

Review Memo for Amendments 13, 15, 16, 19, 24, and 29 - Rotarix

- **MEMORANDUM**

DATE: March 28th, 2008

FROM: Dino Feigelstock

SUBJECT: Review Memo for amendments 13, 15, 16, 19, 24, and 29 of STN 125265/0 Rotarix: Human Rotavirus Vaccine Live, Oral, GlaxoSmithKline Biologicals, CMC section. Comment on sponsor request for exemption of the General Safety Test.

TO: Laraine Henschel, OVRP, DVRPA

THROUGH: Stephen Feinstone, Robin Levis, Anissa Cheung, Phil Krause, Jerry Weir, DVP, OVRP

cc. Loris McVittie, DVRPA

Summary:

Rotarix is a vaccine composed of a monovalent, live, attenuated rotavirus derived from the human 89-12 strain (isolated from a naturally infected child with rotavirus gastroenteritis). GlaxoSmithKline Biologicals submitted a BLA seeking approval of Rotarix on June, 2007, of which I reviewed the CMC section. I raised the issues that I considered more important during the mid-cycle review meeting (November 2007) and wrote my review memo of the original submission on December 2007. In that review memo I posed several questions; the majority of these questions were answered during the Pre-Approval inspection in which I participated (December 2007). This review memo contains my comments after reviewing amendments 13, 15, 16, and 19 sent by the sponsor from December 2007 till February 2008.

Amendment 13:

In response to our question concerning stability, the sponsor presented stability data for the HRV inoculum and a table of corrections to the information submitted in the original BLA. This information is a satisfactory response to the question. I don't have any further comments.

Amendment 15:

The sponsor submitted a document responding to the observations made during the inspection. I don't have any further comments.

Amendment 16:

The sponsor presented the response to CBER question #5, related to the sterility of the contained closure system. I don't have any further comments.

Amendment 19, 24, and 29:

The sponsor presents the response to CBER questions #22 and #23. I have the following comments for each of the responses.

Attached below is CBER question #22 sent to the sponsor and the sponsor's response:

CBER Question #22

In your BLA, you proposed a release specification potency of ----- CCID₅₀ per dose. However, in your pivotal Phase III studies (Rota-023, Rota-036), you used a potency of 10^{6.5} CCID₅₀ per dose. You also did not use a potency of ----- CCID₅₀ per dose in your supportive

GSK Response:

With respect to the potency titer the Company selected a minimum titer limit of $10^{6.0}$ CCID₅₀ (corresponding to approximately $10^{5.5}$ ffu) potency over its shelf life on the basis of the following considerations: -----

received on 3.21.08) indicates a vaccine efficacy of 76.2% for any HRV GE and 84.6% for severe HRV GE at a dose of $10^{6.0}$ CCID₅₀ (versus 82.9% and 90.5%, respectively, at $10^{6.5}$ CCID₅₀).

Attached below is CBER question #23 sent to the sponsor, the sponsor's response, and my review of the sponsor's response:

You ----- for the release specification potency. Please specify.

[illegible]

- The vaccine has demonstrated a good safety profile, not significantly different from the placebo, after administration of more than 70,000 doses of vaccine in infants. It is worth highlighting that the safety and reactogenicity profile was unchanged in GSK's Phase II dose-finding studies in which virus dose ranging from 4.7 to 6.4 log₁₀ ffu were evaluated. These results suggest that there is no correlation between virus load and safety/reactogenicity.

The clinical data shows safety (and a lack of correlation "between virus load and safety") from 4.7 to 6.4 log₁₀ ffu. We don't know the safety of a vaccine containing more than 6.4 log₁₀ ffu (corresponding to approximately 10^{6.9} CCID₅₀). On February 29th 2008, the sponsor submitted by email a histogram showing titers of more than 200 commercial lots manufactured in Europe. The histogram shows that some lots have titers above ----- CCID₅₀.

We should consider that there is ----- . We should also consider that the one already approved rotavirus vaccine ----- can be argued that Rotateq is a combination of five reassortants; therefore it may be more appropriate to ----- to Rotateq than to Rotarix.

- The HRV manufacturing process is robust and the titers achieved are highly consistent. GSK has a procedure in place for monitoring production consistency and to establish internal consistency limits. As per internal monograph CTR019 consistency limits are being set based on a statistical analysis of the results generated on a minimum of -- lots produced in ----- . The titer to be obtained at the finished product level is calculated from the ----- titer and the appropriate ----- is applied at vaccine formulation.

