

REVIEW MEMORANDUM

To: Brenda Baldwin, Ph.D., DVRPA, OVRR, CBER, FDA

From: Marina Zaitseva, Ph.D., DVP, OVRR, CBER, FDA

Through: Hana Golding, Ph.D. Supervisor, DVP, OVRR, CBER, FDA

Through: Jerry Weir, Ph.D., DVP, OVRR, CBER, FDA

Anissa Cheung, Regulatory Coordinator, DVP, OVRR, CBER, FDA

Subject: STN125510/0

Product Name FLUAD 65, Inactivated Human Influenza Virus Type A (H1N1; H3N2) and B Hemagglutinin and Neuraminidase Vaccine, Adjuvanted

Applicant Novartis Vaccines and Diagnostics, Inc.

Proposed Indication For active immunization in persons 65 years of age and older against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine

Cross-reference(s) (b) (4) (Syringes)
(b) (4) (Tip cones)
(b) (4) (Plunger stopper)

Review of the Chemistry, Manufacturing, and Control Information relevant to MF59C.1 Drug Substance and FLUAD Drug Product submitted as part of the Initial Biologics License Application

Table of Contents

1. EXECUTIVE SUMMARY and RECOMMENDATIONS.....	3
1.1 MF59C.1 ADJUVANT DRUG SUBSTANCE.....	3
1.2 FLUAD DRUG PRODUCT	6
2. FULL REVIEW OF MF59C.1 ADJUVANT DRUG SUBSTANCE AND FLUAD DRUG PRODUCT	11
2.1 MF59C.1 ADJUVANT DRUG SUBSTANCE.....	13
2.1.1 General Information, Nomenclature, Structure, and Properties.....	13
2.1.2 Manufacture	14
2.1.2.2 Manufacturer and Overview of the Manufacturing for MF59 Drug Substance	14
2.1.2.3 Detailed manufacturing process.....	15
2.1.2.4 Control of Materials	16
2.1.2.5 Controls of Critical Steps and Intermediates	19
2.1.2.6 Process Validation and/or Evaluation.....	20
2.1.2.7 Manufacturing Process Development	23
2.1.2.8 Characterization.....	31
2.1.3 Control of Drug Substance	34
2.1.3.1 Specification.....	34
2.1.3.2 Analytical procedures	34
2.1.3.3 Batch Analysis	35
2.1.3.4 Justification of Specifications.....	37
2.1.4 Reference standards or materials.....	38
2.1.5 Container Closure System.....	39
(b) (4) , Leachables study	39
2.1.6 Stability	41
2.2 FLUAD DRUG PRODUCT	43
2.2.1 Description and composition of the FLUAD drug product.....	43
2.2.2 Pharmaceutical Development.....	44
2.2.3 Container Closure System (also includes summary from 3.2.P.7 on container closure).....	45
2.2.4 Manufacture	48
2.2.4.1 Batch Formula	48
2.2.4.2 Description of Manufacturing Process and Process Controls.....	50

2.2.4.3 Controls of Critical Steps and Intermediates	55
2.2.4.4 Process Validation and /or evaluation	60
2.2.4.5 Control of Excipient.....	62
2.2.6 Control of Drug Product.....	63
2.2.6.1 Specifications	63
2.2.6.2 Analytical Procedures	64
2.2.6.3 Batch Analysis	65
2.2.6.4 Characterization of Impurities	66
2.2.6.5 Justification of Specifications.....	66
2.2.7 Reference Standards or Materials	68
2.2.8 Stability	68

1. EXECUTIVE SUMMARY and RECOMMENDATIONS

The FLUAD vaccine is an inactivated subunit influenza vaccine for active immunization in persons 65 years of age and older. It is composed of three drug substances representing three viral strain surface antigens and the adjuvant MF59C.1. The vaccine is presented as a 0.5 ml single dose sterile milky-white emulsified suspension for injection in a glass pre-filled syringe.

The three viral surface antigens are isolated from two influenza A strains subtypes H1N1 and H3N2 and one influenza B strain. The antigens represent the viral proteins haemagglutinin (HA) and neuraminidase (NA), 15 µg of HA from each strain, total of 45 µg of HA per dose. The viral antigens are formulated with MF59C.1 adjuvant in the final FLUAD vaccine at pH of 6.9-7.7 without preservative.

The potency of the vaccine is assessed by measuring concentration of the HA protein in the final formulation using the Single Radial Immuno Diffusion (SRID) assay.

This review covers the MF59C.1 adjuvant Drug Substance and parts of FLUAD Drug Product relevant to MF59 adjuvant including stability of the FLUAD Bulk and Final Container.

1.1 MF59C.1 ADJUVANT DRUG SUBSTANCE

(b) (4)

(b) (4)

2 pages determined to be not releasable: (b)(4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

1.2 FLUAD DRUG PRODUCT

Formulation of Monovalent Pooled Harvest (MPH) antigens with MF59C.1 adjuvant is performed at Novartis manufacturing site in (b) (4). The MF59C.1 Bulk adjuvant is received at (b) (4) from the manufacturing site in (b) (4). It is received in (b) (4) containing (b) (4), the adjuvant is (b) (4) for up to (b) (4) months from the date of manufacture.

Sterile filtration of MF59

(b) (4)

1 page determined to be not releasable: (b)(4)

(b) (4)

In addition to parameters characterizing HA content, included parameters that characterized (b) (4) properties as described in Table 3 below:

Table 3 Release specifications for FLUAD Final Filled Container

Test	Method	Specification
Identity		
Haemagglutinin Identity A (H3N2) A (H1N1) B	(b) (4)	positive
Squalene Identity	(b) (4)	positive
Potency/Strength		
Haemagglutinin content A (H3N2), A (H1N1), B	SRID (Potency)	(b) (4)
Squalene Strength	(b) (4)	(b) (4)
(b) (4)		
(b) (4) (b) (4)	(b) (4) (b) (4)	(b) (4) (b) (4)
Quality		
Sterility	(b) (4)	Sterile
Endotoxin	(b) (4)	(b) (4)
Appearance	Visual	Conforms
Visible Particles	Visual	Conforms
(b) (4) (b) (4)	(b) (4)	(b) (4) (b) (4)
pH	(b) (4)	6.9 – 7.7
Extractable volume	(b) (4)	(b) (4) 0.50 ml

Stability of the Formulated Bulk

(b) (4)

Major issues related to MF59C.1 and FLUAD manufacturing and stability identified during review process

1. In IR12 (February 18 2015), the sponsor was asked to revise stability protocol for sterile filtered MF59C.1 (b) (4) to include sterility testing at (b) (4) time point.

