ($1x10^5$ $TCID_{50}$) with A/Indonesia/05/2005 or A/Hong Kong/156/1997, respectively (immunisation with A/Vietnam/1203/2004). A dose-related increase in survival occurred in ferrets immunised with A/Indonesia/05/2005 virus and subsequently challenged with A/Vietnam/1203/2004 virus ($1.5x10^5$ $TCID_{50}$), with survival of 3/8 ferrets at the highest dose of 7.5 µg HA (15 times greater than the clinical exposure). Limited cross-protection against the heterologous reference virus was observed following treatment with A/Vietnam/1203/2004-based vaccine, with only 2/22 treated ferrets with detectable antibody titre.

A clear immune response (100% seroconversion and high antibody titres) validated the use of rats in toxicity studies. The mock-up vaccine was generally well tolerated in a single dose and a repeat dose (3 doses) study in rats, at doses > 200 times the clinical exposure. Toxicity was limited to local effects (inflammation and myofibre necrosis after repeated administration) and lymphoid changes consistent with an immune response.

A rat embryofetal and postnatal development study was conducted, in which females were administered three IM doses of the proposed vaccine formulation (A/Indonesia/05/2005 virus; 4/5th the adult human dose) prior to mating and during gestation. The study was generally adequate, although only one dose was administered during gestation. No embryofetal development study in a second relevant species was submitted. Repeated administration of vaccine doses 30 times the proposed clinical exposure in rats was not associated with overt toxicity to treated females, fetuses or pups. Specific antibodies were detected in both fetuses and pups, indicative of antibody transfer *in utero* and in milk.

The mock-up vaccine (several batches) was not pyrogenic in rabbits administered up to 30 µg HA IV.

Although the different route of administration in immunogenicity studies in mice and guinea pigs precluded the calculation of exposure margins, the mock-up vaccine was highly immunogenic over a wide range of doses, which are likely to encompass the proposed clinical exposure. Limited evidence for efficacy was demonstrated in ferrets due to high exposure margins in lethal challenge studies. Nevertheless, the nonclinical data are generally predictive of clinical efficacy.

The mock-up vaccine was generally well-tolerated in rats, with toxicity restricted to local tolerance effects and lymphoid changes consistent with an immune response, at doses markedly greater than the proposed clinical exposure. There was no overt toxicity to treated females, fetuses or pups following repeated administration to rats prior to mating and during gestation. Embryofetal development studies are usually conducted in two species, although the proposed Australian PI changes are consistent with the submitted data.

The nonclinical data support the use of non-adjuvanted vaccine.

There are no nonclinical objections to the registration of the mock-up pandemic vaccine (reference strains A/Vietnam/1203/2004 and A/Indonesia/05/2005) at an HA dose of 7.5 µg.

## Supplementary Data

Baxter Healthcare Pty Ltd submitted supplementary nonclinical data in support of their application to register Pandemic Vaccine H1N1 Baxter which included an immunogenicity study in mice, and an *in vitro* antibody specificity assay and a GLP-compliant reproductive toxicity study in rats, both conducted with the A/Vietnam/1203/2004 candidate vaccine.

### Pharmacodynamics

Passive immunisation of mice (that is, immunisation with sera from human subjects administered two doses of candidate vaccine [A/Vietnam/1203/2004 virus] during a clinical trial) was associated with detection of functional antibodies (microneutralisation [µN] assay) following administration of neutralising antibody titres $\geq$ 1:20. Survival following passive immunisation and subsequent homologous challenge ($1 \times 10^4$ $TCID_{50}$) was 30% following administration of neutralising antibody titres $\geq$ 1:20, and 50-80% at antibody titres $\geq$ 1:30. $PD_{50}$ values were approximately 1:10. This was similar to passive immunity obtained in mice from immunised mice and guinea pigs in a study in the primary evaluation report (respective $PD_{50}$ values of 1:5 and 1:7), although survival and immunogenicity were reduced compared with that seen in mice passively immunised with guinea pig sera in this study.

An *in vitro* study investigated the specificity of anti-H5N1 neutralising antibodies present in sera from a small number of human subjects (up to 4% of adult subjects and up to 17% of elderly subjects) prior to immunisation in a clinical trial with the candidate vaccine. Anti-H5N1 neutralising activity was completely removed by the presence of recombinant HA (but not with the recombinant neuraminidase) from a candidate virus strain (A/Vietnam/1203/2004) and partially removed by HA protein from a recently-circulating influenza virus strain (H1N1; but not a H3N1 strain). These results imply that some adults may possess immunity to other future pandemic influenza strains, for example the 2009 H1N1 pandemic influenza outbreak.

### Repeat dose toxicity

Concerns were raised in the EMEA assessment report for this product regarding potential liver toxicity and reduced plasma calcium levels in male rats in the pivotal 3-dose toxicity study with the A/Vietnam/1203/2004 candidate vaccine. This study has been evaluated previously by the TGA, but in light of subsequent concerns, the study is re-evaluated in this report, with emphasis on findings in the liver.

#### *Hepatic toxicity*

Elevated levels of alkaline phosphatase (ALP), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were observed on Days 4, 32 and 46 post-dose (3 days after the first dose, and 17 days after the second and third doses) in male rats administered either adjuvanted or non-adjuvanted vaccine. Although often statistically significant, the magnitude of the increase of group means was considered marginal, and in no case represented a doubling of control values. Pre-treatment values were not available. Treated rats received HA doses of 24 µg (with adjuvant) or 36 µg (without adjuvant), which were 144 and 216 times the proposed clinical dose (on a $\mu g/m^2$ basis), respectively.

Gross pathology of the liver on Days 32 and 46, and histopathology on Day 32 identified a number of lesions, including pale areas, accentuated lobular pattern, dark areas, a misshapen left lobe and a mass in one male (gross pathology) and inflammatory cell foci, single cell necrosis, clear cell foci and focal hepatocyte vacuolation (histopathology).

*AusPAR Pandemic Influenza Vaccine H1N1 Baxter Pandemic influenza vaccine*
*Baxter Healthcare Pty Ltd PM-2009-1961-2 Final 9 December 2010*

*Page 16 of 58*

None of these findings were considered treatment-related, for the following reasons:

(i) many were observed at similar incidence in control groups;
(ii) there was no clear correlation between gross pathology and histopathology findings, or with elevated liver enzymes (this included a comparison of individual values for each parameter for each rat);
(iii) the findings were generally at low incidence;
(iv) there was no correlation or pattern of findings between adjuvanted and non-adjuvanted vaccine;
(v) there was no treatment-related effect on the severity of lesions and;
(vi) many findings occurred in only one sex. There were no accompanying effects on absolute or relative liver weights.

The specific concern expressed by the EMEA related to elevated liver enzymes. In their report, the EMEA stated that although the changes were small at group mean levels, some individual ALT values reached 2-fold increase relative to concurrent controls on Day 46. Upon examination of the individual animal data, only one male administered non-adjuvanted vaccine had ALT levels approaching 2-fold the corresponding control mean values on Day 46 (with no accompanying gross pathology findings in the liver) and another on Day 32 in the same treatment group. This rat had slight inflammatory cell foci in the liver (which was documented for 80% of the rats in the study), and no gross pathology findings. In their report, the EMEA did not appear to consider the presence or absence of corresponding gross pathology findings, and only commented on the absence of histopathological examination for Day 46. Historical control data were not provided by the sponsor, however published data for this strain (see www.criver.com ) indicated that most rats in this study, including controls, had ALT levels approaching or exceeding the upper end of the background range (possibly related to the high incidence of inflammatory cell foci in all groups).

Taking into account the small magnitude of the changes in liver enzymes, the absence of clear corresponding pathological changes, the relatively high dose of antigen administered to rats compared with the clinical dose, the lack of an obvious pharmacological mechanism, the absence of similar findings for other similar products and the issues discussed in previous paragraphs, the weight of evidence indicate that any liver toxicity in vaccinated male rats was minor, of limited toxicological concern, and of minimal clinical significance.

### Calcium homeostasis

Plasma calcium levels were reduced, usually significantly, at all time points in male rats in the repeat dose toxicity study. This finding was not considered to be an adverse effect of treatment, as the differences were small in magnitude and only occurred in males. The decreases occurred at very high antigen doses ($\geq 144$ times clinical exposure, based on mg/m$^2$).

## Reproductive toxicity

The sponsor submitted a rat reproductive study, in which females were administered three IM doses of the mock-up vaccine (A/Vietnam/1203/2004 virus), containing 6 μg HA, in a dose volume of 400 μL (80% the adult human dose). This was approximately 30 times greater than the proposed clinical dose, based on body surface area. The study design was essentially identical to an embryofetal and postnatal development study in rats using the A/Indonesia/05/2005 candidate vaccine, evaluated in the primary report. The first two doses were administered 42 and 14 days prior to mating, and the third dose on GD7 (the vaccine was not administered during lactation). Half the rats were sacrificed on GD 20 for fetal examinations, and the remainder raised their pups to PND 21, and pup development was assessed. Offspring (1/sex from 20 litters) were subsequently observed until seven weeks of age.

The study was GLP compliant and the data were generally adequate, although only one dose was administered during gestation and no dose was administered during lactation. The vaccine was well-

*AusPAR Pandemic Influenza Vaccine H1N1 Baxter Pandemic influenza vaccine*
*Baxter Healthcare Pty Ltd PM-2009-1961-2 Final 9 December 2010*

*Page 17 of 58*

tolerated, with no overt toxicity to treated females, fetuses or live offspring. Fetal and pup weights were slightly increased in treated rats, as were the body weights of male offspring in the post-weaning period. This finding was not considered to be adverse, as the magnitude of the increase was ≤ 3% of control values. Similar effects were documented in fetuses in the study with the other candidate vaccine. Several findings occurred in fetuses from treated females (for example, incomplete ossification of several bones, offset alignment of sternebrae, short supernumerary ribs, haemorrhage in a liver lobe and undescended thymus). However, these were not considered treatment-related, as related findings were not documented in live offspring, they occurred at low incidence (<2%) or were within historical control ranges, and did not occur in the study with the other candidate vaccine.

All treated dams had relatively high levels of specific antibodies (HAI assay) after two doses. Specific antibodies were detected in sera from 91% fetuses, with enhanced seroconversion (i.e. greater antibody titres) in pups, indicative of antibody transfer from dams *in utero* and in milk. Antibody titres declined following weaning.

Embryofetal development studies are usually required in 2 species. However, FDA Guidelines state that in most cases, it is sufficient to conduct developmental toxicity studies using only one species for vaccines.[12] Clinical comment was sought regarding use in pregnancy.

### Supplementary Nonclinical Summary and Conclusions

Passive immunity was conferred on mice immunised with sera from human subjects administered two doses of A/Vietnam/1203/2004 virus, at antibody titres ≥ 1:20. Partial protective efficacy was demonstrated following homologous lethal challenge ($1x10^4$ $TCID_{50}$): survival was 30% at antibody titres ≥ 1:20 and 50-80% at ≥ 1:30 ($PD_{50}$ values were approximately 1:10).

Detailed re-evaluation of the pivotal repeat dose toxicity in rats indicated that slightly increased levels of liver enzymes in treated males occurred at very high exposure levels and were not accompanied by adverse pathological findings, and were thus of limited toxicological concern and minimal clinical significance.

A rat reproductive study was conducted, in which females were administered three IM doses of the proposed vaccine formulation (A/Vietnam/1203/2004 virus; 4/5th the adult human dose) prior to mating and during gestation. The study was generally adequate, although only one dose was administered during gestation. No embryofetal development study in a second relevant species was submitted. Repeated administration of vaccine doses 30 times the proposed clinical exposure in rats was not associated with overt toxicity to treated females, fetuses or pups. Specific antibodies were detected in both fetuses and pups, indicative of antibody transfer *in utero* and in milk.

Based on both primary and supplemental data, there are no nonclinical objections to the registration of the mock-up pandemic vaccine (reference strains A/Vietnam/1203/2004 and A/Indonesia/05/2005) at an HA dose of 7.5 μg.

## IV.  Clinical Findings

### Introduction

The vaccine immunogenicity has been evaluated in two clinical studies:

Study 810601 in 583 healthy adults in total, who were stratified into two groups 18-59 years and ≥60 yrs age. This was a Phase III study.

Study 810501 was a Phase I/II study in 284 healthy adults aged 18-45 years. This initial dose-ranging Phase I/II study also examined the use of adjuvant at different doses. The vaccine used in the Phase III study 810601 was non-adjuvanted as there was no evidence of benefit of adjuvant on response (adjuvanted vaccines typically provoked lower levels of antibody and lower rates of seroconversion).

## Pharmacodynamics

The types of pharmacodynamic studies for influenza vaccines can include the characteristics of the immune response, including:

- Level of specific antibody (Ab) produced
- Subclass of Ab produced
- Function of specific Ab produced
- Lag time for appearance of Ab
- Duration of adequate Ab titres
- Induction of cell mediated immunity
- Formation of neutralizing Ab
- Formation of cross reacting Ab
- Interactions with pre-existing Ab
- Immunological interference between Pandemic Vaccine H1N1 Baxter other concomitantly administered vaccines

The sponsor submitted that the protective efficacy of pandemic influenza vaccines *cannot* be established in clinical trials and referred to the TGA-adopted EU guideline on this subject.[13] The sponsor submitted efficacy data particularly in relation to level of specific Ab produced, duration of Ab titres up to D180, formation of Ab cross-reacting between clade 1 and clade 2 or clade 3 avian influenza strains, and states data from study 810501 were gathered for future estimation of cell mediated immunity (CMI) responses.

## Pharmacology studies

The measures of protective immunity conferred by the H5N1 vaccine were predominantly seroconversion rate, and levels of Ab measured using haemagglutinin inhibition (HI), microneutralisation (MN) and single radial haemolysis (SRH).

The EU major criteria for assessing efficacy of influenza vaccines in adult populations, prepared by the CPMP and referred to by the sponsor as evidence of efficacy are:[8]

• Number of seroconversions, or significant increase in anti-HA antibody >40%
• Mean geometric increase in antibody >2.5
• Proportion of subjects achieving a HI titre $\geq 40$ or SRH titre >25mm$^2$ should be >70%.

## Dose Response Studies

Dose response was examined in study 81050. Doses varied between 3.75 µg and 30 µg, with and without adjuvant. Comparisons between non-adjuvanted and adjuvanted preparations at different doses indicate:

- Higher doses (30 µg and 15 µg) were not associated with higher geometric mean titres (GMT) or greater numbers of responders

- Analysis of covariance indicated a significantly higher HI response to non-adjuvanted vaccine at the 7.5 µg dose at Day 21 (D21), but a non-significant increase at D42 and D180.

- Analysis of covariance (ANCOVA) indicated a significantly higher MN response to non-adjuvanted vaccine at the 7.5 µg dose at D21, D42 and D180. These findings extended to cross-reacting antibody responses at D21, D42 and D180 to A/Indonesia and A/Hong Kong also.

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[13] EMEA (24 January 2007). Committee for Proprietary Medicinal Products (CPMP). Guideline on influenza vaccines prepared from viruses with the potential to cause a pandemic and intended for use outside of the core dossier context. (EMEA/CHMP/VWP/263499/2006).

- ANCOVA indicated a significantly higher SRH response to non-adjuvanted vaccine at the 7.5 µg dose at D21, D42 and D180. These findings were not investigated using SRH for cross-reacting antibody responses.

The immunogenicity of H5-containing vaccines may be different to other subtypes of influenza virus, and the measurement of immunogenicity of H5-containing vaccines may also be different from human inter-pandemic strains – the measurement of H5 Ab using HI is less sensitive than measurement using MN or SRH [Wood 1994, Wood 2002].[14,15] This does not, however, necessarily indicate that MN or SRH are better correlates of clinical protection, as HI, MN and SRH are all accepted as surrogate measures of clinical protection, in the absence of the ability to perform placebo-controlled trials of H5 influenza vaccine [Wood, 2002].

