Date: Aug. 14, 2009
From: Ira Berkower, MD/PhD, DVP, OVRR, CBER
To: Anissa Cheung, DVP, OVRR
Through: Jerry Weir, Ph.D., Division Director, DVP, OVRR, CBER
Re: BLA for Agrippal, inactivated influenza vaccine (STN 125297)

Chemistry, Manufacturing, and Controls

3.2.S Drug Substance.
The biological substance is a pool of three monovalent bulk harvests of split, inactivated influenza A types H1N1 and H3N2, and influenza B. Each strain was grown individually on embryonated eggs and inactivated by formaldehyde and ----b(4)------. The vaccine is preservative free (eg., no thimerosal). The three vaccine strains for 2007/8, as recommended by WHO, were:
- A/Solomon Islands/3/2006 (H1N1)-like strain, reassortant virus IVR 145
- A/Wisconsin/67/2005 (H3N2)-like strain: Reassortant virus NYMCX-161b
- B/Malaysia/2506/2004-like strain

3.2.S.1.1 Nomenclature.
The influenza strains are identified by: influenza type/ location of isolation/ isolate number/ year of isolation (hemagglutinin subtype and neuraminidase subtype).

3.2.S.1.2 Structure
Influenza virus is a globular particle surrounded by a lipid bilayer. Two spike proteins are anchored in the lipid layer, hemagglutinin and neuraminidase. Antibodies to hemagglutinin protein are primarily responsible for vaccine-induced protection. Each lot of the drug substance is standardized based on hemagglutinin content.

3.2.S.2 Manufacture of Drug Substance.
3.2.S.2.1 Manufacturer.
The product is manufactured by Novartis Vaccines and Diagnostics, S.r.l. of Sienna, Italy, which is a division of Novartis AG, Basel, Switzerland.
The sponsor's US office is located at:

Novartis Vaccines and Diagnostics, Inc.
350 Massachusetts Ave.
Cambridge, MA 02139

The production facilities are located at:

Novartis Vaccines and Diagnostics S.r.l.
Via Fiorentina 1
53100 Siena, Italy

and at: Novartis Vaccines & Diagnostics S.r.l.

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3.2.S.2.2 Description of manufacturing process and process control.

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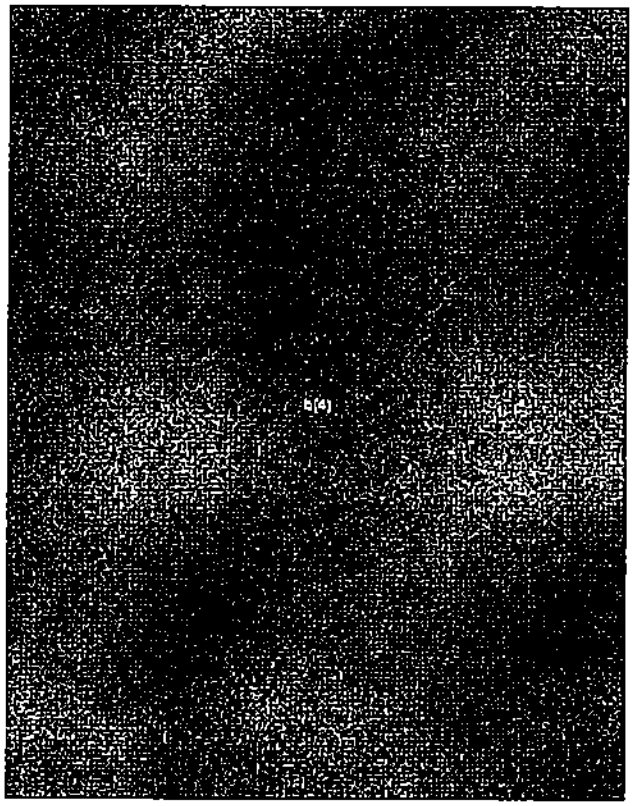

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MPH lots used in the main clinical trials:

Clinical Study V71P5S Final product Lot 070201				
[redacted]	NYMC X-161B (H3N2)	May 04. 2007	Clinical Study	Summary Protocol /

Batch Number	Strain	Date of Manufacture	Batch Use	Batch Analysis Data Location
[redacted]	IVR-145 (H1N1)	April 30. 2007	Clinical Study	Attachment 3.2.P.5.4-5
[redacted]	B/Malaysia/2506 /2004(B)	March 09. 2007	Clinical Study	