Company's response (Amendment 7, April 17 2015). The sponsor acknowledged that sterility testing at (b) (4) was not originally included in the stability protocol of the sterile filtered MF59C.1 Adjuvant (b) (4). In response to request from CBER, the stability protocol was up-dated in March 2015 and a copy of the up-dated protocol was submitted as Attachment 22.1. In the modified protocol, the sponsor will perform stability study of the MF59C.1 sterile filtered (b) (4) to support (b) (4) shelf life at (b) (4) consistency lots filled at (b) (4) will be put on stability. (b) (4)

Reviewer: I reviewed the up-dated stability protocol for sterile filtered MF59C.1 adjuvant (b) (4). The modified stability protocol is acceptable.

2. In IR12, the sponsor was requested to revise release tests of the FLUAD Final (b) (4) and include all testing that was proposed for FLUAD Final container only.

Company's response (Amendment 7, April 17 2015). Novartis confirmed that the company will conduct and report additional results of release tests at the Final Bulk stage for FLUAD Final Bulk product. Specifically, testing currently conducted on filled syringes for (b) (4) will be conducted on the Final Bulk for the US market. Specifications have been updated to include these tests on the Final Bulk. Testing on Filled Syringes will continue as submitted in the original BLA submission. An up-dated Lot Release Protocol is provided as Attachment 1.

Reviewer: I reviewed the up-dated Lot Release protocol provided in Attachment 1 to this amendment and I confirm that the modified specifications for FLUAD Final Bulk are acceptable.

3. In IR19 (May 28 2015), the sponsor was requested to provide data showing the results of sterility testing of MF59C.1 Adjuvant (b) (4)

Company's response (Amendment 13, June 19 2015). The sponsor submitted the sterility tests results for MF59C.1 (b) (4) performed at (b) (4) facility after sterile filtration. The submitted data cover batches produced between 2009 and 2015. All batches except one were sterile. The investigation of the failed lot (b) (4) found that it was a false positive. Nevertheless, this specific lot of MF59 (b) (4) and lots of Formulated FLUAD Drug product that used this lot of MF59 were discarded.

Reviewer: the company's response and action taken were acceptable.

4. In IR sent on May 15 2015, the sponsor was requested to revise the Master Formula for (b) (4) FLUAD as it has inaccurate information on the content of (b) (4) and MF59C.1 bulk adjuvant.

Company's response: The table describing FLUAD batch formula was revised.

Reviewer: the revised table for FLUAD Master Batch formula is acceptable

Highlights of the review of FLUAD

1. FLUAD 65 will be the first influenza vaccine where protein antigen purified from influenza virus is formulated with MF59 adjuvant during manufacturing process as opposed to mixing prior to injection. Therefore, the manufacturing process, specifications, and testing of the FLUAD vaccine Final Bulk and Final Filled container are different from specifications used to characterize vaccines that contain only antigen. This challenge was approached by the manufacturer by including testing for components of the MF59 adjuvant (Squalene content) as well as testing for the properties of the emulsion (b) (4) in the release specifications of (b) (4) filled container.
2. Following CBER recommendation, the sponsor added tests related to the adjuvant component to the release specifications of the vaccine Final Bulk. The rationale for this recommendation was to expedite release of the commercial vaccine lots.
3. MF59C.1 development was started in 1990 by Chiron, which was later acquired by Novartis. Since the beginning of the pilot production, the chemical composition of MF59 (Squalene, Polysorbate 80, and Sorbitan Triolate) did not change, except for the replacement of water with citric buffer at early stage of development. The MF59 batches used in the pivotal study V70_27 were manufactured in 2009 with all the major changes incorporated in the production process. From then on, changes in the process including (b) (4) were introduced. All these changes had been validated and have no significant impact on the quality of the product. MF59C.1 Adjuvant Bulk Drug Substance described in this BLA is a stable emulsion with a documented (b) (4) (b) (4).
4. The analysis of multiple batches of formulated FLUAD vaccine (bulk and final filled containers) manufactured for 2010/2011, 2011/2012, 2013/2014 season campaigns confirmed that the presence of protein antigen does not affect properties of the emulsion and the presence of MF59C.1 does not negatively affect antigen potency. The proposed shelf life for FLUAD pre-filled syringe is 12 months from the date of manufacture (formulation) when stored at 2 to 8°C

protected from light and is supported by stability data. The sponsor should continue monitoring the stability of FLUAD seasonal vaccines produced post-approval.

Reviewer's Final Recommendation:

Based on the data provided in the BLA 125510 and sponsor responses to all the IR questions regarding the MF59C.1 adjuvant and MF59C.1-adjuvanted vaccine product, I recommend approval of FLUAD 65, Inactivated Human Influenza Virus Type A (H1N1; H3N2) and B Hemagglutinin and Neuraminidase Vaccine, Adjuvanted for active immunization in persons 65 years of age and older against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine manufactured by Novartis Vaccines and Diagnostics, Inc.

2. FULL REVIEW OF MF59C.1 ADJUVANT DRUG SUBSTANCE AND FLUAD DRUG PRODUCT

The following sections were assigned to and reviewed by this product reviewer

3.2.S MF59 DRUG SUBSTANCE

- 3.2.S.2 Manufacture
- 3.2.S.3 Characterization
- 3.2.S.4 Control of Drug Substance
- 3.2.S.5 Reference Standards and Materials
- 3.2.S.6 Container Closure System
- 3.2.S.7 Stability

3.2.P FLUAD DRUG PRODUCT

- 3.2.P.1 Description and Composition of Drug Product
- 3.2.P.2 Pharmaceutical Development
- 3.2.P.3 Manufacture
- 3.2.P.4 Control of Excipient
- 3.2.P.5 Control of Drug Product
- 3.2.P.6 Reference Standards or Materials
- 3.2.P.8 Stability

In addition, reviewer also reviewed and summarized the following attachments:

- *Attachment 1* COA for (b) (4) Squalene, batch (b) (4) and batch (b) (4) (3.2.S.2.3 Control of Materials)
- *Attachment 2* COA for Polysorbate 80 (Amendment 10)
- *Attachment 3* COA for Sorbitan Trioleate (Amendment 10)
- *Attachment 4* COA for (b) (4) (Amendment 10)

- Attachment 4 COA for Sodium citrate dehydrate powder Batch (b) (4) (3.2.S.2.3 Control of Materials)
- Attachment 5 (b) (4) filters Study of extractables (3.2.S.2.5.2 Filter validation)
- Attachment 6 (b) (4) filter extractables (3.2.S.2.5.2 Filter validation)
- Attachment 7 (b) (4) filter extractables study (3.2.S.2.5.2 Filter validation)
- Attachment 8 (b) (4) filter extractables (3.2.S.2.5.2 Filter validation)
- Attachment 20, 21, and 22 (validation for alternate filters)
- Attachments 2 and 3 (protocol and results of testing of MF59C.1 Adjuvant Bulk validation lots (b) (4) on Line (b) (4) (3.2.S.2.6.2.7 The (b) (4) Process)
- Attachment 4 Stability of validation lots manufactured on Line (b) (4) (3.2.S.2.6.2.7 The (b) (4) Novartis (b) (4) Process)
- Attachment 5 and 6 stability of MF59C.1 Adjuvant Bulk manufactured on Line (b) (4) and (b) (4) (3.2.S.2.6.2.7 The (b) (4) Novartis (b) (4) Process)
- Attachments 7 and 8 validation of Line (b) (4) for manufacturing of MF59 adjuvant bulk (3.2.S.2.6.2.7 The (b) (4) Novartis (b) (4) Process)
- Attachments 9 and 10 Long-term stability report Line (b) (4)
- Attachment 11 The process development report for Line (b) (4) (3.2.S.2.6.2.8 The (b) (4) Novartis (b) (4) Process, Building (b) (4))
- Attachments 12 and 13 The Protocol and Report for validation of Line (b) (4) using lots (b) (4) (3.2.S.2.6.2.8 The (b) (4) Novartis (b) (4) Process, Building (b) (4))
- Attachment 14 The compatibility report between lots manufactured using Line (b) (4), Line (b) (4) and Line (b) (4) (3.2.S.2.6.2.8 The (b) (4) Novartis (b) (4) Process, Building (b) (4))
- Attachments 15 and 16 Validation report for change in filtration on Line (b) (4) (3.2.S.2.6.2.8 The (b) (4) Novartis (b) (4) Process, Building (b) (4))
- Attachment 1 Certificate of conformance for (b) (4) from the manufacturer, (b) (4) (3.2.S.6 Container Closure)
- Attachments 2 and 3 Leachables report (b) (4) study) and toxicology report on (b) (4) (3.2.S.6 Container Closure)
- Attachment 1 (b) (4) of MF59C.1 (report from Chiron, 1998) (3.2.S.7 Stability)
- Attachments 2 and 3 Stability of MF59C.1 Adjuvant (b) (4) (b) (4) (3.2.S.7 Stability)
- Attachments 4 and 5 Stability of MF59C.1 Adjuvant (b) (4) (b) (4) (3.2.S.7 Stability)
- Attachment 6 Stability of the M59C.1 Adjuvant (b) (4) (b) (4) (3.2.S.7 Stability)
- This is a pivotal study supporting (b) (4) storage in (b) (4) (3.2.S.7 Stability)
- Attachment 7 Stability of MF59C.1 Adjuvant (b) (4) (b) (4) (3.2.S.7 Stability)
- Attachment 1 Report on “Extractables and leachables from elastomeric primary packaging material (Latex-free rubber formulation) for use as a plunger stopper in Agrippal and FLUAD vaccine filled syringes” from Chiron 2005 (3.2.P.2.4 Container Closure System)

- *Attachment 2* Toxicological assessment of leachables identified in FLUAD Vaccine in contact over 12 months with (b) (4) rubber tip caps (3.2.P.2.4 Container Closure System)
- *Attachment 2* Protocol, results, and stability of MF59 adjuvant (b) (4) batches (b) (4) after sterile filtration at (b) (4) site (3.2.P.3.5 Process validation)
- *Attachment 1* Stability of the FLUAD Vaccine, NH 2010/2011, Fixed Needle, 1 ml (3.2.P.8 Stability)
- *Attachment 2* Stability of FLUAD Vaccine, NH 2011/2012, Fixed Needle, 1 ml (3.2.P.8 Stability)
- *Attachment 3* Stability of FLUAD Vaccine, NH 2012/2013, Fixed Needle, 1 ml (3.2.P.8 Stability)
- *Attachments 4 and 5* Stability report for Canadian Luer Lok Final Product (2011) (3.2.P.8 Stability)
- *Attachment 6* Stability of the Final Formulated (b) (4) (NH 2013/2014) (3.2.P.8 Stability)
- *Attachment 7* Stability of the batches filled using the (b) (4) filling line in Building (b) (4) and stability data for validation lots from 2007/2008 campaign manufactured in Building (b) (4) and Building (b) (4) (3.2.P.8 Stability)
- *Attachment 8* Stability data for assessment of (b) (4) Agrippal Process Technical Transfer Consistency Batches (stability of the formulated vaccine bulk) (3.2.P.8 Stability)
- *Attachment 9* Stability data for assessment of (b) (4) Agrippal Process Technical Transfer Consistency Batches (stability of the filled syringes) (3.2.P.8 Stability)
- *Attachment 10* Stability of US Clinical Batches , Luer Lok syringes (Clinical Trial V70_27, lot to lot consistency trial) (3.2.P.8 Stability)

.1 ADJUVANT DRUG SUBSTANCE

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

2.2 FLUAD DRUG PRODUCT

2.2.1 Description and composition of the FLUAD drug product

The FLUAD vaccine is composed of three drug substances, three viral strain surface antigens, and the adjuvant MF59C.1. It is an inactivated subunit influenza vaccine. The vaccine is presented as a 0.5 ml single dose sterile milky-white emulsified suspension for injection, contained in a glass pre-filled syringe.

The surface antigens are isolated from two influenza A subtypes, H1N1 and H3N2, and one influenza B strain. The antigens represent the viral surface proteins haemagglutinin (HA) and neuraminidase (NA). Each year virus strains from H1N1, H3N2, and B influenza are selected for inclusion in the FLUAD vaccine. The surface antigens are formulated with MF59C.1 adjuvant in the final FLUAD vaccine.

