

General Safety Test Review Memo, November 18, 2013 - Q-Pan

MEMORANDUM

18 November, 2013

To

Administrative File for STN 125419/0

From

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Through

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Subject

Original Biological License Application (BLA): Influenza A (H5N1) Virus Monovalent Vaccine (Q-Pan H5N1): General Safety Test Review.

Conclusion

Based on the review of the information submitted in this Biological License Application (BLA) in support of the General Safety Test (GST) on Q-Pan H5N1, this reviewer finds the GST procedures performed on the Q-Pan H5N1 antigen and AS03 adjuvant final container (FC) products to be acceptable and comply with current testing requirements and CBER guidance and believes GlaxoSmithKline (GSK) has submitted enough evidence to approve their request for an exemption to the GST performed on their H5N1 antigen FC product as a continued lot-release test requirement. The GST exemption for the AS03 adjuvant FC is being reviewed by Dr. Hana Golding, and I refer to her AS03 adjuvant review memo in this STN file.

Background

On 22 February, 2012, GlaxoSmithKline Biologicals, S.A. submitted a BLA for their Influenza A (H5N1) Virus Monovalent Vaccine, with a trade name of Q-Pan H5N1. Prior to the submittal of this BLA, GSK was in contact with CBER regarding guidance on the GST during their Investigational New Drug Application (IND) process, as their product could not be tested as required by 21 CFR §610.11. CBER requested separate GSTs be performed on the Q-Pan H5N1 antigen FC and the AS03 adjuvant FC and suggested qualifying a modification to the GST to perform on their AS03 adjuvant FC

product as a lot-release test requirement, due to the inherent toxicity of the AS03 adjuvant. More details regarding the IND correspondence and the modification of the GST will be reviewed in this memorandum. Dr. Hana Golding, in CBER's Office of Vaccines Research and Review (OVRR), Division of Viral Products (DVP), who has an established history in reviewing the AS03 adjuvant and provided GST guidance to GSK during their IND process, will review GSK's request to exempt the AS03 adjuvant from the GST as part of her review on the AS03 adjuvant product. Since CBER's Division of Biological Standards and Quality Control (DBSQC) primarily reviews product test method qualification, validation and test specifications, this review will focus on assessing the validity and regulatory compliance of the GST and GSK's request for an exemption of the GST for their Q-Pan H5N1 antigen product.

Q-Pan H5N1

Influenza A Virus Monovalent Vaccine (Q-Pan H5N1) is a non-infectious, 2-component monovalent, AS03-adjuvanted vaccine. The vaccine contains an inactivated, split-virion, A/H5N1 influenza antigen suspension component and an AS03 adjuvant system emulsion component. The H5N1 virus, grown in chicken eggs, is inactivated with ultraviolet light followed by formaldehyde, purified by centrifugation and disrupted with sodium deoxycholate. The AS03 adjuvant system is a homogenized, sterile, whitish emulsion composed of squalene, DL- α -tocopherol and polysorbate 80.

Q-Pan H5N1 is supplied as two separate vials, a vial of antigen and a vial of AS03 adjuvant. Once combined, the resulting volume provides 10 doses of a whitish emulsion, formulated to contain 3.75 μ g hemagglutinin (HA) of the A/Indonesia/05/2005 (H5N1) influenza virus strain and 5 μ g thimerosal per 0.5 mL dose. Q-Pan should be administered as a 2-dose series by intramuscular injection, with the interval between the first and second dose being approximately 21 days.

Q-Pan is produced in the GSK's Quebec facility according to the FluLaval® seasonal influenza vaccine manufacturing process that is currently licensed in the United States, with the difference being Q-Pan's monovalent antigen bulk formulation (at 15 μ g HA/mL) contains thimerosal at 20 μ g/mL concentration, whereas the FluLaval® formulation includes three monovalent antigen bulks (each at 30 μ g HA/mL) with a thimerosal concentration of 100 μ g/mL. GSK stated in this BLA (i.e., in section: m1.2; 3:

'Information to determine need for pre-licensure inspection (m1.11.1)), 'Q-Pan is not being manufactured at this time and there are no plans to manufacture the vaccine until there is a declared need for the product. Given the current hiatus in the pandemic vaccine antigen manufacture and considering that 1) the antigen bulk manufacturing process of Q-Pan H5N1 vaccine has followed that for the seasonal FluLaval® bulk manufacturing process at the time of the manufacture and 2) GSK plans to supplement the BLA in the future with the relevant changes to the seasonal bulk manufacturing process...'; CBER interpreted this as GSK intends to supplement this BLA (125419/0) to reflect any corresponding supplement submitted to change their FluLaval® (125163/107) bulk manufacturing process. Thus, CBER can be assured that the GSK manufacturing process for Q-Pan H5N1 antigen and FluLaval® should be considered identical - based on GSK's aforementioned commitment – as only the final product formulations are different as a consequence of the number of strains contained in the FluLaval® seasonal influenza product.