### Interactions with other vaccines and drugs

The applicants provide no data on co-administration of Pandemic Vaccine H1N1 Baxter with other vaccines or drugs.

### Toxicology studies

Toxicology studies were reviewed to determine if any particular toxicities should be investigated in the clinical studies. Animal toxicology in rats (Wistar, CD) and rabbits (New Zealand White) was investigated for LAL, Vero cell DNA, sucrose, benzonase and formaldehyde. The sponsor presented summary data for local reactogenicity and systemic reactions. There were no relevant toxicities for human review.

### Pharmacokinetics

No evaluable clinical data were provided regarding pharmacokinetics of the vaccine. Pharmacokinetic studies are not generally required for vaccines as the information provided is not relevant to dosing recommendations

### Efficacy

The studies reviewed below are 810501, a partially blinded dose-ranging study comparing different doses with and without adjuvant (Al(OH)$_3$), and study 810601 which was to determine immunogenicity as a surrogate for efficacy, and safety.

There were no previous studies submitted. There are now published studies [Treanor 2006] indicating immunogenicity of the 90 µg dose of a subunit vaccine derived from a recombinant vaccine A/PR/8/34 backbone containing the A/Vietnam/1203/04 neuraminidase gene and modified (polybasic deleted) haemagglutinin gene.[16] In this study, the recombinant A/Vietnam – A/PR/8/34 vaccine was egg-grown, non-adjuvanted, subunit vaccine (prepared using standard influenza vaccine processes) that was given intramuscularly at D0 and D28 in doses of 7.5, 15, 45, and 90 µg. Only the 90 µg dose gave an adequate number (~57%) of responders, although the 15, 45 and 90 µg doses all produced some increase in Ab against A/Vietnam, as measured by HI and MN assays. The titres measured in HI were similar to those measured with MN, although the HI results produced a slightly higher GMT [Treanor, 2006].

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[14] Wood JM, Gaines-Das RE, Taylor J, Chakraverty P. Comparison of influenza serological techniques by international collaborative study. Vaccine 1994; 12: 167-174.

[15] Wood JM, Nicholson KG, Stephenson I et al. Experience with the clinical development of influenza vaccines for potential pandemics. Medical Microbiology and Immunology 2002; 191: 197-201.

[16] Treanor JJ, Campbell JD, Zangwill KM, Rowe T, Wol M. Safety and immunogenicity of an inactivated subvirion influenza A (H5N1) vaccine. N Engl J Med 2006; 354: 1345–51.

*AusPAR Pandemic Influenza Vaccine H1N1 Baxter Pandemic influenza vaccine*
*Baxter Healthcare Pty Ltd PM-2009-1961-2 Final 9 December 2010*

*Page 20 of 58*

The sponsor submitted data from studies 810501 and 810601 as evidence of efficacy on the basis of immunogenicity assessed as antibody response, and safety assessed for systemic and local reactions. These were regarded as adequate to assess immediate efficacy and safety issues, on the basis of referral to the TGA-adopted EU guideline [EMEA 2004].[6] The efficacy studies were conducted in healthy adults, who were drawn predominantly from European (Austria, Germany) populations, although study 810501 included subjects from Singapore.

### Exclusion criteria

The exclusion criteria for **study 810601** were individuals who:

- Had a history of exposure to H5N1 virus or previous H5N1 vaccination
- Were at high risk of contracting H5N1 influenza infection
- Had a history of significant cardiovascular, pulmonary, neurological, hepatic, rheumatic, autoimmune, haematological, metabolic or renal disorders.
- Were unable to lead independent life due to physical mental handicap.
- Suffered from immunodeficiency, or treatment within 30 days prior to study entry that effected immune response – such as a dose inhaled corticosteroids, systemic corticosteroids, radiotherapy, immunosuppressive drugs, cytotoxic drugs.
- Had a history of severe allergic reactions including anaphylaxis.
- Had donated blood or plasma within 30 days of study entry, or received blood transfusion or intravenous immunoglobulin within 90 days of the study entry.
- Had a skin condition that might interfere with injection site reaction rating.
- Had asplenia, problems with alcohol abuse, problem with drug abuse, or were administered investigation of drug within 42 days prior to study entry or concurrently.
- Were pregnant or lactating woman.
- Had received live vaccine 28 days prior or inactivated vaccine 14 days prior to study entry.
- Was a member of the team conducting the study or a close relative of one of the investigators.

The exclusion criteria for **study 810501** were individuals who:

- Were at high risk of contracting H5N1 influenza infection (for example, poultry workers);
- Suffered from a significant neurological, cardiac, pulmonary (including asthma), hepatic, rheumatic, autoimmune, haematological or renal disorder;
- Were unable to lead an independent life as a result of either physical or mental handicap;
- Suffered from any kind of immunodeficiency;
- Suffered from a disease or were undergoing a form of treatment that could be expected to influence immune response. Such treatment includes, but was not limited to, systemic or high dose inhaled (>800μg/day of beclomethasone dipropionate or equivalent) corticosteroids, radiation treatment or other immunosuppressive or cytotoxic drugs;
- Had a history of inflammatory or degenerative neurological disease (for example, Guillain Barré syndrome);
- Had a history of severe allergic reactions or anaphylaxis;
- Had a rash, dermatologic condition or tattoos which may have interfered with injection site reaction rating;
- Had received a blood transfusion or immunoglobulins within 90 days prior to study entry;
- Had donated blood or plasma within 30 days prior to study entry;
- Had received any live vaccine within 4 weeks or inactivated vaccine within 2 weeks prior to vaccination in this study;
- Had undergone systemic corticoid therapy within 30 days prior to study entry;
- Had a functional or surgical asplenia;
- Had a known or suspected problem with alcohol or drug abuse;

*AusPAR Pandemic Influenza Vaccine H1N1 Baxter Pandemic influenza vaccine*
*Baxter Healthcare Pty Ltd PM-2009-1961-2 Final 9 December 2010*

*Page 21 of 58*

- Were administered an investigational drug within six weeks prior to study entry or were concurrently participating in a clinical study that included the administration of an investigational product;
- Were a member of the team conducting this study or were in a dependent relationship with the study investigator. Dependent relationships include close relatives as well as employees of the investigator.
- If female: were pregnant or lactating.

**Vaccine immunogenicity**

The vaccine immunogenicity surrogate measures used were MN, SRH, and HI assays for specific antibody against the influenza strain used in the vaccination – A/Vietnam. The assessments were done at D0, D21, D42 and D180 and for the booster vaccinations in study 810601 at D180, D201, D360-450, D381-471, D720 and D741, using either A/Vietnam or A/Indonesia as antigen. The MN results were used as the primary immunogenicity endpoint for the reasons discussed by the sponsor (see below). This is a reasonable approach given the published data on the insensitivity of HI for Ab to avian influenza strains including H5 [Rowe 1999, Stephenson 2005].[17,18]

The cutoff for immunogenicity is less straightforward to define, as the clinical correlation between a given antibody level and protection is very difficult to specify. The sponsor nominated an MN titre of ≥1:20 as showing evidence of seroprotection on the basis of six published studies [Stephenson 2003, Stephenson 2005, Atmar 2006, Bresson 2006, Lin 2006, Treanor 2006] and European guidelines and CPMP criteria [EMEA 2004].[5,6,16,18,19,20,21]

In relation to vaccine immunogenicity, general observations to be made include:

1. Reviews suggest using immunogenicity data derived from neutralizing Ab levels is evidence of seroprotection [Stephenson 2003a, 2005, Atmar 2006, Bresson 2006, Treanor 2006].[22]

2. The CHMP immunogenicity requirements for inter-pandemic vaccines [EMEA 2004] indicate satisfactory response to vaccine is a GMT ratio (pre to post vaccination) of >2.5. This is on the basis of standard HI methods on turkey erythrocytes, a detection limit of 1:10, and a seroprotection threshold of 1:40. An adequate HI response is defined as a titre of ≥1:40.

3. CHMP criteria for licensure in adults are >70% rate of seroprotection based on HI or SRH assays, seroconversion of >40% (HI ≥1:40, SRH >25 mm$^2$), and a GMT increase of >2.5 over baseline for HI and SRH assays [EMEA 2004].

4. H5N1 viruses are classified into clades on the basis of HA sequences. Clade 1 viruses circulated during 2004-2005 in Cambodia, Thailand and Vietnam and were responsible for human infections in those countries. Clade 2 viruses circulated in birds during 2003–2004 in

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[17] Rowe T, Abernathy RA, Hu-Primmer J, Thompson WW, Lu X, Lim W, Fukuda K, Cox NJ, Katz JM. Detection of antibody to avian influenza A (H5N1) virus in human serum by using a combination of serologic assays. J Clin Microbiol 1999; 37: 937-943.

[18] Stephenson I, Bugarini R, Nicholson KG et al. Cross-reactivity to highly pathogenic avian influenza H5N1 viruses after vaccination with nonadjuvanted and MF59-adjuvanted influenza A/Duck/Singapore/97 (H5N3) vaccine: a potential priming strategy. J Infect Dis 2005; 191:1210-5.

[19] Stephenson I, Nicholson KG, Gluck R, et al. Safety and antigenicity of whole virus and subunit influenza A/Hong Kong/1073/99 (H9N2) vaccine in healthy adults: Phase I randomised trial. Lancet 2003; 362: 1959–66.

[20] Atmar RL, Keitel WA, Patel SM, et al. Safety and immunogenicity of nonadjuvanted and MF59-adjuvanted influenza A/H9N2 vaccine preparations. Clin Infect Dis 2006; 43: 1135–42.

[21] Bresson JL, Perronne C, Launay O, et al. Safety and immunogenicity of an inactivated split-virion influenza A/Vietnam/1194/2004 (H5N1) vaccine: Phase I randomised trial. Lancet 2006; 367: 1657–64.

[22] Stephenson I, Nicholson KG, Colegate A, et al. Boosting immunity to influenza H5N1 with MF59-adjuvanted H5N3 A/duck/Singapore/97 vaccine in a primed human population. Vaccine 2003b; 21:1687–93.

China and Indonesia and during 2005–2006 spread to the Middle East, Europe and Africa. The clade 2 viruses have been the major cause of human infections during 2005 and 2006. Clade 2 is further divided into six sub-clades, three of which (subclades 1, 2 and 3) have been largely responsible for human cases in Indonesia (subclade 1), the Middle East, Europe and Africa (subclade 2), and China (subclade 3) [WHO 2006].[23]

5. Observed HI antibody levels are affected by the source of erythrocytes (Study 810501 used horse and turkey erythrocytes, with no consistent difference between the two), age of erythrocyte source animal, storage time of erythrocytes, vial antigen (type – recombinant or native, egg or cell derived), and viral strains used.

**Summary of studies assessing immunogenicity**

The sponsor has submitted data from two studies – study 810601 with enrolment between 10 April 2007 and 2 August 2007, and 810501 with enrolment between 12 June 2006 and 16 February 2007. Both studies used similar methodologies to assess immunogenicity and safety. Both studies were drawn from similar populations. Both studies provided similar broad conclusions – the whole virion vaccines were immunogenic at achievable doses that were much lower than those found to be immunogenic using split virion vaccines in other studies [Treanor 2006], and the vaccines were safe with respect to systemic and local reactions.[16] The continuing issues with the vaccine preparation are discussed further below.

Immunogenicity measurement was using surrogate measures to detect H5N1 specific antibody – haemagglutination inhibition (HI), virus neutralisation (MN), and single radial haemolysis (SRH). In relation to these measures:

- All assays (HI, MN and SRH) assessed antibody against Vero cell derived, influenza strain A/Vietnam/1203/2004 to determine immunogenicity.

- In addition, presence of cross-reacting antibody was determined in MN and SRH assays using A/Indonesia/05/2005 (clade 2), and A/Hong Kong/156/1997 (clade 3) influenza strains as antigen.

- In general, all three assays are adequate for detecting specific antibody to influenza antigens, particularly to HA. The HA antigen is generally accepted as the major target of neutralizing antibody, although the relationship between the amount of neutralizing antibody and clinical protection is imperfect. The role of other non-HA antigens in the protective response against natural influenza infection is also uncertain, although the sponsor indicates the use of whole virion, rather than purified HA and NA antigen, was aimed at inducing improved immune responses. Although this may be the case on the basis of previous studies comparing whole with subunit vaccines [Just 1978, Bernstein 1982], differential responses may also depend upon vaccine strain, the population being studied (immunologically naïve or experienced), and the method used (antigen preparation, detection techniques etc).[2,24]

- Comparison of assays within studies is more reproducible than comparison of assays between studies, notwithstanding this, European regulators make clear levels for protection [EMEA 2004].[6]

The HI assay is known to not detect H5N1 antibody to the same levels as MN and SRH. It is unclear what the reason is for this, and it may depend upon non-haemagglutinin antigens, as some

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[23] WHO 2006 Antigenic and genetic characteristics of H5N1 viruses, 2006.

[24] Just M, Burgin-Wolff A, Berger-Hernandez R, Bachlin A, Ritzel G, Moritz AJ: A/New Jersey/76 influenza vaccine trial in seronegative schoolchildren: comparison of a subunit vaccine with a whole-virus vaccine. Med Microbiol Immunol 1978; 164: 277-284.

avian-human recombinant viruses generate adequate antibody responses as measured using HI. Of note:

- The HI assay is less sensitive for detection of antibodies to avian influenza strains, including H5N1 [Wood 1994, Rowe 1999, Wood 2002].[14,15,17]

- Modification of the HI technique to take account of the use of different receptors used by avian strain influenza viruses (horse erythrocytes used, as avian influenza strains bind the alpha 2,3 Gal sialic acid receptors rather than alpha 2,6 Gal sialic acid receptors) can produce an HI assay that measures avian influenza antibody satisfactorily [Stephenson 2004].[25] The sponsor used both horse and turkey erythrocytes in the HI assays in study 810501, and neither assay gave uniform results, or results that consistently correlated with the MN and SRH results.

- The HI method used in study 810501 and 810601 was a standard and acceptable method [Stephenson, 2004].[25] In part A of study 810501, the HI assay used horse and turkey erythrocytes. The HI method used in study 810601 used horse erythrocytes.

- Any result <1:10 was negative, a result >1:40 was regarded as evidence of immunogenic vaccine response.

Virus microneutralisation (MN) is in general a more variable measure [Stephenson 2004], but provided results in both studies that correlated with SRH results.[25] Of note:

- Viruses used to determine cytopathic effect were H5N1 strains A/Vietnam/1203/2004 (clade 1), A/Indonesia/05/2005 (clade 2), and A/HK/156/1997 (clade 3). The neutralizing titre was calculated in a standard and satisfactory manner [Reed 1938].[26]

- Any MN titre ≥1:20 was regarded as immunogenic, consistent with EMEA guidelines [EMEA 2004].

***Studies assessing immunogenicity of Pandemic Vaccine H5N1 Baxter***

*Study 810601*

This was a Phase III, open label, non controlled study of the inactivated, non-adjuvanted, Vero cell derived A/Vietnam/1203/2004 strain influenza vaccine, used at a dose of 7.5 µg, determined from a previous dose-ranging study (810501). The primary immunogenicity endpoint was the number of subjects with Ab response to the vaccine strain (A/Vietnam/1203/2004) associated with protection 21 days after the second vaccination (D42) defined as titre measured by MN test ≥1:20. The significance of the results was assessed separately for age strata 18-59 years and ≥60 years, with 95% confidence intervals calculated.