The potency of the vaccine is assessed by measuring concentration of the HA protein in the final formulation using the SRID assay.

Table 16 Composition of the FLUAD 0.5 ml syringe presentation ^a

Name of ingredient	Quantity per dose	Function
<u>Active ingredients</u>		
Haemagglutinin (HA) and Neuraminidase (NA) antigens from the influenza virus strains recommended by the WHO and endorsed by CBER for the manufacture of influenza vaccine for the current season	15 µg HA (per strain) ^b	Influenza vaccine
<u>Other ingredients</u>		
(b) (4)		
		r
Squalene	9.75 mg	adjuvant
Polysorbate 80	1.175 mg	adjuvant
Sorbitan Trioleate	1.175 mg	adjuvant
sodium citrate (b) (4)	0.66 mg	adjuvant
citric acid	0.04 mg	adjuvant
(b) (4)	(b) (4)	(b) (4)

^a An overfill of up to (b) (4) is included to permit withdrawal of a nominal volume of 0.50 ml.

^b An overage of up to (b) (4) of the HA concentration is included for each virus strain.

Type of Container and Closure Used

- The primary container closure for FLUAD is a (b) (4) 1mL syringe with Plastic Rigid Tip Cap (PRTC) - referred to as a Luer-lok syringe. No needle is present. The Luer-lok adaptor is present at the level of the tip of the syringe to ensure a better and stronger connection of the disposable needle to the syringe.
- The cone of the syringe is sealed by an elastomeric tip cap (Formulation (b) (4)). The tip cap may contain natural rubber latex. The tip cap itself is lodged in a rigid plastic shell which is screwed into the Luer-lok adaptor. The plastic shell protects the tip cap from damage.
- The syringe is closed with a grey, (b) (4) plunger stopper (b) (4). The plunger is not made with natural rubber latex.

2.2.2 Pharmaceutical Development

Components of the drug product

The Drug Product is a combination of Monovalent Pooled Harvests (MPH), MF59C.1 adjuvant bulk and (b) (4). FLUAD is composed of three drug substances, MPH antigens from 3 influenza strains and the MF59C.1 Squalene adjuvant.

MPH Drug Substance and MPH Drug Product are reviewed in detail by CMC reviewer of antigen, Dr. Hang Xie)

The MPH drug substance consists of two purified surface antigens haemagglutinin (HA) and neuraminidase (NA) from three influenza virus strains. Each year, the virus strains change based on the recommendations from the World Health Organization and VRBPAC. The isolation of these antigens from whole virus in the (b) (4)

The (b) (4) is (b) (4) components have been validated by Novartis Vaccines to confer optimal conditions for promoting antigen self-assembly into multimeric structure to ensure the stability and immunogenicity of the (b) (4)

(b) (4)

The (b) (4) system that is used in the production of the (b) (4) was included in the final formulation to provide and maintain the pH of the Drug Product between pH 6.9 and 7.7 (the final product has a pH in the middle of this range).

The components of the (b) (4) are well established excipients for use in parenteral products. (b) (4)

(b) (4) . Structural integrity of influenza antigen ensures immunogenicity.

Table 17 Formulation of MF59C.1 Adjuvant in FLUAD

Component	MF59C.1 (mg/mL)	% w/w
Squalene (b) (4)	(b) (4)	(b) (4)
Polysorbate-80	(b) (4)	(b) (4)
Sorbitan Trioleate	(b) (4)	(b) (4)
Sodium citrate dihydrate	(b) (4)	
Citric acid monohydrate	(b) (4)	
(b) (4)	(b) (4)	

2.2.3 Container Closure System (also includes summary from 3.2.P.7 on container closure)

FLUAD is presented in a single dose pre-filled Luer-lock syringe. The syringe is a (b) (4) 1mL syringe with a Plastic Rigid Tip Cap (PRTC) - referred to as a Luer-lock syringe. No needle is present. The Luer-lock adaptor is present at the level of the tip of the syringe to ensure a better and stronger connection of the disposable needle to the syringe.

Glass syringes are made of glass (b) (4) glass) that complies to the requirements of the (b) (4) for glass containers for injectable preparations.

The Luer Lok Syringe, Tip cap, and Plunger Stopper are manufactured by (b) (4) systems, respectively. The reference to (b) (4) (Syringes), (b) (4) (tip cones), (b) (4) (Plunger stopper) are provided in Table 3.2.P.7.1-1.

The cone of the syringe is sealed by an elastomeric tip cap (b) (4). The tip cap may contain natural rubber latex. The tip cap itself is lodged in a rigid plastic shell which is screwed into the Luer-lock adaptor. The plastic shell protects the tip cap from damage.

The syringe is closed with a grey, (b) (4) plunger (b) (4). The plunger is not made with natural rubber latex. This syringe has been selected on the basis of compatibility with the final product and is used with Novartis Vaccines and Diagnostics' other vaccine products.

This section provides three reports on the suitability of the syringe components for use in the packaging of human biologics. The reports are provided by an approved contract vendor. The work was performed in accordance with the current FDA Guidance for industry "Container closure system for packaging and human drugs and biologics".

The leaching characteristics of the stopper material has been evaluated in previous leachable studies for Agrippal (the European name for the US approved influenza vaccine, Agriflu) and FLUAD vaccine prefilled syringes (b) (4) where syringe stopper was evaluated for the presence of (b) (4) in the worst case scenario such as in presence of water soluble organic compound marker that might have the potential to be leached. The data indicated that there was no safety concern even taking into account worst case scenarios (Attachment 1).

Reviewer: *Study of extractables using rubber stopper*. I reviewed Attachment 1 containing summary report entitled "Extractables and leachables from elastomeric primary packaging material (Latex-free rubber formulation) for use as a plunger stopper in Agrippal and FLUAD vaccine filled syringes" performed by Chiron and dated 06/10/2005. The plunger stopper used in the study was manufactured by (b) (4). It is made of a (b) (4) rubber formulation and is used in pharmaceutical products. The report stated that the study was performed using a (b) (4) as the worst case marker according to FDA Guidance for industry "Container closure systems for packaging human drugs and biologics". The results of leachable studies showed that the levels of (b) (4) were (b) (4) for blank FLUAD matrix, expired FLUAD vaccine, Agrippal matrix, and expired Agrippal vaccine. The obtained data showed that the maximum (b) (4) content was (b) (4) of vaccine and therefore does not pose safety concern.