AS03 Adjuvant

The AS03 adjuvant vial packaged together for distribution with the Q-Pan H5N1 antigen vial is made from squalene, DL- α -tocopherol and polysorbate 80. GSK procures their squalene from -----(b)(4)-----, which it extracts from -----(b)(4)-----, before going through a controlled manufacturing process that includes testing for -----

----- (b)(4)-----
----- to monitor the quality and purity before quality assurance release and distribution by -----(b)(4)----- . The squalene is further characterized by a contract facility (i.e., -----(b)(4)-----, before quality control testing is performed at GSK; please see Dr. Golding review memo for more details on the AS03 adjuvant production process. In humans, squalene is a key intermediate in liver cholesterol synthesis, a component of human blood and is part of the oily secretion of the sebaceous glands that act as a lubricant for hair and skin. Squalene formulated as a vaccine adjuvant has been used in seasonal influenza vaccines in Europe since 1997.

General Safety Test

The GST is performed for the detection of extraneous toxic contaminants. The GST should be performed according to 21 CFR §610.11, except that according to 21 CFR §610.11a for inactivated influenza vaccines the route of administration to guinea pigs may be either IP or subcutaneous. Realizing that some materials subjected to the GST may actually be inherently toxic when administered according to the requirements of 21 CFR §610.11, alternate methods and procedures may be allowed. 21 CFR §610.11 allows CBER to approve modifications to these requirements according to 21 CFR §610.9 Equivalent Methods and Procedures. Approval of an alternate method or procedure is predicated upon review of evidence demonstrating the modification or variation will provide assurance equal to or greater than the assurances provided by the method described in 21 CFR §610.11. Because modifications to the test procedure could - and have - require(d) a change in route of administration or even a reduction in dose, concerns about meeting the requirement that the modified test provided equal or greater assurance of safety are not straightforward.

This concern was addressed in a memorandum entitled 'Proposal to Develop Guidelines to Establish Uniformity in General Safety Test', written by Kathryn C. Zoon, Ph.D. (the Director of CBER) on 03 February 1994. The memo stated previous manufacturer modifications to the GST have involved various combinations of the following: a) reduced volume of the inoculum; b) changing the route of inoculation; c) dilutions of the product; and d) extension of the observation period. However, these modifications provided limited supporting evidence indicating the revised GST procedure could detect an unexpected increase in extraneous toxic contaminants. Therefore, this memo proposed a guidance procedure for manufacturers to establish an acceptable reduced volume dose, should they have products that cannot be tested as required by 21 CFR §610.11. The proposed titration procedure to establish this reduced dose should be carried out with at least three successive lots of product (i.e., a different lot of source material) using at least five animals per reduced volume point tested. It was determined these procedures were sufficient to determine the maximum tolerated dose, while permitting the detection of any lots with an unexpected increase in toxicity. The intent of this memo was for all future GST variation requests received by CBER to

follow these guidelines, while previously approved GST variations would have a year to submit supplements to their license agreements to conform to these guidelines.

General Safety Test Exemption

21 CFR §610.11(g) (2) states: 'for products other than those identified in paragraph (g)(1) for this section, a manufacturer may request from the Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research (see mailing addresses in 600.2 of this chapter), an exemption from the general safety test. The manufacturer must submit information as part of a biologics license application submission or supplement to an approved biologics license application establishing that because of the mode of administration, the method of preparation, or the special nature of the product a test of general safety is unnecessary to assure the safety, purity and potency of the product or cannot be performed. The request must include alternate procedures, if any, to be performed. The Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research, upon finding that the manufacturer's request justifies an exemption, may exempt the product from the general safety test subject to any condition necessary to assure the safety, purity and potency of the product.'