The secondary immunogenicity endpoints were:

• Number of subjects with antibody response associated with protection 21 days after the first vaccination measured by MN assay

• Number of subjects with HI titre ≥ 1:40 measured 21 days after the first (D21) and second (D42) vaccinations

• Antibody titre 21 days after the first and second vaccinations as measured by MN and HI assays

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[25] Stephenson I, Wood JM, Nicholson KG, Charlett A, Zambon μ. Detection of anti-H5 responses in human sera by HI using horse erythrocytes following MF59- adjuvanted influenza A/Duck/Singapore/97 vaccine. Virus Res 2004; 103: 91-5.
[26] Reed LJ, Muench HA A simple method of estimating 50 percent endpoints Am J Hygiene 1938; 27: 493.

• Fold increase of antibody response as compared to baseline 21 days after the first (D21) and second (D42) vaccinations as measured by MN and HI assays

• Number of subjects with seroconversion (defined as a minimum four fold titre increase) 21 days after the first and second vaccinations as measured by MN and HI assays

• Number of subjects with antibody response associated with protection 180, 360-450 and 720 days after the first vaccination and 21 days after a booster vaccination as measured by MN assay

• Number of subjects with HI titre $\geq$ 1:40 measured 180, 360-450 and 720 days after the first vaccination and 21 days after a booster vaccination

• Antibody titre 180, 360-450 and 720 days after the first vaccination and 21 days after a booster vaccination as measured by MN and HI assays

• Fold increase of antibody response 21 days after a booster vaccination as compared to before the booster vaccination at 180, 360-450 and 720 days after the first vaccination as measured by MN and HI assays

• Number of subjects with seroconversion (defined as a minimum four fold titre increase) 21 days after a booster vaccination as measured by MN and HI assays

• Number of subjects with antibody response associated with protection 21 days after the first and second vaccinations defined as SRH area $\geq$ 25 mm$^2$

• Antibody titre 21 days after the first and second vaccinations measured by SRH assay

• Fold increase of antibody response as compared to baseline 21 days after the first and second vaccinations measured by SRH assay

• Number of subjects with seroconversion (defined as either a $\geq$ 25 mm$^2$ haemolysis area after the vaccination in case of a negative pre-vaccination sample [$\leq$ 4 mm$^2$] or a $\geq$ 50% increase in haemolysis area if the pre-vaccination  sample is > 4 mm$^2$) measured by SRH assay 21 days after the first and second vaccinations

• Number of subjects with antibody response associated with protection 180, 360 and 720 days after the first vaccination and 21 days after a booster vaccination defined as SRH area $\geq$ 25 mm$^2$

• Antibody titre 180, 360-450 and 720 days after the first vaccination and 21 days after a booster vaccination as measured by SRH assay

• Fold increase of antibody response 21 days after a booster vaccination as compared to booster vaccination at 180, 360-450 and 720 days after the first vaccination as measured by SRH assay

• Number of subjects with seroconversion (defined as either a $\geq$ 25 mm$^2$ haemolysis area after the booster vaccination in case of a negative pre- vaccination sample [$\leq$ 4 mm$^2$] or a $\geq$ 50% increase in haemolysis area if the pre-vaccination sample is > 4 mm$^2$) measured by SRH assay 21 days after the booster vaccination

For the subset of subjects included in the evaluation of cellular immunity:

• T-cell response after each vaccination as determined by the frequency of cytokine producing T-cells induced by homologous and heterologous influenza antigens

• Increase in frequency of cytokine producing T-cells induced by homologous and heterologous influenza antigens after each vaccination as compared to baseline

The primary immunogenicity end point was assessed using a reciprocal MN titre $\geq$ 1:20 to A/Vietnam at D42 (21 days following the second vaccine dose) as this was assessed as more reliable than the use of HI titres for the aforementioned reasons.  The success of vaccination was

AusPAR Pandemic Influenza Vaccine H1N1 Baxter Pandemic influenza vaccine
Baxter Healthcare Pty Ltd PM-2009-1961-2 Final 9 December 2010

Page 25 of 58

assessed using the CPMP guidelines [EMEA 2004], and essentially the whole virion vaccine used of A/Vietnam at a dose of 7.5µg fulfilled these primary immunogenicity end points.[6]

Secondary immunogenicity endpoints were point estimates and 95% confidence intervals (CI) calculated separately for age strata 18-59 years and ≥60 years. The Ab results from MN, SRH, and HI assays were log transformed, analysed separately for each assay, using analysis of covariance with a model including baseline factors, vaccine dose, vaccine strain used, as covariates, and interaction between dose and strain as influencing factors. If dose and strain were found as influencing factors, analysis of subgroups was performed.

A secondary immunogenicity endpoint that was proposed but not included in the result documentation was evaluation of the T-cell cell mediated immunity (CMI), proposed to be assessed by calculating minimum, maximum, 25% quartiles, 75% quartiles, median and CI before and after each vaccination. Paired baseline and post-vaccine values were to be assessed using Wilcoxon signed rank test, and other T-cell CMI parameters assessed using non-parametric tests.

The outcomes for study 810601 MN data were that:

- Baseline seropositivity was moderately high using A/Vietnam as antigen - for MN assays stratum A (18-59 years) was 4.1% (4.5% for SRH) and for stratum B (≥ 60 years) was 16.9% (5.3% for SRH). This suggests detection of antibody made to human influenza strains that cross-reacts with avian antigens, the alternative (less likely) explanation is previous infection with avian strains [Lynch 2008].[27]

- A reciprocal MN titre of ≥ 1:20 to the vaccine strain A/Vietnam/1203/2004 at 21 days after the second vaccine (D42) demonstrated 72.5% (192/265) of 18-59 year olds, and 74.1% (200/270) of ≥ 60 year olds, in the ITT population, had a positive response assessed by MN;

- Seroconversion defined as a more than fourfold increase in MN titre at D42 occurred in 60.8% (161/265) of subjects 18 – 59 years age, and 26.7% (72/270) of subjects ≥ 60 years age.  This lower rate of seroconversion seen in Stratum B (that is, the older age group) can be explained by the higher percentage (16.9%) of subjects with a pre-existing antibody titre to H5N1 at baseline. This is in agreement with data previously reported that a percentage of the population, particularly the elderly, will have antibodies cross-reactive to H5N1 [Treanor et al 2006] or other potential pandemic viruses [Stephenson et al 2003, Epstein 2006] without having been exposed to this virus. This situation of pre-existing titres occurs frequently with studies with trivalent seasonal influenza vaccines and is accepted as long as the vaccine fulfils one of the two other serological criteria for licensure (that is, seroprotection or fold increase);

- The GMT of MN titres in the 18-59 year olds increased 4.7 fold in the 18-59 year olds, and 2.8 fold D42 in the ≥ 60 year olds.

The SRH data for study 810601 closely correlated with the MN data, demonstrating that at D42, the antibody response to the A/Vietnam/1203/2004 determined by SRH was found in 63.3% (164/249) of subjects 15-59 years, and 67.7% (180/266) in subjects ≥ 60 years.  That is, the 18-59 years and ≥ 60 year subgroups did not achieve a > 70% response rate as suggested by CPMP guidelines [EMEA 2004] assessed using the SRH assay.[6]

- Seroconversion as determined by SRH was found in 60.2% (156/259) of 15-59 year olds, and 62.4% (166/266) of ≥ 60 year olds at D42;

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[27] Lynch GW, Selleck PW, Axell AM et al. Cross-reactive anti-avian H5N1 influenza neutralizing antibodies in a normal 'exposure-naïve' Australian blood donor population. Open Immunol 2008; 1: 3-19.

- The GMT increase assessed using the SRH assay for 15-59 year olds was 4.6 fold, and for ≥ 60 year olds was 4.6 fold at D42;

- Adjustment for covariates (strain effect, dose effect (at D180) with antibody response using HI, MN and SRH assays was not presented;

- Assessment of the cell mediated response was not presented, although the sponsor indicated this analysis will be performed at a later time.

Overall, these data indicate an adequate response based upon MN and SRH assays, albeit that the SRH assay fell slightly short of the CPMP recommendation. The cross reactivity between response to A/Vietnam and clade 2 and clade 3 viruses were not assessed in 810601, but the data presented for study 810501 suggest significant cross reactivity between antibody response to the different clades. The detected cross-reactivity varies depending upon the clade being assessed and varies with time (particularly the D180 measurements in study 810501 consistently showed a decrease of the D180 response compared with the D42 response).

*Study 810501*

The vaccine used for this study was similar to that used for Study 810601 – that is a Vero cell-derived, formaldehyde inactivated, UV inactivated, sucrose gradient-purified whole vary on vaccine derived from cultured A//Vietnam/1203/04 H5N1 virus, but was from different lots. This Phase I/II study utilised different dosages in adjuvanted and non-adjuvanted formulations, in order to determine whether such vaccine was immunogenic and safe. Immunogenicity was assessed using the surrogate measure of antibody titre and seroconversion rate on Day 21 after second vaccination (D42).

The inclusion criteria were men and women aged 18 to 45 years (inclusive) on the day of screening, able to give written informed consent, who agreed to keep a daily record of symptoms and were clinically healthy as determined by medical history and physical examination. The primary immunogenicity criterion was the number of subjects with antibody response 21 days after first and second vaccination to find as either HI titre ≥ 1:40 or MN titre ≥ 1:20. The secondary immunogenicity end points were: antibody response at day 21 after first and second vaccinations (presumably measured by GMT) by HI and MN assays.

The outcomes for study 810501 were that the whole virion vaccine A/Vietnam/1203/2004 produced adequate Ab responses in healthy adults, to lower doses of whole vaccine (7.5 µg and 15µg) than used in previous published studies with subunit, recombinant vaccine [Treanor 2006].[16] These findings were clear whether response was assessed using adjuvanted vaccine, non-adjuvanted vaccine, and response measured using level of response (GMT, fold increase in Ab titre) or number of subjects with "adequate" (≥2 fold increase HI, ≥4 fold increase MN from baseline).

Confounding results were that MN titres were higher for non-adjuvanted than adjuvanted formulations at some doses (that is, 7.5 µg, 15 µg doses), and lower doses (7.5 µg) produced higher numbers of subjects with "protective" Ab response, than higher doses (15 µg) of vaccine. Similar results have been reported with inactivated split-virion (subunit) recombinant vaccines containing polybasic deleted A/Vietnam/1194/04 haemagglutinin and neuraminidase in A/PR/8/34, given at similar doses to similar subjects, with or without $Al(OH)_3$ adjuvant [Bresson 2006].[21] However, higher doses (30 µg) of adjuvanted vaccine did produce the greatest seroconversion rate in previous studies [Bresson 2006]. This contributed to the lack of dose effect between these doses. There was cross-reactivity between the A/Vietnam (clade 1 virus) and other divergent avian influenza viruses (A/Indonesia clade 2 and A/Hong Kong clade 0). In summary, there was no dose response effect demonstrated, nor a beneficial effect of adjuvant, in study 810501.

*AusPAR Pandemic Influenza Vaccine H1N1 Baxter Pandemic influenza vaccine*
*Baxter Healthcare Pty Ltd PM-2009-1961-2 Final 9 December 2010*

*Page 27 of 58*

**Statistical evaluations**

The statistical evaluations for both studies were non-complex and adequate for assessing the primary endpoint. All immunogenicity endpoints assumed protection on the basis of a level of Ab response. The relationship between a given surrogate measure (Ab level) and a clinical outcome (protection of an individual of a given age against influenza challenge) for influenza is based upon general data. Animal studies in ferrets and mice suggest higher amounts of antibody are protective against infection. Human studies show the use of inter-pandemic human influenza vaccine is epidemiologically associated with the population having reduced influenza, assessed by laboratory detection or general practice case detection. Human challenge studies are limited, and cannot be performed for avian influenza due to ethical reasons, and there are few published (and no recent) studies in human inter-pandemic influenza for similar reasons.

Statistical analysis for immunogenicity was using point estimates and 95% CI for secondary immunogenicity end points, and for the primary endpoint, rates of subjects with antibody response at D21 after first and second vaccination, and 95% CI. These were calculated separately for HI, MN and SRH assays. It is notable that the HI results provided lower rates of seroprotection and seroconversion compared with MN, consistent with the HI assay being a less sensitive technique for detecting antibodies to avian vaccines. This does not appear to occur for recombinant human vaccines containing the avian haemagglutinin and neuraminidase genes [Treanor 2006].[16]

### *Study 810601*

The statistical evaluations as summarised above were different for primary and secondary endpoints, although both sets of measurement were appropriate.

### *Study 810501*

The statistical evaluations as summarised above were different for primary and secondary endpoints, although both sets of measurement were appropriate. Immunogenicity primary endpoint was assessed by comparing rates of subjects with Ab titres >1:40 for HI and >1:20 for MN, with 95% CI calculated. All secondary endpoints were assessed using point estimates and 95% CI. Comparison of Ab response non-adjuvanted and adjuvanted vaccines was using analysis of covariance, with baseline values as covariates and dose, presence of adjuvant and interaction between these as influencing factors. Logistic regression was used to compare subjects with Ab titres associated with protection and subjects seroconverting after first and second vaccination (with different doses and with or without adjuvant). In study 810501, 249 subjects available after the day 21 vaccination for immunogenicity were sufficient sample size to detect a two-fold increase in antibody response between adjuvanted and non-adjuvanted formulations.

The safety primary endpoint was assessed by calculating rates of subjects with ≥1 systemic and 95% CI after first and second vaccinations. Secondary safety endpoints were calculated as point estimates and 95% CI.

**Overall**

The dose-ranging study 810501 clearly demonstrated that the dose chosen for the Phase III study (7.5 µg) was adequate at producing responses in healthy adult subjects that were satisfactory, as assessed using CPMP guidelines [EMEA 2004].[6] There was no benefit of Al(OH)$_3$ adjuvant at lower (7.5 µg) or higher (15 µg doses). The choice of non-adjuvanted vaccine, at a dose of 7.5 µg for use in the Phase III study was appropriate.

The Phase III study was adequately powered to demonstrate efficacy of the vaccine in healthy adult subjects. This study and study 810501 were not necessarily adequately powered to detect rare adverse events (such as Guillain Barré syndrome [GBS]) occurring in previous studies of non-

*AusPAR Pandemic Influenza Vaccine H1N1 Baxter Pandemic influenza vaccine*
*Baxter Healthcare Pty Ltd PM-2009-1961-2 Final 9 December 2010*

*Page 28 of 58*

human vaccines [Sencer 2004].[28] Data from the HI assays in study 810501 and study 810601 were inconsistent, despite apparently being conducted in a technically appropriate fashion, using two different detection methods (horse and turkey erythrocytes) [Stephenson 2004].[25] This still may result in findings that are inconsistent between laboratories [Wood 1994], and additional measures of CMI may be more closely associated with efficacy [Wood 2003].[14,29] This notwithstanding, the Phase III study produced antibody responses in healthy adults (whether 18-59 years age or $\geq 60$ years age) that were adequate under the CPMP guidelines [Wood 2003, EMEA 2004].[6,29]

## Safety

Safety was assessed for study 810601 via a subject diary, where injection site reactions, body temperature, systemic adverse effects (AE), and other AE were recorded. Other information gathered was medication taken post vaccination, and travel to regions with previous H5N1 HPAI activity. Blood parameters gathered were haematology profile, differential blood count analysis, at D0, D180, D360, D720 and ALT at D7 post-first vaccination and D7 post-second vaccination. Safety was evaluated using summary tables of occurrence of observed AE. Point estimates with 95% CI, and probability of occurrence of queried symptoms with 95% CI were calculated for all safety endpoints separately for 18-59 years and $\geq 60$ years strata. It is reasonable to expect the data provided would detect adverse events at a frequency of $\geq 1\%$ [EMEA guidelines CPMP/VEG/471/03 p.14].[6] It is unlikely rare events such as GBS would be detected given the numbers of subjects in study 810501 and 810601.