Reviewer: IR was submitted on May 22 (IR18) to request description of the conditions or duration of the leachables study for stoppered (Manufactured by (b) (4)). IR also requested information on whether the sponsor analyzed other compounds in addition to (b) (4).

Company's update (Amendment 18): The leachables study was started on August 31, 2005. The analysis was performed for plunger stoppers on Agrippal and Fluad vaccines stored at 2-8°C after 3, 6, and 12 months. Only (b) (4) was analyzed. Reviewer: the updated information is acceptable.

The leaching characteristics of the rubber tip cap were evaluated in a separate study that assessed additional volatile organic compounds in FLUAD that might be found in long term presence with the rubber tip. FLUAD is not in direct contact with the tip cap.

Attachment 2 provides toxicological assessment of leachables identified in FLUAD Vaccine in contact over 12 months with (b) (4) rubber tip caps.

Summary of the data provided in the Attachment 2.

The FLUAD was subjected to (b) (4) to determine volatile organic compounds over time. The reporting limit for this semi-quantitative analysis in the sample was (b) (4)

An exposure limit or safety threshold is a level of exposure below which adverse effects are not expected to occur in humans, or a level of exposure associated with a minimal risk to humans. Safety thresholds were developed by the Product Quality Research Institute (PQRI; <http://www.pqri.org>) Leachables and Extractables Working Group in 2006 for leachables in orally inhaled or nasally delivered pharmaceuticals. The current threshold for SCT (safety concern threshold) and QT (qualification threshold) are set as (b) (4), respectively. Compounds below the SCT are considered exempt from identification and from compound-specific risk assessment. Compounds below the QT and without alerts for carcinogenicity (or genotoxicity) or irritation do not require compound-specific risk assessment.

Out of (b) (4) compounds detected using (b) (4) compounds were detected at levels above SCT threshold: (b) (4).

(b) (4)

Reviewer: Based on this toxicological risk assessment, no safety issues are predicted for the (b) (4) volatile leachables detected in FLUAD vaccine stored up to 12 months in syringes with (b) (4) Rubber Tip Caps.

Reviewer: In addition, stability studies on the final product also support the compatibility of the components of the container with the final product (studies are described in section 3.2.P.8.3 and were reviewed)

Reviewer: IR was sent on May 22 to clarify whether a leachable study was performed on the final container closure system of FLUAD (b) (4)

Company's update (Amendment 16): The sponsor confirmed that a leachable study was performed on the final container closure system of FLUAD (described in section 3.2.P.2.4 Container Closure System).

The syringe is evaluated for extractable volume to ensure the syringe delivered volume is accurate. The extractable volume is determined by (b) (4) per (b) (4)

, the mean extractable volume is determined using the calculations described in Section 3.2.P.5.2. The specification for extractable volume is 0.50 ml. The method is described in 3.2.P.5.2

Secondary Packaging

The pre-filled syringe and the plunger rod are contained in blister packs, sealed with pelable paper, or the syringes are packed as "separates" in a box. The blisters are packed together with the package insert, into cardboard box. The batch number and expiry date of the batch are printed on the box containing the blisters. 10 syringes are packed in each box in a double layer.

2.2.4 Manufacture

Manufacturers

The following sites are involved in manufacturing activities for production of FLUAD

- Formulation, filling, inspection and packaging, Batch Release: Novartis Vaccines and Diagnostics (b) (4)
- Quality Control Testing: Novartis Vaccines and Diagnostics (b) (4)
- Quality Control Testing: Novartis Vaccines and Diagnostics Ltd (b) (4)
- Quality Control Testing: Novartis Vaccines and Diagnostics (b) (4)

2.2.4.1 Batch Formula

(b) (4)

- (b) (4)

The formulation of FLUAD final bulk is achieved through the sequential addition of each component. To account for the decline in the drug product stability during shelf life a (b) (4) inherent overage for each antigen is included in the final formulation. The calculation is made on the basis of volume. However, the components are added on the basis of weight (assuming density of each component added is (b) (4)).

Based on these assumptions, the Master Formula for 350 L FLUAD Batch is as follows

Table 18 Master formula for FLUAD batch (b) (4) (Table 3.2.P.3.2.1-1)

Solution	Final Concentration
(b) (4)	(b) (4)
(b) (4)	(b) (4)
Monovalent Pooled Harvest(s) (A type-H1N1)	15µg HA/dose (b) (4)
Monovalent Pooled Harvest(s) (A type-H3N2)	15µg HA/dose (b) (4)
Monovalent Pooled Harvest(s) (B type)	15µg HA/dose (b) (4)
(b) (4)	(b) (4)
(b) (4) adjuvant	(b) (4)
(b) (4)	

Reviewer: The Master Formula for (b) (4) shown in Table 3.2.P.3.2.1-1 is somewhat confusing as it shows that MF59C.1 is added at (b) (4) volume, but (b) (4) is added at (b) (4).

In IR sent on May 15 2015, the reviewer requested that the sponsor revised Master Formula for (b) (4) FLUAD as it has inaccurate information on the content of (b) (4) and MF59C.1 bulk adjuvant.

Company's up-date (Amendment 15, July 15 2015): The table describing FLUAD (b) (4) batch formula was revised and is shown below

Component	Properties
(b) (4)	(b) (4)
Monovalent Pooled Harvest	(b) (4)
(b) (4)	(b) (4)
MF59C.1 Adjuvant Bulk	(b) (4)
(b) (4)	(b) (4)

Reviewer: the revised table describing FLUAD (b) (4) batch formula is acceptable

Reviewer: I reviewed Table 3.2.P.3.2-2 that shows steps for calculation of theoretical Batch formula. If the volume of the Batch is (b) (4), then first, the volume of required (b) (4)

(b) (4). The volume of MF59C.1 is however exactly (b) (4) of (b) (4). Also see comments on the next page regarding calculation of the batch formula.

Reviewer: tables that describe Batch Formula for (b) (4) and for MF59C.1 Bulk adjuvant, tables 3.2.P.3.2.1-2, 3.2.P.3.2.1-3, and 3.2.P.3.2.1-4, respectively, were reviewed and are acceptable.