Clinical Study V71P6 Final product Lot 070801A				
[redacted]	NYMC X-161B (H3N2)	June 22, 2007	Clinical Study	Summary Protocol / Attachment 3.2.P.5.4-6
[redacted]	IVR-145 (H1N1)	May 25, 2007	Clinical Study	
[redacted]	B/Malaysia/2506 /2004(B)	June 19, 2007	Clinical Study	
Clinical Study V71P6 Final product Lot 070904B				
[redacted]	NYMC X-161B (H3N2)	February 16, 2007	Clinical Study	Summary Protocol / Attachment 3.2.P.5.4-7
[redacted]	NYMC X-161B (H3N2)	February 20, 2007	Clinical Study	
[redacted]	IVR-145 (H1N1)	May 22, 2007	Clinical Study	
[redacted]	IVR-145 (H1N1)	May 25, 2007	Clinical Study	
[redacted]	B/Malaysia/2506 /2004(B)	April 04, 2007	Clinical Study	
Clinical Study V71P6 Final product Lot 071303A				
[redacted]	NYMC X-161B (H3N2)	June 26, 2007	Clinical Study	Summary Protocol / Attachment 3.2.P.5.4-8
[redacted]	IVR-145 (H1N1)	June 05, 2007	Clinical Study	
[redacted]	B/Malaysia/2506 /2004(B)	June 29, 2007	Clinical Study	

3.2.S.2.3 Control of materials.

3.2.S.2.3.1 Virus seed bank system.

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3.2.A.2 Adventitious agent safety evaluation.

3.2.A.2.1 TSE evaluation.

The product is produced in hens' eggs and has negligible risk of TSE contamination. Polysorbate 80 is manufactured ----b(4)---------- --b(4)---------- is produced ---b(4)---------- materials, except for the use of a small amount of -b(4)- derived from -b(4)- for which current regulations regarding TSE risk are not applicable.

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3.2.S Drug Product.

The drug product, Agrippal, is a trivalent, inactivated split influenza vaccine. It is supplied as a sterile, preservative-free, pre-filled, 1ml syringe containing 15 ug each of three HA antigens per 0.5 ml volume. The actual amount in each syringe is slightly greater (0.545 ml) than the intended dose.

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Primary packaging components: Vaccine is packaged in a prefilled, 1ml glass --b(4)-------syringe.

1. Evaluation of the consistency of drug product manufacturing process

Formulation: Drug product consistency lots.
The trivalent bulk was formulated in -----b(4)----------

[b(4)]

Consistency was shown as follows:

[b(4)]

Although these tables indicate a lower confidence limit of --b(4)--------- dose, as used in the EU, CBER requires a mean of at least 13.5ug/0.5 ml on three tests, as indicated to the sponsor in a teleconference on 10/23/07. As indicated in their amendment of 2/27/09 (section 2.3.P.8 stability), the sponsors have committed to using ---b(4)---------- dose, as indicated in their most recent stability testing (Tables 5 and 6 on p. 36). All --b(4)-- production lots met the CBER criteria.

Filling

[b(4)]

Packaging involves several machines, including:
Labeling, blister machine, case packer, weight checker, boxing, and box labeler.

Executed batch records (above) show formulation, filling, and release testing of three lots of final trivalent bulk. They provide validation of formulation and filling of drug product for process consistency.

2. Validation of sterilization process for components and materials used in drug product manufacturing. Each batch was tested for sterility and ---b(4)---- content. All passed.

3. Validation of aseptic formulation filling operations.
Sterile filling was tested by filling media into -b(4)------ syringes per run, and the syringes were consistently free of bacterial contamination.

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3.2.P.7 Container closure system.

The final product is filled in a 1 ml --b(4)---- syringe with an -b(4)- rubber stopper.

[b(4)]

A. Stability Product stability was measured for the vaccine filled in -b(4)---- syringes with plastic rigid tip cap. They tested --b(4)---------- of trivalent vaccine filled into three lots of syringes. The syringes were stored on their -b(4)- to allow contact with the stoppers and caps.