### Summary of safety studies

There were no serious adverse events associated with administration of doses up to 30 µg on two occasions, of whole virion, Vero cell derived vaccine, in study 810501 (Table 2). There were no serious adverse events associated with the proposed vaccine dose in the Phase I/II study 810501. There was one episode (0.4%) of serious AE in the Phase III study 810601, although the nature of this was unclear. Importantly, the local reactogenicity in both studies was relatively minor, which is of significance given previous significant levels of local inflammation in previous studies of whole virion human vaccines, although this is not a universal finding in such studies [Just 1978, Bernstein 1982].[3,24]

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[28] Sencer DJ, Millar JD. Reflections on the 1976 swine flu vaccination program Emerg Infect Dis 2006; 12: 29-33.

[29] Wood JM, Newman RW, Ploss K. The use of correlates of immunity in European Union licensing of influenza vaccines. pp 9-16 in Brown F, Haaheim LR, Schild GC (eds) Laboratory correlates of immunity to influenza – A reassessment. Developmental Biology 2003; Vol 115.

*AusPAR Pandemic Influenza Vaccine H1N1 Baxter Pandemic influenza vaccine*
*Baxter Healthcare Pty Ltd PM-2009-1961-2 Final 9 December 2010*

*Page 29 of 58*

Table 2: Summary of safety data at D21 and D42 from studies 801601 and 810501 for non-adjuvanted, 7.5 µg dose only

| | Study 810601 | | | | Study 810501 | |
|---|---|---|---|---|---|---|
| | 18-59 years Stratum A | | ≥60 years Stratum B | | 18-45 years | |
| **Population** | 281 | | 280 | | 45 | |
| | D21 | D42 | D21 | D42 | D21 | D42 |
| **Total systemic No. (%)** | 63/276 (22.8%) | 39/265 (14.7%) | 64/275 (23.3%) | 36/268 (13.4%) | 11/45 (24.4%) | 6/42 (14.3%) |
| **Systemic severe No. (%)** | 1/281 (0.4%) | 0/269 (0.0%) | 1/280 (0.4%) | 1/270 (0.4%) | 0/45 (0.0%) | 0/42 (0.0%) |
| **Total local reactions No. (%)** | 48/281 (17.1%) | 39/269 (14.5%) | 24/280 (8.6%) | 17/270 (6.3%) | 5/45 (11.1%) | 6/42 (14.3%) |
| **Severe local reaction No. (%)** | 1/281 (0.4%) | 0/269 (0.0%) | 0/280 (0.0%) | 0/270 (0.0%) | 0/45 (0.0%) | 0/42 (0.0%) |
| **Injection site pain No. (%)** | 44/281 (15.7%) | 37/269 (13.8%) | 16/280 (5.7%) | 8/270 (3.0%) | 4/45 98.950 | 5/42 (11.9%) |

**Studies assessing safety of Pandemic Vaccine H1N1 Baxter**

*Study 810601*

Safety evaluations were assessed after the first vaccination, 95% CI calculated separately for age strata 18-59 years (vaccination 1 n=281, vaccination 2 n=269), and ≥60 years (vaccination 1 n=280, vaccination 2 n=270). The primary safety endpoint was the number of subjects with a systemic reaction after first vaccination.

The secondary safety endpoints were:

• Number of subjects with systemic reactions after the second and booster vaccinations

• Number of subjects with injection site reactions after the first, second and booster vaccinations

• Number of subjects with fever, malaise or shivering with onset within 7 days after the first, second and booster vaccinations

• Frequency and severity of occurrence of AEs observed during the entire study period

*Systemic reactions*

After first vaccine (D0-21) the probability of occurrence of fever in Strata A (18-59 years) was 2.2%, and 1.1% in Strata B ( ≥60 years); all were mild, and <2 days duration. There were nine serious AEs, with eight unrelated and one possibly related - malaria reactivation at eight days following vaccination – that is D8. This event was not clearly related to the vaccine, although it was classified as causally related by the investigators. Review of the case suggested it would be an uncommon event in developed countries (malaria reactivation), although would be a more common situation in developing countries.

*AusPAR Pandemic Influenza Vaccine H1N1 Baxter Pandemic influenza vaccine*
*Baxter Healthcare Pty Ltd PM-2009-1961-2 Final 9 December 2010*

*Page 30 of 58*

*Laboratory parameters*

Laboratory parameters were recorded after the first (D7) and second (D28) vaccine dose. There were no recorded vaccine-related changes in the laboratory parameters for haematology, renal tests (creatinine, urea), and biochemistry (electrolytes, ALT, AST, gamma-glutamyltransferase [GGT], ALP). There were changes noted in the ALT level of three subjects, all determined as unrelated to vaccination on the basis all were small increases, two of the subjects had pre-existing ALT elevations, and these two had continuing minor increases after the second vaccination. The other subject had a normal post-second vaccination ALT level.

*Local reactions*

After the first vaccine (D0 - D21), 17.1% of 18-59 years and 8.6% ≥60 years had local pain or swelling; all except one were mild (pain lasted for 4 days in one subject) and <2 days duration. After the second vaccine (D21 - D42), 14.5% of 18-59 years and 6.3% ≥60 years had local pain or swelling; all were mild and <2 days duration. Importantly, the local reactogenicity did not result in higher than expected rates of non-adherence to visit schedules.

### Study 810501

The primary safety endpoint was the number of subjects with a systemic reaction after first and second vaccinations (Table 3). Subjects measured from D0 (vaccination) until D6 body temperature orally once every evening, and every 4-8 hours if fever occurred

There were three serious adverse events between Day 42 and D180, all three were judged as unrelated to the vaccine, and review of these suggests this is a reasonable conclusion. The listing of systemic adverse events indicates the rate of systemic symptoms whether related or unrelated post vaccination was similar between different groups (Table 3). Overall, the rate of systemic adverse events was extremely low. There were no results from vital signs, physical findings, or laboratory parameters as these were not evaluated during this study. There was only a single systemic event and it was judged by investigators as possibly related to vaccination in the follow up period from D42 to D180. The rates of related and unrelated post vaccination symptoms in this period were similar between the different vaccine groups, and were not directly related to the use of adjuvant in the vaccine.

Table 3: Number of subjects with systemic symptoms (related and unrelated) after vaccination in the period between Day 42 and Day 180 by severity grade, in study 810501.

| Study Group | Severity of systemic reactions | | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|---|
| | No reaction | | Mild | | Moderate | | Severe | | Total |
| | N | % | N | % | N | % | N | % | N |
| 3.75 µg adjuvanted | 21 | (50.0%) | 20 | (47.6%) | 1 | (2.4%) | 0 | (0.0%) | 42 |
| 7.5 µg adjuvanted | 18 | (46.2%) | 18 | (46.2%) | 3 | (7.7%) | 0 | (0.0%) | 39 |
| 7.5 µg non-adjuvanted | 20 | (47.6%) | 17 | (40.5%) | 5 | (11.9%) | 0 | (0.0%) | 42 |
| 15 µg adjuvanted | 24 | (58.5%) | 15 | (36.6%) | 2 | (4.9%) | 0 | (0.0%) | 41 |
| 30 µg adjuvanted | 34 | (77.3%) | 10 | (22.7%) | 0 | (0.0%) | 0 | (0.0%) | 44 |
| **Total** | **139** | **(55.8%)** | **97** | **(39.0%)** | **13** | **5.2%)** | **0** | **(0.0%)** | **249** |

**Safety evaluations of particular interest**

It was particularly important to assess in study 810501 and study 810601:

- Severe systemic reactions due to possible severe or unexpected outcomes as were seen for swine influenza vaccination in the USA. This is particularly of relevance for large scale vaccination of healthy populations, where the background rate of rare complications (in the case of swine influenza, GBS) may be associated incorrectly or correctly with the use of new vaccines [Sencer 2006].[28]

- Local reactogenicity, which was a feature of previous whole virion vaccines [Just 1978], and as current human influenza vaccines do not give comparable figures for local reactogenicity, as they are inactivated, split subunit vaccines.[24]

- Given the likelihood any pandemic strain of avian derived influenza will be introduced into a human population largely without previous exposure (as evidenced by the low rate of pre-existing antibody to the A/Vietnam strain used in study 810501 and 810601), and previous studies demonstrating low antibody response to usual (15 µg in current human vaccines [NHMRC 2008]) doses of avian influenza antigen [Treanor 2006], the studies reviewed here used whole virion vaccine.[1,16] Whole virion human influenza vaccines have been eschewed for many years in favour of subunit vaccines due to older studies demonstrating higher reactogenicity of the whole virus preparation [Just 1978].[24] More recent studies in small numbers (100-200) of young adult recipients suggest less difference between the subunit and whole virus preparations [Bernstein 1982, Carle 1988].[3,4] Such studies were done in younger populations to assess response of immunologically unprimed subjects, and hence data on elderly subjects is largely unavailable, as elderly subjects are almost universally previously exposed to influenza.

### Derivation of vaccine

The vaccine was derived from culture in a serum-free Vero cell system, which the sponsor uses to produce other vaccines using a microcarrier-based fermentation technology. The influenza viruses the sponsor has grown in this system include subtypes H1N1, H3N2, H5N3, H7N1, H9N2, and the H5N1 strains investigated in study 810501 and 810601. The virus is formaldehyde and UV inactivated, purified on a sucrose gradient, and does not contain preservative.

### Deaths

There were no deaths recorded in study 810501. There no deaths recorded in study 810601, at the conclusion of part A.

### Withdrawals and dropouts

Study 810601 had two strata – prior to vaccination there were 14 withdrawals aged 18-59 years (Stratum A), of whom three were not included because of previous allergic reactions, and eight ≥60 years (Stratum B), of whom one had previous allergic reactions. After the first vaccination, there were 13 subjects aged 15-59 years, and 10 subjects aged ≥60 years who were not vaccinated due to failure to return, and three additional subjects aged 15-59 years who did not have laboratory parameters determined as blood was not drawn. An additional six subjects were vaccinated but did not fulfil inclusion criteria or had an exclusion criterion. Reasons for withdrawal and dropout of subjects included non-adherence to schedule (typically in the range of 0.7-1.9%) and in one case relationship to the investigators.

### Subjects receiving concomitant vaccines

These individuals were specifically excluded from the study at enrolment and review.

### Laboratory adverse events

There were no significant laboratory parameter abnormalities in study 810601. Laboratory parameters were not assessed in study 810501.

## Clinical Summary and Conclusions

The virus culture system used has been used for production of other vaccines, and is satisfactory for production of influenza whole virion vaccines. The mock up of pandemic strains, using recent avian strains, produces satisfactory immunogenicity, and within the constraints of assessing the most common adverse effects, appears to produce a reasonably safe vaccine. No indication was sought, nor were data provided for use of the Pandemic Vaccine H1N1 Baxter vaccine in children or pregnant women – the latter being an at risk group for influenza [NHMRC 2008].[1] The technical nature of the product is reasonably straightforward, and the sponsor suggests upscaling of production would be relatively uncomplicated. It is recommended that the mock-up vaccine is a practical method for addressing production of pandemic influenza vaccines. The lack of recent experience with whole virion influenza vaccines is an issue, as are the other outstanding issues listed below.

### Issues arising in relation to administration

The study vaccine for protocol 810601 was dispensed from multi-dose vials, and the sponsor proposed these for the final vaccine formulation. This is no longer a common form of vaccine preparation, as single dose vials have largely replaced multi-dose vials to reduce the risk of cross infection. In particular, all formulations of the influenza vaccine currently used in Australia are in single use prefilled syringes [NHMRC 2008].[1] The sponsor should provide further discussion of reasons for, and issues with the use of multi-use vials.

### Issues outstanding

The use of a mock vaccine to simulate production of a pandemic vaccine with novel influenza strain/s is an area that is unusual in relation to technical, regulatory, clinical and adverse event aspects. These have been tested in few settings (swine influenza vaccine [Sencer 2006], animal vaccines such as for equine influenza etc) and will raise unique issues to be addressed by vaccine manufacturers.[28]

*Major issues*

- The relationship between level of antibody and protection against clinical infection remains an issue that although informed by previous studies is still unresolved in relation to different vaccine formulations.

- The loss of antibody with time (measured between D42 and D180 HI and MN assays) is significant in assessing long term protection. This suggests any protective antibody will be lost in a significant proportion (approximately in half of the 810501 study participants, depending upon assay used) of the vaccinated population. This effect tends to be less at higher doses of vaccine (15 µg, 30 µg) whether adjuvanted or non-adjuvanted. At some doses, 80% of subjects (8/10 responders on MN assay) had antibody falls from ≥1:40 to <1:40 between D42 and D180.

*Minor issues*

- It was unclear why HI titres were reported as ≥2 and ≥4 fold increase over baseline when the CHMP guidelines suggest ≥2.5 is the criterion for response on the HI assay.

- The HI data suggest at baseline 1/38 or 2/42 (4.8%) of healthy individuals in Austria in study 810501 have a protective titre of antibody to A/Vietnam. This suggests presence of cross-reacting antibody, either from human influenza or avian influenza strains acquired by these individuals. The actual rate varies slightly, dependent upon the type and amount of antigen used in the HI assay.

*AusPAR Pandemic Influenza Vaccine H1N1 Baxter Pandemic influenza vaccine*
*Baxter Healthcare Pty Ltd PM-2009-1961-2 Final 9 December 2010*

*Page 33 of 58*

## Supplementary Clinical Data

The sponsor addressed each of the four issues discussed above in its response to the clinical evaluation report. This response was considered to be supplementary data and was reviewed below along with the evaluator's comment.

### Major issue 1

The relationship between level of antibody and protection against clinical infection remains an issue that although informed by previous studies, is still unresolved in relation to different vaccine formulations.

*Sponsor's response*

In response, the sponsor has referred to studies in ferrets and further challenge studies in mice in which vaccination with H5N1 vaccine was shown to be protective against disease. In addition, studies of passive immunisation with neutralising antibodies in mice and guinea pigs have also demonstrated efficacy.

In its clinical development program, Baxter primarily used a cut-off threshold of 1/20 for MN antibody titres as the clinical correlate of protection. The designation of $\geq$ 1/20 MN was argued based on agreement between MN and SRN assays using the kappa statistic as shown in Table 4.

Table 4: Correlation analysis of MN and SRH

**Correlation analysis of MN and SRH on Part A data using Kappa Coefficient of Agreement method**

| MN Cut-off Value | Kappa | 95% CI |
|---|---|---|
| 1:10 | 0.34 | 0.31 to 0.36 |
| 1:20 | 0.54 | 0.50 to 0.57 |
| 1:40 | 0.32 | 0.29 to 0.36 |
| 1:80 | 0.11 | 0.09 to 0.14 |

**Correlation analysis of MN and SRH on Part A and B (up to Day 180) data using Kappa Coefficient of Agreement method**

| MN Cut-off Value | Kappa | 95% CI |
|---|---|---|
| 1:10 | 0.26 | 0.24 to 0.28 |
| 1:20 | 0.53 | 0.50 to 0.56 |
| 1:40 | 0.35 | 0.31 to 0.38 |
| 1:80 | 0.12 | 0.10 to 0.15 |

In all clinical studies, correlates based on specific antibodies to haemagglutinin were also presented using various assay methods.

*Evaluator's comment*

In the absence of any opportunity to carry out clinical efficacy studies in humans, the animal model studies with ferret model are considered important supporting evidence and have previously been considered by the TGA as well.