2.2.4.2 Description of Manufacturing Process and Process Controls

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

2.2.4.4 Process Validation and /or evaluation

Introduction

The FLUAD formulation and filling process is performed in Building (b) (4). The rooms for these activities are summarized in Table 3.2.P.3.5.1-1 (summary of the table is shown below). The process is composed of three process steps each of which has been validated.

The process is composed of three process steps each of which has been validated:

1. (b) (4)

Validated analytical methods have been used during process validation.

A description of these methods is provided in Section 3.2.P.5.2 is reviewed by DPQ reviewer

Validation of Sterile Filtration Process for MF59C.1

(b) (4)

(b) (4)

(b) (4)

2.2.4.5 Control of Excipient

Materials Management

All materials used are received, stored, and released according to internal SOPs. All materials have to comply with the quality parameters defined in the specifications.

Material approval and supplier auditing are performed regularly according to a specific internal SOP (SOP 236759) and Novartis' Quality Manual to assure raw material quality.

All suppliers are evaluated and classified according to SOP 201426 into one of three categories:

1. Approved supplier: all materials coming from an approved supplier have a complete test set
2. Qualified supplier: all materials coming from a qualified supplier have the identity test and critical tests if applicable
3. Certified supplier: all materials coming from a certified supplier have only the identity test.

(b) (4)

The analytical procedures used to test the ingredients used in the formulation of FLUAD are all (b) (4) analytical methods do not require validation if applied exactly as specified in the monograph; only verification should be conducted. Verification is not required for basic compendial procedures that are routinely performed.

Excipients of Human or Animal Origin

Squalene is the only substance of animal origin used in the MF59C.1 Drug Substance and in FLUAD Drug Product. Please refer to the section on Squalene in MF59C.1 Drug Substance.

2.2.6 Control of Drug Product

2.2.6.1 Specifications

Proposed specifications for the Final Bulk (Table 3.2.P.5.1-1) and the Finished Product (Table 3.2.P.5.1-2) including the requirements of the (b) (4) for Influenza Vaccine (Surface Antigen, Inactivated)

(b) (4)

Table 27 Final Filled Vaccine Release Specification

Test	Method	Reference	Specification
Identity Haemagglutinin Identity A (H3N2), A (N1N1), B	(b) (4)	Internal	positive
Squalene Identity	(b) (4)	Internal	positive
Potency/Strength Haemagglutinin content A (H3N2), A (H1N1), B	SRID (Potency)	Internal	(b) (4)
Squalene Strength	(b) (4)	Internal	(b) (4)
(b) (4)			
(b) (4)	(b) (4)	Internal	(b) (4)
(b) (4)	(b) (4)	Internal	(b) (4)
Quality			
Sterility	(b) (4)	(b) (4)	Sterile
Endotoxin	(b) (4)	(b) (4)	(b) (4)
Appearance	Visual	Internal	Conforms
Visible Particles	Visual	(b) (4)	Conforms
(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)
pH	(b) (4)	(b) (4)	6.9 – 7.7
Extractable volume	(b) (4)	(b) (4)	(b) (4) 0.50 ml

Reviewer: Squalene Identity and Strength and the parameters of Emulsion Stability (b) (4)
(b) (4); Quality parameters including (b) (4)
(b) (4) are all measured in the filled vaccine and not in the (b) (4). This approach may not
be optimal. IR was sent to the manufacturer. See submitted IR and sponsor's up-date in 3.2.P.3.5.4
"Hold Time Study for Final Formulated (b) (4)

Lot release protocol is provided in 3.2.P.5.1 and is reviewed by DBSQC

2.2.6.2 Analytical Procedures

Table 28 Analytical methods

Test	Method	Site
Appearance	Visual Inspection	(b) (4)
Cetyltrimethyl-ammonium bromide (CTAB)	(b) (4)	(b) (4)
Endotoxin	(b) (4)	(b) (4)
Extractable volume	(b) (4)	(b) (4)

Test	Method	Site
Formaldehyde	(b) (4)	(b) (4)
Haemagglutinin (HA) Content (b) (4)	Single Radial Immunodiffusion (SRID)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
pH	(b) (4)	(b) (4)
Squalene Identity and Content	(b) (4)	(b) (4)
Sterility	(b) (4)	(b) (4)
Total Protein	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)

General Safety Testing

Reviewer: Since the request to perform GST on vaccine Final Container was removed as of August 3 2015, the sponsor no longer needs to request a waiver.

2.2.6.3 Batch Analysis

The company provides analysis of multiple batches of formulated Bulk and for filled syringes of FLUAD manufactured between 2010 and 2013 and using MPH produced at (b) (4) or at (b) (4) facilities. These include: batches for commercial use, for consistency and stability studies and for use during previous clinical trial.

Reviewer: Below I summarize the list of batches that were used for the studies described above and that are shown in this section in individual tables. Importantly, data provided in tables that describe results of analytical testing for each listed batch confirm that the analytical results for all listed batches (Final Bulk and Filled syringes) were within specification.

- NH 2010/2011 Commercial Batches (produced using (b) (4) MPH)
Final Bulk, (b) (4) Commercial use
Final Lot, (b) (4) syringes (b) (4) Commercial use and stability
- NH 2011/2012 Commercial Batches (produced using (b) (4) MPH)
Final Bulk, (b) (4) Commercial use
Final Lots, (b) (4) syringes, (b) (4) Consistency study
- NH 2012/2013 Commercial Batches (produced using (b) (4) MPH)
Final Bulk, (b) (4) Commercial use
Final Lots, (b) (4) syringes, (b) (4) Commercial use.
- NH 2011/2012 Canadian Commercial Batches in Luer-lock Syringes (produced using (b) (4) MPH)
Final Bulk, (b) (4) Commercial use

Final Lots, (b) (4) syringes (b) (4)
(b) (4) Commercial use and Stability study (117701 and 117903)

5. NH 2012/2013 Canadian Commercial Batches in Luer-lock Syringes (produced using (b) (4) MPH)
Final Bulk, (b) (4) Consistency study
Final Lots, (b) (4) syringes (b) (4) Consistency study

6. (b) (4) Batches (produced using (b) (4) MPH)
Final Bulk, (b) (4) for validation
Final Lots, (b) (4) syringes (b) (4) Validation and
Stability studies