IND GST Review

Memorandum 'Review comments regarding BB-IND 13413.0000'

On 04 November, 2007, Dr. Carmen M. Collazo-Custodia wrote a memorandum to GSK regarding the review of the GST information submitted to CBER with their IND. In this memo, it was documented that GSK indicated it was not possible to carry out the GST in accordance with 21 CFR §610.11 on the adjuvant component alone due to its inherent toxicity¹. A reference was also made to a teleconference between CBER and GSK on 30 October, 2007, in which CBER recommended GSK conduct the GST on the AS03 filled product and not as a characterization test on the reconstituted H5N1/AS03 product. CBER acknowledged that based on the GST information provided, a modified GST would be appropriate on their IND product. In addition, CBER recommended GSK conduct serial dilution experiments of their product, starting with undiluted adjuvant to evaluate decreasing amounts with the goal of establishing a toxicity threshold and submit a draft protocol(s) of the proposed serial dilutions studies to establish a modified AS03 adjuvant GST to the IND for CBER's review and concurrence prior to initiating these studies. Dr. Collazo-Custodio stated that once a serial dilution protocol was agreed upon, it should be tested on at least 5 animals per reduced volume point with at least three successive product lots².

1) *Despite the inherent toxicity at the arbitrary toxicity threshold in 21 CFR §610.11, preclinical toxicological studies (i.e., single-dose, repeat-dose, genotoxicity, reproductive and developmental toxicity) indicate no associated toxicity, and after the completion of the subsequent human clinical trials the data and analyses reveal the AS03-adjuvanted H5N1 influenza vaccine has a safety profile similar to that observed with unadjuvanted influenza vaccines and saline, with respect to the medically important endpoints assessed.*

2) *Dr. Collazo-Custodio's directive is in alignment with Dr. Zoon's proposed guidelines for uniformity in modifications to the GST.*

GSK's Responses to CBER

On 04 November, 2007, GSK submitted their response to CBER's questions regarding

the GST and their results from the requested serial dilution experiments. These serial dilution experiments were performed on --(b)(4)- adjuvant AS03 lots, which were not necessarily consecutive but were sourced from different lots. (b)(4) animals per dilution point were used and resulting data (m3.2.P.2 'Pharmaceutical Development for Q-Pan Vaccine' and m3.2.R 'General Safety Test Supportive Data') was provided to CBER. Based on these experiments, GSK proposed that future release specification for the GST will include testing on the FC of each component (i.e., antigen and adjuvant) alone. The antigen GST will be 21 CFR §610.11 compliant, whereas the dose volumes of the AS03 adjuvant will be mixed with an equal volume of physiological saline (intended to mimic the antigen) and administered to guinea pigs and mice in dose volumes of 0.5 and 0.2 mL, respectively; a human equivalent dose (HED) in guinea pigs and 2/5 HED in mice. In addition, GSK also conveyed their intentions of requesting an exemption from the GST after 30 lots of AS03 adjuvant FC have been tested by the modified procedure and shown to conform to specification.

CBER's Review of GST Development Data Submitted by GSK

In a memo dated 16 March, 2008, to Dr. Carmen M. Collazo-Custodia and DVRPA reviewers, from Dr. Hana Golding (CBER/OVRR/DVP), GSK's documents (i.e., m3.2.P.2 and m3.2.R) were reviewed. Following the review, Dr. Golding recommended GSK increase the number of guinea pigs to five animals per adjuvant lot and five animals for antigen lot. Dr. Golding also concluded that since the antigen and adjuvant are produced and stored separately and are mixed only prior to vaccination, performing a lot-release GST on the AS03 adjuvant FC and the Q-Pan H5N1 antigen FC is reasonable and appropriate. In addition, Dr. Golding found the use of saline to dilute the AS03 (1:1) prior to inoculation for the GST acceptable. Comments were concluded by a statement that if GSK plans to generate multi-dose vials of antigen plus adjuvant for long time storage, a GST should be conducted on the reconstituted and mixed adjuvanted vaccine containers.

Agency/Sponsor Meeting

On 16 September, 2008, CBER had a 'face to face' meeting with GSK where GSK wanted confirmation that CBER agrees with their plan to perform the GST on the Q-Pan H5N1 antigen product lots and the modified GST on the AS03 adjuvant product lots until such a time as a waiver for these tests can be pursued. CBER agreed with their plan to perform the GST and acknowledged their plans to request a waiver for the GST when sufficient data is available.