*AusPAR Pandemic Influenza Vaccine H1N1 Baxter Pandemic influenza vaccine*
*Baxter Healthcare Pty Ltd PM-2009-1961-2 Final 9 December 2010*

*Page 34 of 58*

The use of neutralising antibody titres as primary outcome is acceptable. The validity of a cut off value of 1/20 is less certain. However, as also noted by the sponsor, no deaths were reported among poultry workers with neutralising antibody titres ranging from 1/10 to 1/40 who were exposed to H5N1 during 1997 outbreak. A protective level of 1/20 has therefore been postulated in the literature.

The evaluator noted that agreement between the 2 assays based on kappa statistic shown above is only moderate, although the best MN cut-off value was 1/20 MN.

**Major issue 2**

The loss of antibody with time (measured between D42 and D180 HI and MN assays) is significant in assessing long term protection. This suggests any protective antibody will be lost in a significant proportion (approximately in half of the 810501 study participants, depending upon assay used) of the vaccinated population. This effect tends to be less at higher doses of vaccine (15 μg, 30 μg) whether adjuvanted or non-adjuvanted. At some doses, 80% of subjects (8/10 responders on MN assay) had antibody falls from ≥1:40 to <1:40 between D42 and D180.

*Sponsor's response*

The waning of antibody levels against H5N1 at 6 months after primary immunisation has been known. In response, the sponsor has provided booster data in subjects from studies 810501 and 810601.

The extension of study 810501 was **study 810703** in which immunogenicity of a single booster dose of non-adjuvanted whole virion, Vero cell derived H5N1 vaccine (7.5 μg, A/Indonesia) administered 12-17 months after completion of primary vaccination with A/Vietnam vaccine strain was assessed. A total of 77 subjects participated from 141 available eligible subjects.

The results were provided and are summarised below for the baseline 7.5μg unadjuvanted group, that is, the dose subsequently tested in Phase III clinical trial 810601 and proposed for registration:

The protective levels (≥ 1/20) of neutralising antibodies against A/Indonesia were obtained in 12/12 (100%) subjects at 21D post-booster and 8/12 (67%) subjects at 180D post booster.

The protective levels (≥ 1/20) of cross-reacting neutralising antibodies against A/Vietnam were obtained in 10/12 (83%) subjects at 21D post-booster and 10/12 (83%) subjects at 180D post-booster.

The protective levels (≥ 25 mm$^2$) of specific antibodies with SRH assay against A/Indonesia were obtained in 8/12 (67%) subjects at 21D and 8/12 (67%) subjects at 180D.

The protective levels (≥ 25 mm$^2$) of specific antibodies with SRH assay against A/Vietnam were obtained in 10/12 (83%) subjects at 21D and 7/12 (58%) subjects at 180D.

The protective levels (≥ 1/40) of specific antibodies with HI assay against A/Indonesia were obtained in 3/12 (25%) subjects at 21D and 2/12 (17%) subjects at 180D.

The protective levels (≥ 1/40) of specific antibodies with HI assay against A/Vietnam were obtained in 4/12 (33%) subjects at 21D and 4/12 (33%) subjects at 180D.

The results of booster administration in study 810601 were as follows:

The participants in **study 810601** had been primed with 2 doses of unadjuvanted H5N1 vaccine (A/Vietnam) containing 7.5μg HA antigen per dose with patients stratified into adults (stratum A) and elder adults (stratum B).

Half of the subjects in each age stratum (116 and 127 from strata A & B respectively) were randomised to receive a single booster dose at 6 months (unadjuvanted 3.75μg or 7.5μg of either A/Vietnam or A/Indonesia). The results were included in the report.

*AusPAR Pandemic Influenza Vaccine H1N1 Baxter Pandemic influenza vaccine*
*Baxter Healthcare Pty Ltd PM-2009-1961-2 Final 9 December 2010*

*Page 35 of 58*

The remaining subjects were randomised into 2 equal groups.

One group received unadjuvanted vaccine booster (3.75µg or 7.5µg A/Indonesia) at 12-15 months. A total of 61 and 66 subjects participated from strata A and B respectively. The results were included in this report.

The other group is to receive (unadjuvanted) booster (3.75µg A/Indonesia) at 24 months. The results will be reported in future.

The results for booster at 6 months were and summarised for the 7.5µg booster dose group below:

In 18-59 years old stratum, the protective levels ($\geq$ 1/20) of neutralising antibodies against A/Vietnam were obtained in 19/29 (66%) and 17/30 (57%) subjects with A/Vietnam and A/Indonesia booster respectively at 21D post-booster. The respective rates at 180D were 8/29 (28%) and 11/30 (37%).

In 18-59 years old stratum, the protective levels ($\geq$ 1/20) of neutralising antibodies against A/Indonesia were obtained in 7/29 (24%) and 9/30 (30%) subjects with A/Vietnam and A/Indonesia booster respectively at 21D. The respective rates at 180D were 2/29 (7%) and 7/30 (23%).

In $\geq$ 60 years old stratum, the protective levels ($\geq$ 1/20) of neutralising antibodies against A/Vietnam were obtained in 17/32 (53%) and 20/32 (63%) subjects with A/Vietnam and A/Indonesia booster respectively at 21D post-booster. The respective rates at 180D were 11/30 (37%) and 14/32 (44%).

In $\geq$ 60 years old stratum, the protective levels ($\geq$ 1/20) of neutralising antibodies against A/Indonesia were obtained in 11/32 (34%) and 17/32 (53%) subjects with A/Vietnam and A/Indonesia booster respectively at 21D. The respective rates at 180D were 7/30 (23%) and 9/32 (28%).

In 18-59 years old stratum, the protective levels ($\geq$ 1/40) of specific antibodies against A/Vietnam using HI assay were obtained in 1/29 (3%) and 1/30 (3%) subjects with A/Vietnam and A/Indonesia booster respectively at 21D post-booster. The respective rates at 180D were 1/29 (3%) and 4/30 (13%).

In 18-59 years old stratum, the protective levels ($\geq$ 1/40) of specific antibodies against A/Indonesia using HI assay were obtained in 1/29 (3%) and 2/30 (7%) subjects with A/Vietnam and A/Indonesia booster respectively at 21D. The respective rates at 180D were 0/29 (0%) and 1/30 (3%).

In $\geq$ 60 years old stratum, the protective levels ($\geq$ 1/40) of specific antibodies against A/Vietnam using HI assay were obtained in 4/32 (13%) and 4/32 (13%) subjects with A/Vietnam and A/Indonesia booster respectively at 21D post-booster. The respective rates at 180D were 4/30 (13%) and 5/32 (16%).

In $\geq$ 60 years old stratum, the protective levels ($\geq$ 1/40) of specific antibodies against A/Indonesia using HI assay were obtained in 2/32 (6%) and 1/32 (3%) subjects with A/Vietnam and A/Indonesia booster respectively at 21D. The respective rates at 180D were 2/30 (7%) and 2/32 (6%).

In 18-59 years old stratum, the protective levels ($\geq$ 25 mm$^2$) of specific antibodies against A/Vietnam using SRH assay were obtained in 16/29 (55%) and 18/30 (60%) subjects with A/Vietnam and A/Indonesia booster respectively at 21D post-booster. The respective rates at 180D were 6/29 (21%) and 5/30 (17%).

In $\geq$ 60 years old stratum, the protective levels ($\geq$ 25 mm$^2$) of specific antibodies against A/Vietnam using SRH assay were obtained in 19/32 (59%) and 19/32 (59%) subjects with A/Vietnam and A/Indonesia booster respectively at 21D post-booster. The respective rates at 180D were 7/30 (23%) and 5/32 (16%).

*AusPAR Pandemic Influenza Vaccine H1N1 Baxter Pandemic influenza vaccine*
*Baxter Healthcare Pty Ltd PM-2009-1961-2 Final 9 December 2010*

*Page 36 of 58*

The results for booster at 12-15 months were provided and summarised for the 7.5µg booster dose group below:

In 18-59 years old stratum, 21D following booster (A/Indonesia), the protective levels (≥ 1/20) of neutralising antibodies against A/Vietnam were obtained in 11/29 (38%) subjects compared to 5/28 (18%) subjects against A/Indonesia. The D180 proportions were 7/29 (24%) and 4/29 (14%) for antibodies against A/Vietnam and A/Indonesia strains respectively.

In ≥ 60 years old stratum, 21D following booster (A/Indonesia), the protective levels (≥ 1/20) of neutralising antibodies against A/Vietnam were obtained in 15/31 (48%) subjects compared to 10/31 (32%) subjects against A/Indonesia. The D180 proportions were 11/31 (36%) and 4/31 (13%) for antibodies against A/Vietnam and A/Indonesia strains respectively.

In 18-59 years old stratum, 21D following booster (A/Indonesia), the protective levels (≥ 1/40) of specific antibodies against A/Vietnam using HI assay were obtained in 1/29 (3%) subjects compared to 1/29 (3%) subjects against A/Indonesia with no change in percentages at D180.

In ≥ 60 years old stratum, 21D following booster (A/Indonesia), the protective levels (≥ 1/40) of specific antibodies against A/Vietnam using HI assay were obtained in 6/31 (19%) subjects compared to 1/31 (3%) subjects against A/Indonesia. The D180 proportions were 4/31 (13%) and 2/31 (6.5%) for antibodies against A/Vietnam and A/Indonesia strains respectively.

In 18-59 years old stratum, 21D following booster (A/Indonesia), the protective levels (≥ 25 mm$^2$) of specific antibodies against A/Vietnam using SRH assay were obtained in 16/29 (55%) subjects compared to 4/29 (14%) at 180D. In ≥ 60 years old stratum, the respective percentages were 14/31 (45%) and 8/31 (26%) at D21 and 180D respectively. At 180D, with respect to antibodies against A/Indonesia, the proportions were 2/29 (7%) and 3/31 (10%) for the 18-59 and ≥ 60 years age strata respectively.

Based on the booster studies, the sponsor has argued that the data indicate rapid antibody response due to persisting immunological memory despite declining antibody levels 6-12 months post priming. The results also support a cross-clade prime-boost strategy whereby priming with one strain/clade and boosting with an emergent strain/clade can be expected to boost the levels of cross neutralising antibodies reactive against divergent strains of avian influenza virus H5N1.

*Evaluator's comment*

Decline of antibodies 6-12 months post primary H5N1 vaccination has been known in other H5N1 vaccine studies and is also consistent with experience with inter-pandemic flu. The evaluator agreed with the conclusion that booster data suggest persisting immune memory and a degree of cross immunity. However, it should be noted that the vaccine is not proposed for use in the pre-pandemic phase.

The booster studies further validated poor sensitivity of haemagglutinin inhibition assay and relatively better correlation of single radial haemolysis with neutralising antibody titres.

**Minor issue 1**

It was unclear why HI titres were reported as ≥2 and ≥4 fold increase over baseline when the CHMP guidelines suggest ≥2.5 is the criterion for response on the HI assay.

*Sponsor's response*

The 4 fold increase in titre from baseline refers to seroconversion (CHMP criterion of > 40% and > 30% in adults and elderly respectively).

The 2.5 fold increase refers to GMT titres (CHMP criterion of >2.5 fold and >2.0 fold in adults and elderly respectively).

*AusPAR Pandemic Influenza Vaccine H1N1 Baxter Pandemic influenza vaccine*
*Baxter Healthcare Pty Ltd PM-2009-1961-2 Final 9 December 2010*

*Page 37 of 58*

The study 810501 was the first clinical study with Baxter's Vero cell derived influenza vaccine. The rate of subjects with a ≥ 2 fold increase in HI titre as compared to baseline has also been assessed in this study.

*Evaluator's comment*

It is not clear from the sponsor's response whether a cut-off point of 2 or 2.5 was used for seroconversion using HI assay. As mentioned earlier, the sponsor was using MN titres and this is considered acceptable. A further clinical study was provided in this response.

**Minor issue 2**

The HI data suggest at baseline 1/38 or 2/42 (4.8%) of healthy individuals in Austria in study 810501 have a protective titre of antibody to A/Vietnam. This suggests presence of cross-reacting antibody, either from human influenza or avian influenza strains acquired by these individuals. The actual rate varies slightly, dependent upon the type and amount of antigen used in the HI assay.

*Sponsor's response*

This presence of pre-existing cross-reacting antibodies against H5N1 is in agreement with data previously reported particularly in elderly. The literature indicates that these antibodies are detectable by HI assay, SRH and MN assays. The findings are not restricted to Austria but have also been reported from other areas such as USA, Belgium, France, Australia and China.

Pre-absorption experiments on sera from study 801601 have been conducted and have demonstrated that anti-H5N1 neutralising antibodies can be removed with purified recombinant haemagglutinins derived from avian H5N1 (A/Vietnam/1203/2004) and from recently circulating human H1N1 (A/New Caledonia/20/99) strain.

Furthermore, partial inhibition of anti-H5N1 neutralising activity was achieved in some, not all, positive baseline samples after pre-absorption with purified recombinant haemagglutinin derived from circulating human H3N2 (A/Wisconsin/67/2005) strain. In contrast, purified recombinant neuraminidase proteins derived from H5N1 (A/Vietnam/1203/2004) failed to inhibit anti-H5N1 neutralising activity.

The sponsor concluded that existing immunity to circulating human H1N1 (not H1N1 2009) and H3N2 may be responsible for baseline seropositive individuals to H5N1 in the general population.

*Evaluator's comment*

The conclusion is considered acceptable. A proportion of baseline seropositive population has been noted previously in other studies of H5N1.

**Additional Clinical Study 801701**

This was a Phase I/II immunogenicity study in 110 healthy adult subjects randomised 1:1 to receive the Baxter's experimental (Vero cell cultured; inactivated whole virion) vaccine (3.75 or 7.5 µg non-adjuvanted) using A/Indonesia/05/2005 clade 2 strain. The inclusion exclusion criteria were similar to the previous studies 810501 and 810601. Children and pregnant women were excluded.

Two doses of the experimental vaccine were administered on D0 and D21 by the IM route. The immunogenicity outcomes were assessed at D42, that is, 21 days after completion of primary vaccination. The study was conducted in Hong Kong and Singapore.

The results are summarised in Table 5 for MN and SRH assays:

Table 5: Study 810701- MN and SRH Ab responses

*AusPAR Pandemic Influenza Vaccine H1N1 Baxter Pandemic influenza vaccine*
*Baxter Healthcare Pty Ltd PM-2009-1961-2 Final 9 December 2010*

*Page 38 of 58*

| Dose level | Assay | % [95% confidence interval] | | | | | GMI[a] | |
|---|---|---|---|---|---|---|---|---|
| | | Seroprotection[a] | | | % Seroconversion[a] | | | |
| | | Day 0 | Day 21 | Day 42 | Day 21 | Day 42 | Day 21 | Day 42 |
| 3.75µg | MN | 0.0% [0.0% ; 6.5%] | 36.4% [23.8% ; 50.4%] | 82.7% [69.7% ; 91.8%] | 40.0% [27.0% ; 54.1%] | 82.7% [69.7% ; 91.8%] | 3.0 [2.4 ; 3.7] | 8.0 [6.4 ; 10.1] |
| | SRH | 0.0% [0.0% ; 6.5%] | 38.2% [25.4% ; 52.3%] | 71.2% [56.9% ; 82.9%] | 38.2% [25.4% ; 52.3%] | 71.2% [56.9% ; 82.9%] | 2.8 [2.1 ; 3.8] | 5.0 [3.8 ; 6.6] |
| 7.5µg | MN | 0.0% [0.0% ; 6.8%] | 19.2% [9.6% ; 32.5%] | 86.5% [74.2% ; 94.4%] | 25.0% [14.0% ; 38.9%] | 86.5% [74.2% ; 94.4%] | 3.1 [2.6 ; 3.7] | 8.3 [6.8 ; 10.1] |
| | SRH | 1.9% [0.0% ; 10.3%] | 40.4% [27.0% ; 54.9%] | 69.2% [54.9% ; 81.3%] | 38.5% [25.3% ; 53.0%] | 67.3% [52.9% ; 79.7%] | 2.5 [1.8 ; 3.4] | 5.4 [4.1 ; 7.1] |

Microneutralization (MN) and Single Radial Hemolysis (SRH) Antibody Responses to the Homologous Virus Strain (A/Indonesia/05/2005) After the First and Second Vaccine Doses (Study 810701, ITT dataset)

[a] For reference, CPMP/BWP/214/96 states the following serological assessments should be considered, and at least one of the three criteria should be fulfilled in adults: seroconversion rate >40%; mean geometric fold increase (GMI) >2.5; seroprotection rate (≥40 HI titer or SRH area ≥25 mm$^2$) >70%

The reverse cumulative distribution tables included immunogenicity results at D180 indicative of loss of protective immune levels at 6 months consistent with those seen in previous studies.