My comment:

I agree that the manufacturing process is robust and the titers achieved are highly consistent. However, the point doesn't answer our concern.

- GSK Biological's HRV vaccine is a stable vaccine. Real-time stability data have demonstrated here is ----- upon storage up to the end of the proposed - years of shelf-life. Therefore, in contrast to other live attenuated vaccines, there is ----- (and it is not the Company's interest) to include ----- at vaccine formulation to compensate for the ----- -- ----- during lyophilization and storage.

My comment:

I agree that the vaccine is very stable, but the sponsor does indeed show some drop off in titers between 24 and -- months. I also agree that it may not be in the company interest to --- -----, but it seems to me that it should be regulated by us: if for some reason, in the future the company decides to --- ----- to the vaccine, they will have the right.

- As mentioned earlier, there is no official requirement to ----- for vaccines for live attenuated virus vaccines. Per the --- Guideline, ----- at release in order to guarantee the ----- titer per dose, established on the basis of efficacy results obtained following administration of 2 doses of *Rotarix* lots in dose-ranging clinical studies.

My comment:

We should consider the fact that --- agrees with this approach.

- This approach has been approved in more than 100 countries including the European Union, Australia, New Zealand and Switzerland. Furthermore, GSK has been informed of the ---
- pre-qualification for Rotarix vaccine (on January 26, 2007) by which vaccine with its characteristics and specifications has been found acceptable in principle for purchase by United Nations agencies.

My comment:

We should consider the fact that so many institutions agree with this approach.

My conclusion to answer to question #23:

My concern for ----- is that the sponsor could --- ----- -- to the final formulation, and we don't know the safety of a vaccine with ----- of virus than the amount used in the clinical trials.

We should also consider that it seems unlikely that the sponsor will formulate vaccines with - ----- (as the sponsor notes). In addition, potency is part of the tests performed in final container as part of the Lot Release Protocol; so a batch of vaccine having a ----- will be detected. Finally, the --- and many countries agreed to -----.

During the telecom on February 29th 2008, the sponsor agreed to respond to CBER the potency issue. On March 6th 2008, we received an email from the sponsor proposing (based on clinical trials) a maximum release specification of ----- CCID₅₀ per dose. In a

telecom on March 17th 2008, we explained the sponsor that the clinical studies supported an ----- CCID₅₀ per dose. The sponsor stated that they will respond to us. On March 20th, 2008, we received an email from the sponsor suggesting an ----- of ----- CCID₅₀ per dose.

The sponsor suggestion of an ----- of ----- CCID₅₀ per dose is acceptable.

Minor issues:

Sample size for quality control tests on final container.

The sponsor didn't provide a statistical basis to justify the number of samples taken for quality control test on final container. In a telecom on February 29, 2008, the sponsor agreed to provide a justification for the elected sample size. On March 6th 2008, we received an email from the sponsor justifying the selected sample size. These are my comments after reviewing the sponsor's email:

Rotarix vaccine, -----: the sponsor ----- vials, and makes --- ----- . The justification provided is "technical aspects". It is not clear to me the justification provided.

Rotarix vaccine, moisture content: the sponsor measure moisture content of --- vials, and makes an ----- . The justification provided is "technical and validation aspects". It is not clear to me the justification provided. In addition, the SPEC states ----- It is not clear to me if the ----- should be -----, or -----

Diluent, identity -----: -----, and --- ----- is obtained. The justification provided is ----- I'm not familiar with these regulations, but it seems to me that --- ----- may not be enough to represent up to ----- syringes.

Diluent, identity -----: ----- and ----- is obtained. The justification provided is ----- I'm not familiar with these regulations, but it seems to me that ----- may not be enough to represent up to ----- syringes.

Diluent, volume: ----- syringes are measured and ----- . The justification provided is ----- I'm not familiar with these regulations. It is not clear to me if the ----- -- should be at -----ml, or ----- should be at ----- ml.

Diluent, ----- and ----- is obtained. The justification provided is ----- I'm not familiar with these regulations, but it seems to me that --- ----- may not be enough to represent up to ----- syringes

Diluent, calcium carbonate content by ----- are measured and ----- . The justification provided is "technical and validation aspects". It is not clear to me the justification provided. In addition, it is not clear to me if the ----- should be ----- --g, or ----- should be -----.