Accelerated stability testing showed that the product was stable for ------b(4)----------
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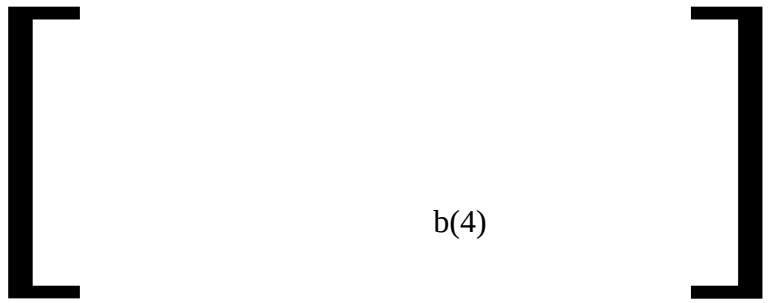

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3.2.P.8 Stability Testing

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[b(4)]

Samples have been tested in CBER for identity. The sponsors have received CBER letters confirming the strains, and these have been submitted back to us for the file.

Summary and conclusions:

1. Agrippal is a trivalent inactivated seasonal influenza vaccine produced in hens' eggs. The manufacturing process is well controlled and produces a consistent product that functions well in clinical trials of influenza vaccine potency.

2. Inactivation of influenza virus ---b(4)----------: formaldehyde inactivation ---b(4)----------. For the past two years, they have had difficulty in showing complete inactivation of the -b(4)- strain by formaldehyde. In addition, it is not feasible to show inactivation by a ---b(4)----------, due to limitations on the size of the sample tested. Thus, it was important that they document viral inactivation due ---b(4)----------. They have now done this, and this allows them to add the --b(4)---------- at both steps. In this way, they have achieved an acceptable margin of safety for the overall manufacturing process.

3. Regarding adventitious agents: inactivation of one model virus, b(4) as well as -b(4)---------- depended on the ----b(4)----------. The --b(4)---------- is important both for influenza inactivation and for removal of potential adventitious agents.

4. With regard to the b(4) method for determining HA content:
a. The b(4) assay has been optimized about as far as it can go. They have switched over to using CBER standard reagents, so their potency results are now comparable to other licensed products. The assay and measurements of --b(4)---------- do not need to be repeated.
b. The sponsor has changed from the --b(4)-- method to the --b(4)-------- method of interpreting -b(4)- results, as requested by CBER.
c. The CBER method of plotting ----------b(4)--------- input is not giving straight lines in up to 40% of cases. This would be important for calculating ----------b(4)----and comparing their ----b(4)-----, as the measure of ---b(4)---- potency. This problem manifests itself as the failure to meet plate acceptance criteria. Our statistician is working to come up with new criteria to resolve these questions. It is critical to have a working -b(4)- assay, since the potency of the product depends on the HA concentration, as determined by the -b(4)- assay.

5. With regard to the hemagglutination inhibition assay (HAI): review of additional information in SOP 101076-04 shows that HAI antibody titers were determined correctly.

6. The manufacturing plan allows them to inactivate influenza virus in formaldehyde at --b(4)---------- for most strains and b(4) for resistant strains, such as the b(4) strain of the last two years. This --b(4)---------- was shown to produce more rapid and reliable inactivation of this strain, but it may cause problems with key antigenic determinants on hemagglutinin.

Although inactivation at the ---b(4)---------- had little or no effect on ----b(4)--------- ---------- steps, it caused a significant amount of --b(4)----------, as shown by the appearance of prominent new ----b(4)---------- corresponding to ----b(4)----------

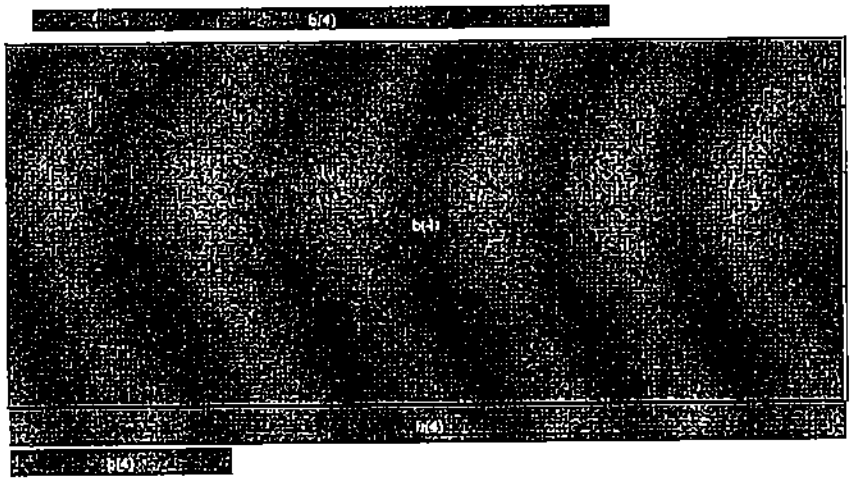
The material produced at b(4) passed all of the lot release specifications, yet the same -b(4)--- process that caused extensive ----b(4)---------- could also damage key antigenic determinants. I have several suggestions for controlling these potential problems:

a. In dealing with a product that may be inactivated at either of ---b(4)----------, I proposed an improved protocol for deciding when the virus will be inactivated --b(4)----------

b. Testing immunogenicity of the material inactivated at b(4). This could be done as part of the routine immunogenicity testing that accompanies a strain change in the EU. If immunogenicity remains adequate, there is no problem. If, however, the product inactivated at b(4)fails to raise adequate HAI titers, the explanation could be a loss of key antigenic determinants.

c. Better control of vaccine quality, including persistence of important antigenic determinants and absence of aggregation. Although -b(4)- is adequate as a measure of the quantity of antigen in the vaccine, it is based on -----b(4)---------- This depends on many antigenic determinants other than neutralizing determinants. We cannot rely on -b(4)- alone to detect a decline in HA quality due to loss of key antigenic determinants. The risk is that crosslinking with formaldehyde at b(4) may damage key antigenic determinants long before they cause any decrease in -b(4)-

Recommendation: The product is acceptable for a US license for use in adults. However, it could be better. If my CMC questions of the last 3 months (part 6 above) were communicated to the sponsor, this would have provided a way to inform them of potential problems and allowed them to address them in a timely manner.



Long term stability testing at b(4) has only been completed for the first -b(4)--------, and the product is stable so far. The sponsors are committed to completing an ---b(4)----- study. However, the study began last August, so the --b(4)---------- timepoints should be available by now.

Table 6. Agrippal In [redacted] syringes. Stability Results at 2°-8°C

Lot nr.	Storage time (months)	Haemagglutinin Content [redacted]			Appearance (clear colourless liquid)	pH [redacted]	Sterility (sterile)	[redacted]
		H1N1 (IVR 148)	H3N2 (X-176C)	B (B/Florida)				
[redacted]	0	36.9	33.9	34.6	conform	7.4	sterile	[redacted]
	3	36.3 *36.0**	34.0 *32.3**	32.8 *32.6**	conform	7.5	NR	
	6							
	9							
	12							
	[redacted]							
[redacted]	0	36.5	34.4	33.2	conform	7.4	sterile	[redacted]
	3	35.8 *36.4**	34.0 *33.6**	33.4 *32.4**	conform	7.5	NR	
	6							
	9							
	12							
	[redacted]							
[redacted]	0	36.6	34.1	33.8	conform	7.4	sterile	[redacted]
	3	36.4 *37.3**	34.4 *33.2**	33.6 *33.3**	conform	7.5	NR	
	6							
	9							
	12							
	[redacted]							

*: The table report the result for the [redacted] and in *italics* the results for the second [redacted] no significant variation could be observed between the two results.

The sponsors are seeking a dating period of 12 months.

1. Three lots of trivalent vaccine from the 2008-2009 season were tested for HA content (all three subtypes) over time. (3 months data as of Feb. 2009):

Table 6. Agrippal 2008/2009 Production lots. Stability Results at 2°-8°C

Lot nr.	Storage time (months)	Haemagglutinin Content [redacted]						Appearance (clear colourless liquid)	pH [redacted]	Sterility (sterile)	[redacted]
		H1N1 (IVR-148)		H3N2 (X-175C)		B/Malaysia					
		mean	LCL	mean	LCL	mean	LCL				
[redacted]	0	17	16	17	16	17	16	conform	7.5	sterile	[redacted]
	3	17	16	17	16	17	17	conform	7.6	-	
	6	IP	IP	IP	IP	IP	IP	conform	7.6	-	
	9									-	
	12									-	
	[redacted]										
[redacted]	0	17	15	18	17	18	18	conform	7.4	sterile	[redacted]
	3	17	16	17	17	18	17	conform	7.3	-	
	6	IP	IP	IP	IP	IP	IP	conform	7.6	-	
	9									-	
	12									-	
	[redacted]										
[redacted]	0	18	17	17	17	17	15	conform	7.5	sterile	[redacted]
	3	17	17	16	16	18	17	conform	7.5	-	
	6	IP	IP	IP	IP	IP	IP	conform	7.8	-	
	9									-	
	12									-	
	[redacted]										