### Evaluator's comment

All 3 CPMP criteria were satisfactorily met using SRH assay (marginal failure for seroprotection rate which fell slightly short of the required 70%) on D42.

It should be noted that some regulatory agencies require lower limit of 95% CI rather than the point estimate to be above the designated cut-off thresholds.

The correlation with MN assay was good. As in other studies, the poor sensitivity of HI assay in case of avian H5N1 influenza virus was also demonstrated in the results obtained in this study.

### Safety

### Introduction

For adverse effects (AEs) reported in the above studies, a summary is presented below for the 7.5µg unadjuvanted groups:

In study 810703, specifically queried and reported symptoms were pain at injection site 3/12 (25%), fatigue 1/12 (8%), headache 4/12 (33%) and arthralgia 2/12 (17%).

In study 810601 (18-59 years stratum) following booster at 6 months with A/Vietnam vaccine, specifically queried and reported symptoms were injection site induration 1/29 (3.4%), injection site erythema 1/29 (3.4%), injection site pain 5/29 (17%), fatigue 1/29 (3.4%), headache 1/29 (3.4%), myalgia 1/29 (3.4%) and arthralgia 2/29 (7%).

In study 810601 (18-59 years stratum) following booster at 6 months with A/Indonesia vaccine, specifically queried and reported symptoms were injection site erythema 1/30 (3%), injection site pain 8/30 (27%), injection site haemorrhage 1/30 (3%), fatigue 1/30 (3%), headache 1/30 (3%), hyperhidrosis 1/30 (3%) and arthralgia 1/30 (3%).

In study 810601 (≥ 60 years stratum) following booster at 6 months with A/Vietnam vaccine, specifically queried and reported symptoms were injection site pain 2/32 (6%), fatigue 1/32 (3%) and headache 1/32 (3%).

*AusPAR Pandemic Influenza Vaccine H1N1 Baxter Pandemic influenza vaccine*
*Baxter Healthcare Pty Ltd PM-2009-1961-2 Final 9 December 2010*

*Page 39 of 58*

In study 810601 (≥ 60 years stratum) following booster dose with A/Indonesia vaccine, specifically queried and reported symptoms were fatigue 1/32 (3%) and hyperhidrosis 1/32 (3%).

In study 810601 (18-59 years stratum) following booster (A/Indonesia) at 12-15 months, specifically queried and reported symptoms were injection site induration 1/29 (3.4%), injection site pain 3/29 (10%), injection site haemorrhage 1/29 (3.4%), fatigue 3/29 (10%), hyperhidrosis 1/29 (3.4%), myalgia 2/29 (7%) and arthralgia 1/29 (3.4%).

In study 810601 (≥ 60 years stratum) following booster (A/Indonesia) at 12-15 months, specifically queried and reported symptoms were fatigue 1/31 (3%), headache 1/31 (3%), hyperhidrosis 3/31 (10%), myalgia 2/31 (6.5%) and arthralgia 1/31 (3.2%).

In study 810701, following dose 1, specifically queried and reported symptoms were fatigue 9/54 (17%), headache 5/54 (9%), injection site pain 5/54 (9%), myalgia 2/54 (4%), injection site erythema 2/54 (4%), and one case each of injection site swelling, injection site induration, hyperhidrosis and arthralgia (2% each).

In study 810701, following dose 2, specifically queried and reported symptoms were injection site pain 8/52 (15%), headache 4/52 (8%), fatigue 3/52 (6%), injection site erythema 2/52 (4%), and one case each of injection site induration, injection site haemorrhage and hyperhidrosis (2% each).

Fever with onset later than Day 7 (Day 6 in study 810701) after vaccination was specifically queried in all but not reported in any.

*Safety Assessment*

No new or unexpected, local or systemic adverse events were reported in the short term in these studies.

## List of Questions

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a "list of questions" to the sponsor is generated.

The following additional information will be useful in final consideration of risk benefit analysis for the proposed vaccine:

(1) Cell Mediated Immunity (CMI) data have been collected but not included in the trial reports. The sponsor is requested to indicate if these are available now and provide these to the TGA.

(2) This mock up vaccine was registered in Europe and updated to H1N1 2009 strain during last year's pandemic. Since there is currently no seasonal influenza inactivated, whole virus vaccine based on cell culture, information on clinical efficacy and safety of this updated product will be useful. Whilst a separate application consisting of clinical data will be needed to approve H1N1 vaccine, the sponsor is requested to comment on the availability of field efficacy data of Baxter's H1N1 vaccine used during last year's pandemic in Europe. Administration in subgroups such as previous recipients of H5N1 mock up vaccine in clinical trials and in immunocompromised individuals will be special of interest.

(3) The vaccine is proposed as a multi-dose vial. Although multi-dose vial products have been approved in previous H5N1 mock up vaccines, the sponsor should be requested to consider the feasibility of supplying the product as single dose vials.

## Supplementary Clinical Summary and Conclusions

This review should be read as an addendum in conjunction with the initial evaluation.

*AusPAR Pandemic Influenza Vaccine H1N1 Baxter Pandemic influenza vaccine*
*Baxter Healthcare Pty Ltd PM-2009-1961-2 Final 9 December 2010*

*Page 40 of 58*

Since this application was submitted a number of H5N1 mock up vaccines have been approved including adjuvanted vaccines but all have been split virion products with virus gown in fertilised hens' eggs.

This is the first inactivated, whole virion vaccine with virus propagated on Vero cells. The product is monovalent containing 7.5µg HA avian H5N1 antigen. This is a mock up vaccine proposed as two injections 3-4 weeks apart by intramuscular route for prevention of influenza following official declaration of a pandemic. Paediatric and pregnancy data are currently not available for this product.

The sponsor's response to the initial clinical evaluation report which included results of an additional immunogenicity study was considered satisfactory. The use of neutralising antibodies correlated with SRH for a virus which is not circulating in humans at present is a satisfactory approach.

However, additional information in relation to a number of matters which have been identified under the list of questions above will be useful. It is proposed that finalisation of the application should proceed only after comments from the sponsor have been sought for these.

It should be noted that for a mock up vaccine it is understood that a strain update or update to a divergent subtype of influenza virus will require provision of immunogenicity and immunogenicity/vaccine dose data respectively in an actual pandemic.

## V.   Pharmacovigilance Findings

There was no Risk Management Plan submitted with this application as it was not a requirement at the time of submission.

## VI.   Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

### Quality

The drug substance is the Vero cell-derived, formaldehyde- and UV-inactivated and sucrose gradient purified whole virions of influenza virus. This is manufactured in the 4 main steps of Vero cell propagation, virus propagation and harvest, inactivation, purification and sterile filtration. There are no outstanding issues in relation to manufacture/quality control, including viral safety, endotoxin and sterility evaluations. The sponsor has been requested to provide results from ongoing stability studies.

The sponsor has justified the use of multi-dose vials on the basis of use during large vaccination campaigns during a pandemic. Other pandemic influenza vaccine registered in the ARTG also include multi-dose vial presentations.

The sponsor's response on a cross-contamination event at Baxter facilities was considered acceptable.

### Nonclinical

Primary and supplementary evaluations have been undertaken on nonclinical data.

Data submitted in support of the application were generally adequate, and relevant studies were GLP compliant.

The mock-up vaccine was highly immunogenic in mice and guinea pigs over a wide range of doses. Protective efficacy was demonstrated in mice following homologous lethal challenge. Limited evidence of efficacy in ferrets was demonstrated, due to high exposure margins.

Cross-protection from other H5N1 viruses (usually the heterologous reference virus) was demonstrated in mice, guinea pigs and ferrets, although immunogenicity was lower than with

homologous virus. Passive immunity was conferred on mice immunised with sera from human subjects vaccinated with A/Vietnam/1203/2004 virus in clinical trials. The nonclinical data were generally predictive of clinical efficacy.

In toxicity studies in rats the mock-up vaccine was generally well tolerated in a single dose and a repeat dose (3 doses) study in rats, at doses markedly greater than proposed clinical exposure. Toxicity was limited to local effects (inflammation and myofibre necrosis after repeated administration) and lymphoid changes. Increased liver enzymes in male rats following repeated administration of candidate vaccine were considered to be of limited toxicological concern and minimal clinical significance.

A rat embryofetal and postnatal development study was conducted, in which females were administered three IM doses of the proposed vaccine formulation (A/Indonesia/05/2005 virus) prior to mating and during gestation. Repeated vaccine administration was not associated with overt toxicity to treated females, fetuses or pups. There was no overt toxicity to treated females, fetuses or pups following repeated administration to rats prior to mating and during gestation.

There were no nonclinical objections to registration of the mock-up pandemic vaccine (reference strains /Vietnam/1203/2004 with supporting data from A/Indonesia/05/2005).

## Clinical

### Efficacy and Immunogenicity

Immunogenicity data were provided from a Phase I/II dose finding clinical study (810501) involving 284 health adults aged 18-45 years, and from a Phase III study in (810601) involving 583 healthy adults stratified into groups 18-59 years and $\geq$ 60 years.

Clinical study 810501 is a randomised, partially blinded, assessment of 6 vaccine groups who received H5N1 strain A/Vietnam/1203/2004 in two dose (Day 0, 21) primary vaccination series administered by IM injection, at dose levels:

7.5µg HA, N = 45 ;
15µg HA, N=45 ;
3.75µg HA+ alum adjuvant , N = 45
7.5µg HA+ alum adjuvant, N = 45
15µg HA+ alum adjuvant, N = 46
30µg HA+ alum adjuvant, N = 49

Immune response was assessed by anti-HA antibodies by haemagglutination inhibition (HI) and single radial haemolysis (SRH); neutralizing antibodies by microneutralisation (MN) and cell mediated immune response in a subset. Antibody was assessed at Days 21, 42 and at Day 180 for persistence (Table 6). Cross reactivity of antibody detected by MN and HI assays was assessed between A/Vietnam and related influenza strains. Interpretation of the HI and SRH results was linked to the immunogenicity requirements defined by the TGA-adopted EU guideline on influenza vaccines.[8]

*AusPAR Pandemic Influenza Vaccine H1N1 Baxter Pandemic influenza vaccine*
*Baxter Healthcare Pty Ltd PM-2009-1961-2 Final 9 December 2010*

*Page 42 of 58*

Table 6: Seroconversion in Study 810501

| Defined from D0 to D21 and D0 to D42 | Age | |
|---|---|---|
| | 18 to 60 years | > 60 years |
| Seroconversion*or significant increase† rate of titre | >40% | >30% |
| Mean Geometric fold increase‡ | >2.5 | >2.0 |
| Seroprotection rate (HI titre ≥ 1:40, SRH area ≥ 25mm²) | >70% | >60% |

* Proportion of subjects with a pre-vaccination HI titre <1:10 to a post-vaccination HI titre ≥1:40
Proportion of subjects with a baseline haemolysis area of ≤4 mm² and an area of ≥25 mm² post vaccination
† Proportion of subjects with HI titres ≥ 1:10 before vaccination and ≥ 4-fold increase of the titre.
Proportion of subjects with a ≥ 50% increase in haemolysis area if the pre-vaccination area is > 4 mm²
‡ Geometric mean of individual ratios (post-/pre-vaccination titres: D21/D0 or D42/D0)


The primary endpoint in Study 810501was the proportion with antibody level associated with protection 21 days after the first and second vaccination defined as either HI titre ≥ 1:40 or MN titre ≥1:20.

The study was conducted in 284 health adults aged 18-45 years in centres in Austria and Singapore. At baseline approximately 5% of subjects had HI titres regarded as protective to A/Vietnam suggesting presence of cross-reacting antibody.

Immunogenicity results were shown as GMT (Table 6). The HI seroconversion criteria for homologous strain was satisfied after one dose in unadjuvanted 7.5 μg and 15 μg groups, and with lower response in adjuvanted 7.5 μg and 15 μg dose groups.

Both the SRH and the MN assay fulfilled all three CPMP requirements for homologous strain following two immunisations in the non-adjuvanted 7.5μg group with seroprotection rate of 78.6% by SRH assay and seroneutralisation rate of 76.2% by MN assay, seroconversion rates of 69.0% and 73.8% and a GM fold increase of 5.3 and 6.3, respectively.

Data were provided on antibody persistence to D180. Of subjects who achieved protective antibody titres by HI or MN assay at D42, this was lost in approximately half by D180.

Cross reacting antibody to A/Indonesia (clade 2) and A/Hong Kong (clade 0) was shown. The evaluator considered selection of the non-adjuvanted 7.5 μg dose for the Phase III clinical study was appropriate.

Study 810601 is a Phase III, open-label, multicentre study which assessed 7.5 μg HA of H5N1 strain A/Vietnam/1203/2004 vaccine in a two dose (Day 0, 21) series and with booster of 3.75μg HA or 7.5μg HA prepared from H5N1 strains A/Vietnam/1203/2004 or A/Indonesia/05/2005 at 6 months, 12-15 months or 24 months. The objective was to assess immunogenicity and safety in adults and the elderly, and need for a booster dose. Anti-HA antibodies by HI; SRH; neutralizing antibodies by MN were measured in all subjects and cell mediated responses in a subset. The primary endpoint was proportion of subjects with antibody response defined as protective measured by MN (≥1:20) at 21 days after the second dose.

An interim report after the primary series was submitted. The study enrolled 583 healthy adults stratified into groups 18-59 years and ≥ 60 years. In the ≥ 60 stratum approximately 80% of subjects were between 60 and 70 years old. Gender was balanced.

A total of 561 subjects (280 Stratum A, 281 Stratum B) received the first vaccination and 539 subjects (269 Stratum A, 270 Stratum B) received the second vaccination. In Stratum B approximately 80% of subjects were between 60 and 70 years old. Gender was balanced.

*AusPAR Pandemic Influenza Vaccine H1N1 Baxter Pandemic influenza vaccine*
*Baxter Healthcare Pty Ltd PM-2009-1961-2 Final 9 December 2010*

*Page 43 of 58*

Baseline seropositivity was observed using MN assay in 4.1% for Stratum A and 16.9% for Stratum B. This suggests cross reaction with antibody to human influenza strains. The study was conducted in centres in Austria and Germany. Results for the primary endpoint are shown in Table 7.

Table 7:  Study 810601  MN assay to A/Vietnam/1203/2004

| | Age groups | | | | | |
|---|---|---|---|---|---|---|
| | 18-59 yrs | | | ≥60 yrs | | |
| Seroneutralisation rates (MN titer >=1:20) 21 days after 1st/2nd vaccination | | | | | | |
| Day | n/N | % | 95% CI | n/N | % | 95% CI |
| 0 | 11/270 | 4.1 | 2.1; 7.2 | 46/272 | 16.9 | 12.7; 21.9 |
| 21 | 137/270 | 50.7 | 44.6; 56.9 | 148/272 | 54.4 | 48.3; 60.4 |
| 42 | 192/265 | 72.5 | 66.7; 77.7 | 200/270 | 74.1 | 68.4; 79.2 |
| 180 | 85/243 | 35.0 | 29.0; 41.3 | 104/257 | 40.5 | 34.4; 46.7 |

Seroconversion defined as 4 fold increase in MN titre at Day 42 was reported in 39.6% in 18-59 year group and 60.8% in ≥ 60 year group. GMTs of MN titre increased 4.7 fold in 18-59 year group and 2.8 in ≥ 60 year group.