7. Consistency Batches (produced using (b) (4) MPH)
Final Bulk, (b) (4)) Consistency
and Stability studies
Final Lots, (b) (4) syringes (b) (4)
Consistency and Stability studies

8. US Clinical Batches in Luer-lock Syringes (produced using (b) (4) MPH)
Final Bulk, (b) (4) Batches: (b) (4), (b) (4) each (b) (4) Clinical use (Clinical trial
V70_27)
Final Lot, (b) (4) lots: A52P14H1, A52P14H1, A52P16H1, (b) (4) syringes (b) (4) Clinical use and
Stability study (US clinical trial V70_27)

2.2.6.4 Characterization of Impurities

Process Impurities

The only process impurities in the drug product are those carried over from the manufacture MPH and MF59C.1 DS. These impurities are controlled at the (b) (4)

Product Related Impurities

The MF59C.1 product related impurities are derived mostly through (b) (4) promotes (b) (4) leading to the formation of (b) (4) such as (b) (4)

Reviewer: (b) (4) are monitored during stability testing of MF59C.1 Adjuvant (b) (4) (3.2.S.7.3) and testing for (b) (4) in MF59 (b) (4) is summarized in this review in the MF59C.1 (b) (4) section. In brief, (b) (4) are tested by (b) (4). The presence of each of these (b) (4) in the MF59C.1 (b) (4) is detected at (b) (4), respectively, and does not pose a safety concern.

2.2.6.5 Justification of Specifications

(b) (4)

MF59C.1 (b) (4) of a Squalene. Following drug product formulation, there is approximately a (b) (4) of the original (b) (4). The amount of Squalene, MF59C.1, added to the DP formulation varies depending on the number of factors described in Batch Formula calculation (3.2.P.3.2). Due to this variation in the amount of MF59C.1 added in the formulation process, the Squalene content varies from lot to lot. However a target final Squalene content in FLUAD vaccine has been set at (b) (4). This corresponds to a specification of (b) (4).

67

In IR sent on May 15 2015, the sponsor was requested to clarify” factors that affect calculation of Squalene content” during FLUAD Batch Formula calculation

Company’s up-date (Amendment 15, July 15 2015): Section 3.2.P.5.6 “Justification of specification for Squalene content” has been corrected. The sponsor provided clarification on the rational for (b) (4) specification for Squalene in the (b) (4) . Early development and stability studies showed that the optimal Squalene content to maintain stable emulsion with (b) (4) particles requires Squalene concentration of (b) (4) of Squalene in (b) (4) . Considering that the average concentration of Squalene in MF59C.1 is (b) (4) and that (b) (4) of the final volume of the Drug Product (DP) is containing MF59C.1 the expected Squalene concentration in the DP is (b) (4) and for this reason the drug product specification was defined as (b) (4)

Reviewer: revised justification of specifications for Squalene content and clarification is acceptable.

Squalene Identity

Reviewer: The Identity of Squalene is confirmed using (b) (4) and a reference standard for Squalene. The determination is based on the difference in retention time (Rt) between the sample and the (b) (4) Squalene standard. This difference in the retention time should be within (b) (4) . The respective (b) (4) should have similar profiles. If these two conditions are satisfied then identity is considered positive. **The justification of specification is acceptable.**

2.2.7 Reference Standards or Materials

Reviewer: For MPH, the sponsor refers to Section 3.2.S.5.

Reviewer: There is no information in this section on reference standard for Squalene that is measured by (b) (4) against reference standard as part of release specification of Final Filled Vaccine (Table 3.2.P.5.1-2). This is an important issue as the company described that during the stability analysis of filled vaccine, an Out of Limit (OOL) deviation in concentration of Squalene was observed (3.P.P.8.3 Stability attachment 7; 3.1.1) due to “a degradation of Squalene standard used for the analysis”.

In IR sent on May 15 2015, the sponsor was requested to provide information on the source of Squalene reference standard

Company’s update (Amendment 15, July 15 2015) The Squalene reference standard is purchased from (b) (4) The manufacturer applies a (b) (4)

The company prepares a (b) (4)

expiry date. **Reviewer: all information is acceptable.**

2.2.8 Stability

Stability Summary and Conclusion

All methods are those used to release the drug product. There are no analytical methods that are unique to the stability program. A list of quality attributes, test methods and specifications is provided in Table 3.2.P.8.3-1.

Reviewer: in summary, all data gathered under the intended storage conditions have met the proposed stability specifications, and demonstrated no significant change for any quality attributes assessed. Accelerated data was performed for information only. The proposed shelf life for FLUAD vaccine is 12 months from the date of manufacture (formulation) when stored at 2 to 8°C, protected from light is justified. The stability data for both formulated vaccine bulk and filled vaccine is acceptable.

Below I summarize the detailed final reports on stability studies performed by Novartis.

Final Product Stability

- Each flu season, three lots of final product are placed into the ongoing stability program at the intended storage condition of $5 \pm 3^{\circ}\text{C}$ for up to (b) (4) months. Additionally, samples of at least (b) (4) lot are held under accelerated and stressed conditions of (b) (4) (for information only). Syringes are stored (b) (4) to permit contact between the vaccine and all components of the container/closure system
- Stability testing was performed on filled syringes stored at $5 \pm 3^{\circ}\text{C}$ for 1, 3, 6, 9, 12, (b) (4) months; stored at (b) (4) and stored at (b) (4), and (b) (4).
- Parameters evaluated in filled syringes stored at 2 to 8°C: pH and HA, at Release (R) and at 3, 6, 9, 12, (b) (4) months; (b) (4) at release, 6, 12, (b) (4) months to evaluate the possibility of extending the shelf life; Squalene content, endotoxin, and sterility, at release, 12 months, (b) (4) months for the future extension of shelf life.
- Parameters tested in filled syringes stored at (b) (4) HA only at (b) (4)
- Novartis plans to market FLUAD in pre-filled Luer Lok syringes containing 0.5 mL of vaccine. Final Product Stability provides information from the last three Northern Hemisphere (NH) campaigns in a staked needle presentation (1 ml syringes) (data is shown in attachments 1, 2, 3).