Note: - test not selected

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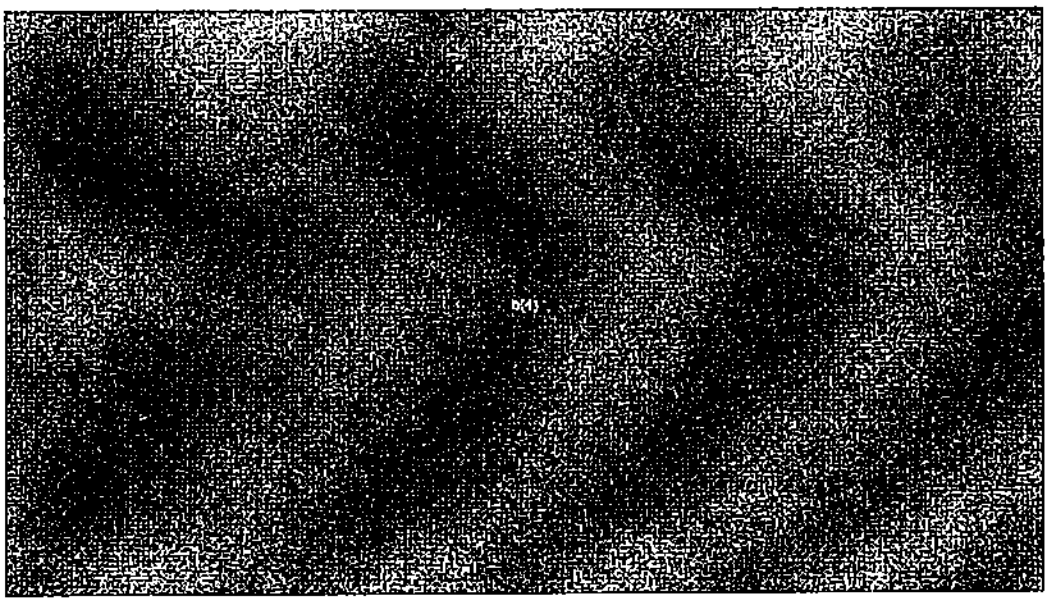
[redacted]



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2. Real time stability data with the 2007-2008 vaccine were as follows (12 months data):

Table 6a. Agrippal 2007-2008 Production lots. Stability Results at 2°-8°C. (Lots filled in bldg b(4))

Lot nr.	Storage time (months)	Haemagglutinin Content b(4)						Appearance (Clear colourless liquid)	pH b(4)	Sterility (sterile)	b(4)
		H1N1		H3N2		B Malaysia					
		mean	LCL	mean	LCL	mean	LCL				
b(4)	0	16	15	17	16	15	15	pass	7.5	pass	b(4)
	3	17	16	17	16	15	15	pass	7.6	-	
	6	17	16	16	16	15	15	pass	7.6	-	
	9	16	15	16	15	15	15	pass	7.6	-	
	12	16	15	15	14	15	15	pass	7.6	pass	
	b(4)	b(4)	b(4)	b(4)	b(4)	b(4)	b(4)	b(4)	b(4)	b(4)	
b(4)	0	16	16	17	16	16	15	pass	7.5	pass	b(4)
	3	17	16	17	16	16	16	pass	7.5	-	
	6	16	16	16	15	16	15	pass	7.6	-	
	9	17	16	16	16	15	15	pass	7.6	-	
	12	16	15	16	15	15	15	pass	7.6	pass	
	b(4)	b(4)	b(4)	b(4)	b(4)	b(4)	b(4)	b(4)	b(4)	b(4)	
b(4)	0	17	15	17	16	15	15	pass	7.4	pass	b(4)
	3	16	16	16	16	16	16	pass	7.5	-	
	6	16	15	16	16	16	15	pass	7.5	-	
	9	16	16	17	16	16	16	pass	7.5	-	
	12	16	16	17	16	15	15	pass	7.6	pass	
	b(4)	b(4)	b(4)	b(4)	b(4)	b(4)	b(4)	b(4)	b(4)	b(4)	

Note - results not reported
P: in progress

The HA titer was stable for at least one year. Contrary to what the tables indicate, the sponsors -----b(4)---------- Similar stability results were obtained for material filled in the old bldg b(4)

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Notes: * = out of specification

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