SRH antibody response defined as protective at D42 was reported in 63.3% (95% CI: 57.1, 69.2) in 18-59 year group and 67.7% (95% CI: 61.7, 73.3) in ≥ 60 year group. Seroconversion at D42 was reported in 60.2% (95% CI: 54, 66.2) in 18-59 year group and 62.4% (95% CI: 56.3, 68.2) in ≥ 60 year group. GMT increase at D42 was 4.6 fold (95% CI: 4.0, 5.4) in 18-59 year group and 4.6 fold (95% CI: 4.0, 5.3) in ≥ 60 year group.

Although the SRH fell below CPMP criteria for seroprotection in the 18-59 year group, the clinical evaluator considered that the MN and SRH results indicated an adequate response. Cross reactivity of antibody against Clade 2 and Clade 0 H5N1 viruses was not assessed in this study.

Study 810501 and study 810601 were not consistent for HI assay results, perhaps reflecting differences in methods (horse erythrocytes versus turkey erythrocytes).

**Safety**

In Studies 810501 and 810601 a total of 602 subjects received at least one dose of the vaccine formulation (7.5µg HA non-adjuvanted) proposed for pandemic use.

Safety was assessed using subject diary for 7 days after vaccination, post-vaccination physical findings, blood parameters at D0, D21 and D42 and scheduled for later time points (D180, D201, D360-450, D381-471, D720 and D741) in Study 810601.  No comparator vaccine was assessed in 810601. Study 810501 provided comparative assessment of different doses and adjuvanted vaccine but no comparative safety data with a registered vaccine.

In Study 810601 for age strata 18-59 years safety was evaluable in 281 subjects after vaccination 1 and in 269 subjects after vaccination 2. For age strata ≥ 60 years safety was evaluable for 280 subjects after vaccination 1 and in 270 subjects after vaccination 2.

Table 2 shows a summary local and systemic events reported in Study 810601 and systemic events reported in Study 810501.

In 810601 in the 18-59 year group systemic events were reported in 22.8% after the first dose and 14.7% after the second dose. Local reactions were reported in 17.1% after the first dose and 14.5% after the second dose. Injection site pain was reported in 15.7% after dose 1 and in 13.8% after dose 2.

In 810601 in the ≥ 60 year group systemic events were reported in 23.3% after the first dose and 13.4% after the second dose. Local reactions were reported in 8.6% after the first dose and 6.3% after the second dose.

There were no vaccine related changes in laboratory parameters

Severe local and severe systemic reactions were limited to 0 or 1 (0.4%) subjects per stratum after each dose. Nine serious adverse events were reported of which eight were reported as unrelated to vaccine. A reactivation of malaria at 8 days after vaccination was considered possible vaccine related. There were not significant dropouts and no withdrawals due to adverse events following study vaccine. No deaths were reported.

For Study 810501, Table 3 shows systemic events of mild severity in 39.0% and of moderate severity in 5.2%, with frequencies similar across treatment groups. Three serious AE between D42 and D180 were reported as unrelated to vaccine. Two withdrawals were related to adverse events of mild severity after the first dose. No deaths were reported.

### Clinical Evaluation Conclusion

The evaluator considered the mock up vaccine formulation (7.5 µg HA of H5N1 strain A/Vietnam/1203/2004) in a two dose (day 0, 21) regimen produced satisfactory immunogenicity and the adverse event profile for common events appeared satisfactory in the study populations. No study data are available for children, pregnant women, immunocompromised patients or special patient groups. There is a lack of recent experience with whole virion vaccines. The developmental program does not allow for assessment of rare complications, particularly GBS.

The evaluator identified two major issues arising from the clinical studies:

- the relationship between level of antibody and protection against clinical infection that is unresolved in relation to different vaccine formulations;

- significant loss of antibody at 6 months after primary vaccination.

Two minor issues raised by the evaluator were:

- reporting of HI titres increase of ≥ 2 fold and ≥ 4 fold ;

- apparent cross-reacting antibody present at baseline.

The sponsor submitted supplementary data to address issues identified in clinical and nonclinical evaluation reports.

The evaluator's conclusions on the supplementary data were:

1. The relationship between level of antibody and protection against clinical infection is unresolved in relation to different vaccine formulations.

The sponsor has referred to protection demonstrated in nonclinical challenge studies which is accepted as relevant. In its clinical development program, Baxter primarily used a cut-off threshold of 1:20 for MN antibody titres as clinical correlate of protection. The designation of ≥ 1:20 MN was argued based on agreement between MN and SRH assays using the kappa statistic. The evaluator has accepted the threshold of 1:20 for MN antibody titres as reasonable for analysis of the clinical studies.

2. Loss of antibody with time.

The sponsor has provided booster data in subjects from Studies 810501 and 810601.

Study 810703 is an extension of 810501 in which immunogenicity of a single booster dose of non-adjuvanted whole virion, Vero cell derived H5N1 vaccine (7.5 μg, A/Indonesia) administered 12-17 months completion of primary vaccination with A/Vietnam vaccine strain was assessed. Results were provided for the 7.5 μg non-adjuvanted group.

Study 810601 protocol provided for booster vaccination. Results for the booster were provided.

Based on the booster studies, the sponsor has argued that the data indicate rapid antibody response due to persisting immunological memory despite declining antibody levels 6-12 months post priming. The results also support a cross-clade prime-boost strategy whereby priming with one strain/clade and boosting with an emergent strain/clade can be expected to boost the levels of cross neutralising antibodies reactive against divergent strains of avian influenza virus H5N1.

The evaluator concluded that booster data support persisting immune memory and a degree of cross immunity. It was noted, however, that the vaccine is not proposed for use in the pre-pandemic phase. The booster studies further validated poor sensitivity of haemagglutinin inhibition assay and relatively better correlation of single radial haemolysis with neutralising antibody titres.

3. Minor issue - reporting of HI titres increase of ≥ 2 fold and ≥ 4 fold.

The sponsor has noted that 4 fold increase in titre from baseline refers to seroconversion (CHMP criterion of > 40% and > 30% in adults and elderly respectively). The 2 fold increase refers to GMT titres (CHMP criterion of >2.5 fold and >2.0 fold in adults and elderly respectively).

4. Minor issue - apparent cross-reacting antibody present at baseline.

The sponsor response commented that presence of pre-existing cross-reacting antibodies against H5N1 is in agreement with data previously reported particularly in elderly. The literature indicates that these antibodies are detectable by HI assay, SRH and MN assays. The findings is not restricted to Austria but have also been reported from other areas

The evaluator accepted the sponsor's comments.

**Clinical Study 810701.** A report of this study was included in the supplementary data

This was a Phase I/II immunogenicity study in 110 healthy adult subjects randomised 1:1 to receive the Baxter's Vero cell cultured; inactivated whole virion vaccine (3.75 or 7.5 μg non-adjuvanted using A/Indonesia/05/2005 clade 2 strain.

Two doses of the vaccine were administered on D0 and D21 by intramuscular route. After 2 doses CPMP criteria were satisfactorily met using SRH assay (except for marginal failure for seroprotection rate which fell slightly short of the required 70%). The correlation with MN assay was good. As in other studies, the poor sensitivity of the HI assay in the case of avian H5N1 influenza virus was also seen in this study.

The evaluator reviewed adverse effects in submitted studies. No new or unexpected, local or systemic adverse events were reported in the short term in these studies.

### Conclusion

The sponsor's response to the clinical evaluation report which included additional immunogenicity study was considered satisfactory. The use of neutralising antibodies, correlated with SRH for a virus which is not circulating in humans at present was a satisfactory approach. No new or unexpected, local or systemic adverse events were reported in the short term in these studies.

The sponsor has provided a response on cell mediated immunity data as requested by the evaluator.

*AusPAR Pandemic Influenza Vaccine H1N1 Baxter Pandemic influenza vaccine*
*Baxter Healthcare Pty Ltd PM-2009-1961-2 Final 9 December 2010*

*Page 46 of 58*

This mock up vaccine was registered in Europe and updated to H1N1 2009 strain during last year's pandemic. Some information on clinical efficacy and safety of this updated H1N1 2009 product was provided including a brief summary of adverse event experience in Adult and Elderly study 820902, Paediatric Study 820903 and the EMA Pandemic Pharmacovigilance Update Reports which support a positive benefit-risk balance of Pandemic Vaccine H1N1 Baxter.

The sponsor would consider the feasibility of supply in a single dose presentation but has data on stability only in Readyject (glass) syringes.

## Risk-Benefit Analysis

Protective efficacy of pandemic influenza vaccines cannot be assessed in clinical studies prior to the emergence of a pandemic situation. Registration guidelines for pandemic and pre-pandemic vaccines have adopted anti-HA antibody endpoints that have been used and correlated with protection for seasonal influenza vaccines. These correlates relate to reduction of influenza-like illness when most of the vaccinated population has some degree of pre-existing immunity against inter-pandemic strains, and may not be valid for pandemic vaccines. HI antibody assays for H5 and H7 show poor sensitivity when performed with chicken or turkey RBC. Use of horse RBC in H5N1 HI assays has improved sensitivity but variability remains. EMA Pandemic influenza guidelines have recommended measurement of neutralizing antibody responses. Viral neutralization assay methods are not standardised and correlates with protection have not been established. Cell mediated immunity assays are not standardised. The TGA-adopted EU guideline on pandemic influenza vaccines recommends supplementation of clinical immunological data with nonclinical challenge studies.[6]

The clinical studies for this H5N1 whole virion, Vero cell derived, inactivated vaccine included haemagglutination inhibition (HI) assay for anti-HA antibodies. Antibody responses to vaccine measured by HI were low and did not meet CHMP criteria consistently. Antibody responses to this vaccine measured by SRH generally met CHMP criteria (except for marginal failure for seroprotection in the younger age cohort in Study 810601 and Study 810701). Antibody response to vaccine measured by the MN assay showed good correlation with SRH results. The sponsor justification for a MN cut-off threshold of 1:20 was accepted. Taking account of protective efficacy of the vaccine demonstrated in animal challenge studies, the Delegate considered the SRH and MN responses are adequate to support registration of this vaccine.

The numbers of subjects assessed for safety in clinical studies were modest with a total of 602 subjects receiving the 7.5 µg dose in studies 810501 and 810601 and an additional 55 subjects in Study 810701. In these studies the adverse event profile appeared acceptable. There was no comparative safety data with currently registered vaccines. Older studies of whole virion influenza vaccines have demonstrated increased reactogenicity compared to subunit vaccines, particularly in children. The clinical development program did not include children. This limited clinical study safety data is now balanced by post-marketing experience with Pandemic Vaccine H1N1 Baxter in 2009 and 2010 reported in EMA Pandemic Pharmacovigilance Update Reports.

The European Risk Management Plan (RMP) for Pandemic Vaccine H1N1 Baxter included a paediatric study which was conducted using Pandemic Vaccine H1N1 Baxter (Study 820903) with an abbreviated report concluding that systemic reaction rates were low (excluding fever) and injection site reaction rates were low. Fever related to vaccination with 7.5 µg or 3.75 µg doses was reported in the 9 to 17 year stratum in 0% and 2%, in the 3 to 8 year stratum in 5.9% and 8.2%, in the 12 to 35 month stratum in 12.2% and 5.9% and in the 6 to 11 month stratum in 23.5% and 7.1%.

The Delegate considered that the clinical study program supports registration of the pandemic influenza vaccine (whole virion, Vero cell derived, inactivated) Pandemic Vaccine H5N1 Baxter as a mock-up pandemic vaccine for H5N1 influenza virus. The Delegate recommended submission of

*AusPAR Pandemic Influenza Vaccine H1N1 Baxter Pandemic influenza vaccine*
*Baxter Healthcare Pty Ltd PM-2009-1961-2 Final 9 December 2010*

*Page 47 of 58*

further clinical study data to support appropriate dosage if Pandemic Vaccine H5N1 Baxter were to be registered for other influenza subtypes.

In its pre-ACPM response, the sponsor was asked to comment on the availability of data arising from pharmacovigilance activities identified in the European Risk Management Plan (RMP) for Pandemic Vaccine H1N1 Baxter (Celvapan) which include the conduct of a study with at least 9,000 patients across different age groups, recruited at the start of the vaccination campaign, a specific monitoring of special populations such as pregnant women (through a pregnancy registry in several EU countries), children and immunocompromised subjects, and the monitoring of adverse events of special interest. Effectiveness studies developed and conducted in accordance with the standard protocols published by the ECDC will be performed. This application was submitted before TGA requirements for inclusion of a draft RMP in the submission were introduced.

The Delegate proposed to register pandemic influenza vaccine (whole virion, Vero cell derived, inactivated) Pandemic Vaccine H5N1 Baxter which contains 7.5 microgram haemagglutinin per 0.5 mL dose for the indication:

*Prophylaxis of influenza in an officially declared pandemic situation. Pandemic influenza vaccine should be used in accordance with official recommendations.*

*Pandemic Vaccine H5N1 Baxter has been evaluated in adults aged 18-60 years and elderly over 60 years following a 0, 21 day schedule. A 0.5 mL dose should be followed with a second dose given at an interval of at least 3 weeks. Administration is by intramuscular injection into the deltoid muscle.*

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal and recommended approval for the indication:

*For prophylaxis of influenza in an officially declared pandemic situation. Pandemic influenza vaccine should be used in accordance with official recommendations.*

In making this recommendation, the ACPM advised that it was not appropriate to include reference to safety in patients with egg protein hypersensitivity in the indication for this agent and that this information should be included in the appropriate section of the PI and CMI.

The ACPM further highlighted their ongoing concerns with the safety of multidose units, however recognised that the production times for single vials were impractical in the context of pandemic management.

The specific conditions of registration should include the provision of the data arising from pharmacovigilance activities in the EU Risk Management Plan for Pandemic Vaccine H1N1 Baxter (H1N1 2009) vaccine.

## Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Pandemic Influenza Vaccine H5N1 Baxter suspension for injection containing pandemic influenza virus H5N1 (whole virion, Vero cell derived, inactivated) haemagglutinin 7.5 micrograms per 0.5 ml dose for the indication:

*Pandemic Influenza Vaccine H5N1 Baxter is indicated for prophylaxis of influenza in an officially declared pandemic situation. Pandemic influenza vaccine should be used in accordance with official recommendations.*

Included among specific conditions of registration are the following:

1. It is a condition of registration that this product should not be supplied unless there is an official declaration of a pandemic and where the TGA and Commonwealth Department of Health and Ageing have agreed to supply commencing. Furthermore, if there is a need to make new stock with

*AusPAR Pandemic Influenza Vaccine H1N1 Baxter Pandemic influenza vaccine*
*Baxter Healthcare Pty Ltd PM-2009-1961-2 Final 9 December 2010*

*Page 48 of 58*

a different antigen, an application to the TGA for a variation to the antigen type and content must be processed and approved before release of the product.

2. It is a condition of registration that the sponsor provides to the TGA pharmacovigilance activity data arising from H1N1 vaccine 2009 (Celvapan) in accordance with the European Union Risk Management Plan (RMP).

3. For each batch of vaccine imported into Australia the sponsor should supply the following documentation:

- Complete protocols for the manufacture of final product including all steps in production.