Attachment 1: FLUAD Vaccine, NH 2010/2011, Fixed Needle, 1 ml

- (b) (4) manufactured (b) (4) consistency/clinical batch and (b) (4) consistency batches, respectively)
- Storage at $5 \pm 3^{\circ}\text{C}$ and testing at R and 3, 6, 9, 12 (b) (4) months (all (b) (4) lots); (b) (4) (only lot (b) (4)).
- Stability data up to (b) (4) months for filled batches of syringes met all acceptance criteria at the intended storage temperature of $5 \pm 3^{\circ}\text{C}$
- At accelerated conditions, a sharp reduction in HA content for all three strains was observed. For H3N2 and H1N1, the HA levels were low at (b) (4) but still within specification (b) (4); for B strain, the levels of HA dropped to (b) (4) at (b) (4), respectively.

Attachment 2 FLUAD Vaccine, NH 2011/2012, Fixed Needle, 1 ml

- (b) (4) manufactured (b) (4) (consistency batches)

- Storage at $5 \pm 3^{\circ}\text{C}$ and testing at release and 3, 6, 9, 12 (b) (4) months (all (b) (4) lots); (b) (4) (lot (b) (4)).
- Stability data up to (b) (4) months for filled batches of syringes met all acceptance criteria at the intended storage temperature of $5 \pm 3^{\circ}\text{C}$
- At accelerated conditions, HA levels remain within specification for H3N2 HA; for H1N1 strain, HA dropped to (b) (4) and for strain B, HA dropped to (b) (4) weeks, respectively.

Attachment 3 FLUAD Vaccine, NH 2012/2013, Fixed Needle, 1 ml

- (b) (4) manufactured (b) (4) (consistency batches)
- Storage at $5 \pm 3^{\circ}\text{C}$ and testing at release and 3, 6, 9, 12 (b) (4) months (all (b) (4) lots); (b) (4)
- Stability data up to (b) (4) months for filled batches of syringes met all acceptance criteria at the intended storage temperature of $5 \pm 3^{\circ}\text{C}$.
- At accelerated conditions, HA levels remain within specification for H3N2 HA for storage at (b) (4) and were reduced to (b) (4) for storage at (b) (4). H1N1 HA was detected at reduced levels (b) (4) on (b) (4) after storage at (b) (4) but not at (b) (4). B strain HA was within specifications after storage at (b) (4) and was reduced to (b) (4).

Stability report for Canadian Luer Lok Final Product (at CBER's request, Novartis included stability data for FLUAD Luer Lok lots supplied to the Canadian market, attachments 4 and 5)

- (b) (4) lots were tested: (b) (4) manufactured in (b) (4) in (b) (4). Syringes, consistency batches.
- Storage at $5 \pm 3^{\circ}\text{C}$ and testing at release and 3, 6, 9, 12 (b) (4) months (all (b) (4) lots); (b) (4) only (b) (4). Data is shown in attachment 4 (final report) and 5 (interim report).
- Stability data up to (b) (4) months for filled batches of syringes supplied for Canadian market met all acceptance criteria at the intended storage temperature of $5 \pm 3^{\circ}\text{C}$
- The seasonal vaccine stability results are provided for 2011 and 2012 (pre BLA Follow-up response February 24, 2012 telecom IND14368 CRMTS#8235).

Final Formulated Bulk Stability (attachment 6)

(b) (4)

(b) (4)

(b) (4)

Stability of the batches filled using the (b) (4) line in Building (b) (4)

(b) (4) lots were placed on stability testing:

- (b) (4) manufactured in (b) (4) syringes
- (b) (4) manufactured in (b) (4) syringes
- (b) (4) manufactured in (b) (4) syringes

Testing at $5 \pm 3^{\circ}\text{C}$ at time 0 and after 3, 6, 9, 12, (b) (4) months (all (b) (4) lots); at (b) (4). Data are shown in attachment 7

In addition, attachment 7 contains stability data for validation lots from 2007/2008 campaign manufactured in (b) (4)

Summary of the results in attachment 7:

Deviations: there was one Out of Limit (OOL) during Squalene content testing and was attributed to degradation of Squalene standard. The standard was changed. The other 3 deviations were related to HA content.

Results: Stability data up to 12 months shelf life met all acceptance criteria at the intended storage temperature of $5 \pm 3^{\circ}\text{C}$. Accelerated data was performed for information only and showed sharp reduction in HA content for all three strains starting (b) (4)

Consistency Batches: Stability data for assessment of (b) (4) Agrippal Process Technical Transfer Consistency Batches

The antigens for FLUAD are derived from the Agriflu DS process. The Agriflu DS process was transferred to (b) (4) as part of the Agrippal transfer. As part of the transfer of the Monovalent Pooled Harvest (MPH) process from Novartis Vaccine and Diagnostic (NVD) (b) (4), MPH consistency batches manufactured at the (b) (4) site (using the 2010/2011 seasonal strains) were subsequently used to produce trivalent bulk formulated and filled vaccine batches. (b) (4) filled batches have been placed on stability under the same conditions and criteria as used for the stability of seasonal vaccine.

a. (b) (4)

- (b) (4)

Results and summary:

At 2 - 8°C, HA content in all three lots was (b) (4) 15 µg/dose up to 12 months and was (b) (4) months; no change in Squalene content were found between testing at release and at 12 (b) (4) months; no change in (b) (4). Small change in the number of (b) (4) was detected but the results were within specification.

Stability data up to (b) (4) months for filled batches (attachment 9) and (b) (4) months for (b) (4) met all acceptance criteria at the intended storage temperature of $5 \pm 3^\circ\text{C}$

Stability of US Clinical Batches , Luer Lok syringes (Clinical Trial V70 27, lot to lot consistency trial)

- A52P14H1 manufactured in (b) (4)
- A52P15H1 manufactured in (b) (4)
- A52P16H1 manufactured in (b) (4)
- For storage at $5 \pm 3^\circ\text{C}$ testing at release and 1, 3, 6, 9, 12, (b) (4) months (all three lots) ; for storage at (b) (4), and (b) (4) (lot (b) (4)); for storage at (b) (4), and (b) (4) (lot (b) (4)) (attachment 10)
- Stability data met all acceptance criteria at the intended storage temperature of $5 \pm 3^\circ\text{C}$ up to (b) (4) month confirming the proposed 12-months shelf life. Accelerated data is for information only.

RESPONSES TO INFORMATION REQUESTS were all included in the body of the memo