Bohumil Facility, Czech Republic: A fully GMP Licensed Plant Dedicated to the Production of Cell Culture Influenza Vaccines

Capacity:

Upto 20 Million doses trivalent bulk per year with 15 µg HA per strain

Characteristics of Baxter‘s Vero Cell-Derived Pandemic-Like H5N1 Candidate Influenza Vaccine

Monovalent: Doses in the range of 3.75 µg – 45 µg of hemagglutinin; non-adjuvanted or adjuvanted with 0.2% aluminium hydroxide

Grown on a qualified continuous cell line (Baxter‘s serum protein free Vero cells) using egg-derived wildtype virus provided by CDC

Double inactivated for enhanced safety affecting two different targets: protein by formalin treatment and viral RNA by UV irradiation

Sucrose gradient purified whole virus vaccine

Free of preservatives and antibiotics

Sterile filtrated and filled in single-use syringes or vials

Immunogenicity of an Inactivated Purified Wildtype H5N1 Viet Nam 1203 Whole Virus Antigen Preparation in Mice and Guinea Pigs

Immunization	anti H5 rHA ELISA Titer		anti H5N1 ELISA Titer		Micro NT Titer		HI Titer	
	Mice	Guinea Pigs	Mice	Guinea Pigs	Mice	Guinea Pigs	Mice	Guinea Pigs
H5N1 Antigen 0.2% $Al(OH)_3$ 1.7 µg HA)	11,994	51,200	95,543	162,550	293	4305	13	453
Buffer Control	< 100	< 100	< 100	< 100	≤ 28	≤ 28	5	5

rHA: recombinant Baculo-derived hemagglutinin
NT: neutralisation
HI: hemagglutination

Protection of Mice Against Intranasal Infection with Infectious H5N1 Viet Nam 1203 Virus after 2 Immunizations with an Inactivated Purified H5N1 Viet Nam 1203 Whole Virus Antigen Preparation

Immunization	Mean – anti H5 rHA ELISA Titer	Mean – Micro NT Titer	Surviving animals
H5N1 Antigen 0.2% $Al(OH)_3$ 1.7 µg HA	25,600	494	10 / 10
Buffer Control	$\leq$ 100	$\leq$ 7	0 / 10

rHA = recombinant Baculo-derived hemagglutinin NT = neutralisation titer

- Immunization an inactivated purified H5N1 Viet Nam 1203 whole virus antigen preparation (2 doses of 1.7 µg HA each) protected 100% of the immunized mice against intranasal challenge with 10^5 $TCID_{50}$ (= $2x10^2$ LD_{50}) infectious Viet Nam 1203 virus, whereas all control animals died between 4 and 8 days after infection

Immunogenicity in Mice of Adjuvanted MVB of H5N1 Candidate Vaccine: Effective (ED_{50}) and Protective (PD_{50}) Dose 50%

MVB 13/07/05		MVB 14/07/05	
- Trypsin		+ Trypsin	
ED_{50}	PD_{50}	ED_{50}	PD_{50}
week 3			
426 ng	n.d.	487 ng	n.d.
week 6			
67 ng	169 ng	67 ng	143 ng

n.d. not determined

H5N1 Candidate Vaccine Development Program

- **Development of a safe and immunogenic inactivated purified Vero cell derived whole virus H5N1 candidate vaccine and production of GMP clinical grade material using H5N1 wildtype virus A/Viet Nam/1203/2004**
  - **Establishment & testing of viral banks – completed**
  - **Process development – completed**
  - **Pre-clinical testing – in progress**
  - **Formulation, fill & finish of the vaccine – beginning 2006**
- **Planned formulations**
  - **3,75 µg + adjuvant**
  - **7,5 µg +/- adjuvant**
  - **15 µg +/- adjuvant**
  - **45 µg - adjuvant**
- **Clinical Studies**
- **Filing of EU Mock-up Dossier and US IND**

NIH Contract

Baxter is working with the National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health, to develop a cell culture-based (Vero) H5N1 candidate pandemic influenza vaccine. Baxter will be providing the candidate vaccine to NIAID for clinical testing. Clinical testing is expected to be initiated in 2006

Advantages of Baxter's Vero Cell Derived Pandemic Vaccine Production

- **So far all strains of human and animal origin (H1, H2, H3, H5, H7, H9) tested show high and consistent growth; with even significantly higher growth of the recent H5N1 human wild type isolates**
- **No supply issue with eggs; Vero cell production can be started at any time and on a continuous basis**
- **All plants (Orth, Bohumil) designed for BSL (Biosafety Level) 3**
- **No need for High Growth Reassortant or attenuated reverse genetic strain(s) for production; thus allowing start of vaccine production directly after receipt of wild type strain with the first batch available in 10 – 12 weeks**
- **The Vero cell technology involves the production of a whole virus vaccine which should be more effective as a pandemic vaccine than split or subunit vaccines in an unprimed population**