BLA GST Review

Q-Pan H5N1 Antigen Product

GSK performed a GST on (b)(4) FC Q-Pan H5N1 antigen lots, (b)(4) of which were product development lots. These additional development lots were prepared by a similar process, with similar product matrix and process impurities as the lots described in the batch analyses section (m3.2.P.5.4 'Antigens Final Container H5N1') in this BLA; the difference is (b)(4) of these lots were from a different strain (i.e., A/turkey/Turkey/1/2005) or produced earlier in the development where the HA content or thimerosal concentration used in the formulation of A/Indonesia/5/2005 lots were different. All antigen lots were tested according to 21 CFR §610.11, in which each of two mice were injected intraperitoneally with 0.5 mL (one human dose) and each of two

guinea pigs was injected subcutaneously with 5mL (10 x the human dose); all results met the GST release specifications in 21 CFR §610.11.

AS03 Adjuvant Product

GSK has performed a modified GST on (b)(4) commercial AS03 adjuvant lots by (b)(4) - an adequate number of AS03 FCs to obtain sufficient material for testing. This emulsion was then diluted with an equal volume of -----(b)(4)----- to reproduce dilution with the antigen component. Animals were injected intraperitoneally (i.e., 0.2 mL/mouse and 0.5 mL/guinea pig); GSK adhered to the animal testing requirement in 21 CFR §610.11, which CBER finds acceptable. The modified GST was performed at an acceptable reduced volume dose, in accordance to the proposed guidelines outlined by the Director of CBER to determine a sufficient maximum tolerance dose for products that cannot be tested as required by 21 CFR §610.11. Besides the modification of the maximum tolerance dose, all AS03 adjuvant lots were tested according to the GST procedure in 21 CFR §610.11 and their results were in compliance with its release specifications; i.e. all animals survived the test period; did not exhibit any response that is not specific for or expected from the product and could indicate a difference in its quality; and they weighed no less at the end of the test period than at the time of injection.

Q-Pan H5N1 Antigen GST Exemption Request

GSK is requesting an exemption to the GST lot-release requirement under 21 CFR §610.11(g) (2), based on the GST data accumulated from the (b)(4) antigen lots submitted in support of this BLA. In addition, GSK stated this GST exemption request is in alignment with the GST exemption approved by CBER for their FluLaval® product (STN: 125163/107) on 26 May, 2009. Q-Pan H5N1 and FluLaval® are both manufactured at the same facility using an identical manufacturing process; only the final product formulations are different as a consequence of the number of strains contained. In addition, relevant in-process quality control information supporting GSK's request to exempt the H5N1 Antigen from the GST is reviewed in Dr. Surender Khurana's chemistry, manufacturing and control review memo in this file.

AS03 Adjuvant GST Exemption Request

GSK is requesting an exemption to the GST lot-release requirement on their AS03 adjuvant based on the GST data accumulated from the (b)(4) lots submitted in support of this BLA.

The GST on the AS03 adjuvant alone is not a requirement of 21 CFR §610.11, since the adjuvant is not the final product administered to humans and adjuvants are not considered biologic products to be regulated by CBER. However, since further processing of Q-Pan H5N1 antigen after FC filling involves combining with an AS03 adjuvant FC vial before administering to humans, CBER determined it would be prudent to conduct a modified GST on the AS03 adjuvant final container product. This decision was based on the fact - the GST is intended as a lot consistency quality assurance test, but different lots of the Q-Pan H5N1 antigen and AS03 adjuvant final containers may end up distributed together for their combined use. Thus performing the GST on combined Q-Pan H5N1 antigen/AS03 adjuvant would not reflect a consistent representative sample of the product, as the possibility of virtually all combined lot combinations could render the testing of a few single combinations ineffective in terms of safety assurance. Dr. Hana Golding, who has an established history reviewing the

AS03 adjuvant and was involved with this decision at the IND review level, will review GSK's request to exempt the AS03 adjuvant from the GST as part of her review of the AS03 adjuvant product.

Summary

Based on the review of the information submitted in this Biological License Application (BLA) in support of the GST on Q-Pan H5N1, this reviewer finds the GST performed on the FC Q-Pan H5N1 antigen and the modified GST performed on FC AS03 adjuvant acceptable and believes GSK has submitted enough evidence to approve their request for a exemptions to the GST performed on their antigen final container product as a continued lot-release test requirement. This exemption is supported by data accumulated from FC (b)(4) antigen lots submitted in support of the GST in this BLA and by CBER's approval for a GST exemption for FluLaval® seasonal influenza (STN: 125163/107), which is manufactured in the same facility using an identical manufacturing process.