- Number of doses to be released in Australia with accompanying expiry dates for vaccine and diluent.

- Evidence of product stability at release including results of the accelerated thermostability testing.

- Evidence of maintenance of satisfactory transport conditions to Australia.

- Twenty doses of product (including diluent) with the Australian approved labels, PI and packaging for initial shipment, 3 doses for subsequent shipments of the same batch.

- Any other reagents required to undertake testing as specified by the OLSS.

Distribution of each batch is conditional upon fulfilment of these conditions and approval of release by the OLSS.

## Attachment 1.     Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

*AusPAR Pandemic Influenza Vaccine H1N1 Baxter Pandemic influenza vaccine*
*Baxter Healthcare Pty Ltd PM-2009-1961-2 Final 9 December 2010*

*Page 49 of 58*

# Pandemic Influenza Vaccine H5N1 BAXTER

**Name of the medicine**

Pandemic Influenza Vaccine H5N1 Baxter (whole virion, Vero cell derived, inactivated), suspension for injection.

**Description**

Pandemic Influenza Vaccine H5N1 Baxter is a suspension for injection. After shaking, the vaccine is off-white, opalescent, translucent suspension. Whole virion influenza vaccine, inactivated, containing antigen of pandemic strain*:    7.5 micrograms** per 0.5 ml dose.

\* propagated in Vero cells (continuous cell line of mammalian origin)
\*\* expressed in micrograms haemagglutinin
It is presented in a multidose container, and contains as excipients Trometamol, Sodium chloride, Polysorbate and Water for injection.

**Pharmacology**
**Pharmacodynamic properties**

Pharmacotherapeutic group: Influenza, inactivated, whole virus, ATC Code J07BB01.
This section describes the clinical experience with the mock-up vaccine following a
two-dose administration.
Mock-up vaccines contain influenza antigens that are different from those in the currently circulating influenza viruses. These antigens can be considered as 'novel' antigens and simulate a situation where the target population for vaccination is immunologically naïve. Data obtained with the mock-up vaccine will support a vaccination strategy that is likely to be used for the pandemic vaccine: clinical immunogenicity, safety and reactogenicity data obtained with mock-up vaccines are relevant for the pandemic vaccines.
The immunogenicity of the 7.5 µg non-adjuvanted formulation of Pandemic Influenza Vaccine H5N1 Baxter (strain A/Vietnam/1203/2004) has been evaluated in 2 clinical studies in adults aged 18 – 59 years (N=312) and in subjects aged 60 years and older (N=272) following a 0, 21 day schedule.

The seroprotection rate, seroconversion rate and the seroconversion factor for anti-HA antibody as measured by SRH and for neutralizing antibodies as measured by MN in adults aged 18 to 59 years were as follows:

| | SRH assay | | Microneutralization asssay | |
| --- | --- | --- | --- | --- |
| | 21 days after first dose | 21 days after second dose | 21 days after first dose | 21 days after second dose |
| Seroprotection rate* | 55.5% (95% CI: 49.8-61.2) | 65.4% (95% CI: 59.8-70.8) | 49.4% (95% CI: 43.7- 55.1) | 73.0% (95% CI: 67.6-77.9) |
| Seroconversion rate** | 51.3% (95% CI: 45.6-57.0) | 62.1% (95% CI: 56.4-67.6) | 39.1% (95% CI: 33.7-44.8) | 61.9% (95% CI: 56.2-67.3) |
| Seroconversion factor*** | 3.7 (95% CI: 3.2-4.2) | 4.8 (95% CI: 4.2-5.5) | 3.4 (95% CI: 3.1-3.7) | 4.7 (95% CI: 4.3-5.2) |

*        SRH area > 25 mm²; MN titer > 1:20

**       either SRH area $\geq 25$ mm$^2$ (if baseline sample negative) or 50% increase in SRH area if baseline sample >4 mm²; > 4-fold increase in MN titer

***      geometric mean increase

The seroprotection rate, seroconversion rate and the seroconversion factor for anti-HA antibody as measured by SRH and for neutralizing antibody as measured by MN in adults aged 60 years and above were as follows:

| | SRH assay | | Microneutralization asssay | |
| --- | --- | --- | --- | --- |
| | 21 days after first dose | 21 days after second dose | 21 days after first dose | 21 days after second dose |
| Seroprotection rate* | 57.9%% (95% CI: 51.8-63.9) | 67.7% (95% CI: 61.7-73.3) | 54.4% (95% CI: 48.3-60.4) | 74.1% (95% CI: 68.4-79.2) |
| Seroconversion rate** | 52.4% (95% CI: 46.3-58.5) | 62.4% (95% CI: 56.3-68.2) | 14.3% (95% CI: 10.4-19.1) | 26.7% 95% CI: 21.5-32.4) |
| Seroconversion factor*** | 3.6 (95% CI: 3.1-4.2) | 4.6 (95% CI: 4.0-5.3) | 2.1 (95% CI: 1.9-2.2) | 2.8 (95% CI: 2.6-3.0) |

*        SRH area > 25 mm², MN titer > 1:20

**       either SRH area $\geq 25$ mm$^2$ .(if baseline sample negative) or 50% increase in SRH area if baseline sample >4 mm², > 4-fold increase in MN titer

***      geometric mean increase

To date, antibody persistence has been evaluated in 42 subjects up to 6 months after the first vaccination. Data indicate an overall decline in immunogenicity response over time. Further investigations of antibody persistence as well as the response to booster vaccinations are currently ongoing.

No clinical data have been generated in subjects below 18 years of age.

Pandemic Influenza Vaccine H5N1 BAXTER PI Approved 100823                              Page 2 of 9
                                                Baxter

*AusPAR Pandemic Influenza Vaccine H1N1 Baxter Pandemic influenza vaccine*                    *Page 51 of 58*
*Baxter Healthcare Pty Ltd PM-2009-1961-2 Final 9 December 2010*

*Pharmacokinetic properties*
Not applicable.

*Preclinical safety data*
Non-clinical data reveal no special hazard for humans based on conventional studies of safety
pharmacology and repeated dose toxicity.

## Indications

Pandemic Influenza Vaccine H5N1 Baxter is indicated for prophylaxis of influenza in an
officially declared pandemic situation. Pandemic influenza vaccine should be used in
accordance with official recommendations.

## Contraindications

History of an anaphylactic (i.e. life-threatening) reaction to any of the constituents or trace
residues (formaldehyde, benzonase, sucrose) of this vaccine. However, in a pandemic situation,
it may be appropriate to give the vaccine, provided that facilities for resuscitation are
immediately available in case of need.

## Precautions

Caution is needed when administering this vaccine to persons with a known hypersensitivity (other
than anaphylactic reaction) to the active substance(s), to any of the excipients and to trace residues
e.g. formaldehyde, benzonase, or sucrose. Hypersensitivity reactions, including anaphylaxis, have
been reported following use of a similar whole viron, Vero cell derived H1N1 influenza vaccine
administered during a pandemic period.  Such reactions have occurred both in patients with a
history of multiple allergies and in patients with no known allergy.
As with all injectable vaccines, appropriate medical treatment and supervision should
always be readily available in case of a rare anaphylactic event following the administration
of the vaccine.
If the pandemic situation allows, immunization shall be postponed in patients with severe
febrile illness or acute infection.
Pandemic Influenza Vaccine H5N1 Baxter should under no circumstances be administered
intravascularly.
Antibody response in patients with endogenous or iatrogenic immunosuppression may be
insufficient.
A protective response may not be induced in all vaccinees.

**Use in Pregnancy**

No data have been generated with Pandemic Influenza Vaccine H5N1 Baxter in pregnant women. Therefore health care providers need to assess the benefits and potential risks of administering the vaccine to pregnant women taking into consideration official recommendations.
Data from vaccinations with seasonal interpandemic inactivated trivalent vaccines in pregnant women do not indicate that adverse foetal and maternal outcomes were attributable to the vaccine.

**Use in lactation**

The safety of Pandemic Influenza Vaccine H5N1 Baxter in lactation has not been assessed in clinical trials. Physicians should carefully consider the potential risks and benefits for each specific patient before prescribing Pandemic Influenza Vaccine H5N1 Baxter.

**Paediatric use**

No data are available with Pandemic Influenza Vaccine H5N1 Baxter in subjects below 18 years of age. Therefore health care providers need to assess and take account of official guidance.

Children and adolescents 3 to 17 years of age
In an ongoing clinical trial 51 children and adolescents aged 9 to 17 years and 51 children aged 3 to 8 years were administered the 7.5 µg dose of CELVAPAN H1N1v (inactivated H1N1 A/California/07/2009 strain). The incidence and nature of symptoms after the first and second vaccination were similar to that observed in the adult and elderly population using CELVAPAN (inactivated H1N1 A/California/07/2009 strain).

Injection site pain was reported at a higher rate (very common) and headache and fatigue were reported at a lower rate (common) than in adults. Fever ($\geq$38°C) was reported at a frequency of 7.8% and 9.8% after the first and second vaccination in children aged 3 to 8 years. No fever was reported in children and adolescents aged 9 to 17 years.

Children aged 6 to 35 months
In an ongoing clinical trial the 7.5 µg dose of CELVAPAN H1N1v (inactivated H1N1 A/California/07/2009 strain) was administered to 52 infants and young children aged 6 to 35 months. Sleep disorder was reported as very common, and additional symptoms reported at a common frequency in this age group were anorexia, crying, irritability and somnolence. Fever ($\geq$38°C) was reported at a frequency of 13.4% and 11.5% after the first and second vaccination.

**Effects on ability to drive and use machines**

The vaccine is unlikely to produce an effect on the ability to drive and use machines.

Pandemic Influenza Vaccine H5N1 BAXTER PI Approved 100823                        Page 4 of 9
Baxter

*AusPAR Pandemic Influenza Vaccine H1N1 Baxter Pandemic influenza vaccine*                 *Page 53 of 58*
*Baxter Healthcare Pty Ltd PM-2009-1961-2 Final 9 December 2010*

## Interactions with other medicines

Pandemic Influenza Vaccine H5N1 Baxter should not be given at the same time as other vaccines. However, if co-administration with another vaccine is indicated, immunization should be carried out on separate limbs. It should be noted that the adverse reactions may be intensified. Immunoglobulin is not to be given with Pandemic Influenza Vaccine H5N1 Baxter. If it is necessary to provide immediate protection, Pandemic Influenza Vaccine H5N1 Baxter may be given at the same time as normal or specific immunoglobulin. Injections of Pandemic Influenza Vaccine H5N1 Baxter and immunoglobulin should be made into separate limbs.

The immunological response may be diminished if the patient is undergoing immunosuppressant treatment.

Following influenza vaccination, false positive results in serology tests using the ELISA method to detect antibodies against HIV1, Hepatitis C and especially HTLV1 have been observed. The Western Blot technique disproves the results. The transient false positive reactions could be due to the IgM response by the vaccine.

## Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

## Adverse effects

- Clinical trials

In clinical trials with the mock-up vaccine in 606 subjects (326 between 18 and 59 years old, and 280 over 60 years of age), the following adverse reactions were assessed as at least possibly related by the investigator. Most of the reactions were mild in nature, of short duration and qualitatively similar to those induced by conventional seasonal influenza vaccines. There were fewer reactions after the second vaccination compared with the first. The most frequently occurring adverse event was injection site pain, which was usually mild.

Undesirable effects are listed according to the following frequency:

Very common ($\geq$1/10)
Common (($\geq$1/100 to <1/10)
Uncommon ($\geq$1/1,000 to </100)
Rare ($\geq$1/10,000 to <1/1000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

Infections and infestations
Common: nasopharyngitis

Uncommon: herpes zoster, oral herpes, influenza, reactivation of tertian malaria, rhinitis

Blood and the lymphatic system disorders
Uncommon: lymphadenopathy

Metabolism and nutrition
disorders Uncommon: appetite lost

Psychiatric disorders
Uncommon: depression, disorientation, insomnia, sleep disorder, restlessness

Nervous system disorders
Common: headache, dizziness
Uncommon: dysaesthesia, migraine, drowsiness, sleepiness

Eye disorders
Uncommon: conjunctivitis, blepharospasm, dry eye, eye pruritus, eyelid oedema

Ear and labyrinth disorders
Common: vertigo
Uncommon: sudden hearing loss

Vascular disorders
Uncommon: hypotension, hypertension

Respiratory, thoracic and mediastinal disorders
Common: pharyngolaryngeal pain
Uncommon: dyspnoea, cough, increased bronchial secretion, rhinorrhoea, nasal congestion

Gastrointestinal disorders
Uncommon: nausea, vomiting, dyspepsia, abdominal pain, diarrhea, constipation, oral discomfort, glossodynia, oral dys- and hypoaesthesia, parotid gland enlargement, dry tongue, mouth oedema

Skin and subcutaneous tissue disorders
Common: hyperhidrosis
Uncommon: rash, pruritus, urticaria

Musculoskeletal and connective tissue disorders
Common: arthralgia, myalgia
Uncommon: musculoskeletal and back pain

Renal and urinary disorders
Uncommon: cystitis-like symptom

General disorders and administration site conditions
Very common: injection site pain
Common: chills, fatigue, malaise, pyrexia, induration, erythema, swelling and haemorrhage at the injection site
Uncommon: haematoma, irritation, joint pain, foreign body sensation and pruritus at the injection site Influenza like illness, mucosal oedema, peripheral coldness, thirst

Investigations
Uncommon: increased heart rate

- Post-marketing surveillance

There is no post-marketing data available for Pandemic Influenza Vaccine H5N1 Baxter From post-marketing surveillance with a whole virion, Vero cell derived, H1N1 vaccine, the following adverse events have been reported (the frequency of these adverse reactions is not known as it cannot be estimated from the available data):

Immune system disorders
anaphylactic reaction, hypersensitivity

Nervous system disorders
convulsion

Skin and subcutaneous tissue disorders
angioedema

Musculoskeletal and connective tissue disorders
pain in extremity

General disorders and administration site conditions
Influenza-like illness

**Dosage and administration**

Pandemic Influenza Vaccine H5N1 Baxter has been evaluated in adults aged 18-60 years and
elderly over 60 years following a 0, 21 day schedule.
Adults (18 years and older): 0.5 ml.
A second dose of vaccine should be given after an interval of at least 3 weeks.
Immunization should be carried out by intramuscular injection into the deltoid muscle.

Pandemic Influenza Vaccine H5N1 Baxter does not contain egg proteins. The product may
be administered to persons with hypersensitivity to eggs and egg protein.

The rubber stopper should not be removed from the vial for withdrawal of the individual doses by
sterile syringes.

**Overdose**

No case of overdose has been reported.

**Presentation and storage conditions**

*Shelf-life*

2 years

Store in a refrigerator (2°C to 8°C).

Do not freeze.
Store in the original package in order to protect from light.
After first use: Contains no preservative -vial to be used within one vaccination session, or

within 3 hours, whichever is less.
5.0 ml in 10-dose vial (type I glass) with stopper (bromobutyl rubber). Packs of 20. Not all pack sizes may be marketed.

The vaccine should be allowed to reach room temperature before use. Shake before use. Any unused vaccine or waste material should be disposed of in accordance with local requirements.
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**Name and address of the sponsor**

**Baxter Healthcare Pty Ltd**
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NSW 2146

**Poison schedule of the medicine**
S4

**Date of approval**
23 August 2010

Pandemic Influenza Vaccine H5N1 BAXTER PI Approved 100823                    Page 9 of 9
Baxter

*AusPAR Pandemic Influenza Vaccine H1N1 Baxter Pandemic influenza vaccine*          *Page 58 of 58*
*Baxter Healthcare Pty Ltd PM-2009-1961-2 Final 9 December 2010*