The justifications provided are not clear and are incomplete. I recommend that the sample size elected should be reviewed by a statistician. A CBER statistician stated that the sample size will depend on the variability of parameter studied. In a telecom on March 17th 2008, we stated that the information provided was not clear to us and requested a statistical analysis based on historical data of the mentioned parameters. The sponsor stated that they will provide to us the requested information.

On March 20th, 2008, we received an email from the sponsor showing data and an explanation for the sample size elected for ----- and moisture content of the lyophilized vaccine; there is no further clarification for the justification of the sample size elected for the parameters measured in diluent.

For -----, the sponsor shows data from --- lots and shows a "well-controlled product attribute with --- of the determinations lying ----- (see chart below), and 95% of the determinations lying -----". I believe that the data should be analyzed by a statistician. It seems to me that given the low variability of the determinations, the sample size elected could be justified.

For moisture content, the sponsor states that the assay used is precise, reproducible, and has low variability. The assay validation demonstrated that the 95% CI around a ---- moisture content is ----- . This is well below the specification of ----- . Therefore, it seems to me that the sponsor proposal for the elected sample size is acceptable.

My conclusion Sample size for quality control tests on final container.:

Ideally, the sample size elected should be reviewed by a statistician. To me, the sample size elected for moisture and ----- on the lyophilized vaccine could be justified. I believe we should be also sure that the diluent is also within specifications. The reason for that is that the diluent, in the case of the rotavirus oral vaccine, is not just a vehicle for the virus, but also has a special composition (calcium carbonate) to ensure that the virus is not inactivated during the passage through the gut. The sponsor presented studies in animals showing that with -- mg of calcium carbonate in the diluent vaccine take is 80% versus 40% without calcium carbonate. In addition, studies in humans also have shown the value of adding a buffer to the vaccine.

Testing performed for the diluent in final container.

The sponsor proposes to test each batch of diluent for appearance, identity ----- identity -----, volume, and calcium carbonate content. We proposed to the sponsor to perform the "reconstitution test" (consisting of reconstituting a known lyophilized vaccine batch with the new batch of diluent, to find out if a lyophilized vaccines reconstituted with new batches of diluent retains the potency).

In a telecon on February 29, 2008, the sponsor stated that ----- . The sponsor agreed to submit data showing how frequent this test is performed. On March 6th 2008, we received an email from the sponsor stating that they perform the test ----- approx. ----- a year. The sponsor proposes to conduct this reconstitution test as an ----- control ----- . In addition, the sponsor shows extensive data showing that the diluent lots formulated from the ----- do not adversely affect the potency of the vaccine.

Conclusion from testing performed for the diluent in final container: the sponsor proposal is acceptable.

Acceptance criteria for -----

In the BLA, the sponsor states that the integrity of the ----- is tested using ----- . I asked the sponsor what trend analysis is and if there is a statistical analysis and specifications. The sponsor stated that ----- is performed by ----- . The sponsor also stated that ----- from ----- . However, no statistical analysis is performed and specifications are not set.

The sponsor agreed to provide a statistical analysis.

Comment on sponsor request for exemption of the General Safety Test.

The sponsor requested to delete General Safety test (GST) for routine lot release of Rotarix commercial lots. The sponsor based his request in several facts:

1. The route of administration used in GST (intraperitoneal) is not relevant to the route of administration used to deliver *Rotarix* vaccine to humans (oral).
2. Implementation of various technological advances in the manufacture and aseptic processing of vaccines, as well as the incorporation of stringent in-process and final product quality control requirements, the relevance of the animal toxicity testing (ATT) can be questioned.
3. Deletion of this test serve to lessen the number of animals that are routinely used in the production and testing of this vaccine; a decision that would be commensurate with current GSK policy and that of various regulatory authorities world-wide.
4. *Rotarix* is registered and marketed throughout the world; therefore, wherever possible and appropriate, GSK will strive for harmonization of specifications and testing for all markets. In this regard, it is important to note that recent Guidelines were published by WHO (October 1995) in which general safety testing is no longer required for routine release of final container vaccines.

In addition, the sponsor states that General safety test (GST) testing has been performed on all clinical lots and on the first commercial lots produced for commercial purpose (non-US and US production). All lots complied with the requirement of the abnormal toxicity test and the general safety test as specified in 21 CFR 610.11.

Given that measures are taken to detect and avoid contaminants in the product, the limited value of the GST, the consistency and stability this drug product has shown, the trend in reducing test using live animals, the existence of guidelines promoting reducing testing when possible, the sponsor request to withdraw the GST is acceptable.