

# Memo of Device Review (1/17/2008) - Rotarix

- MEMO OF DEVICE REVIEW

**BLA: 125265 Responses 1**

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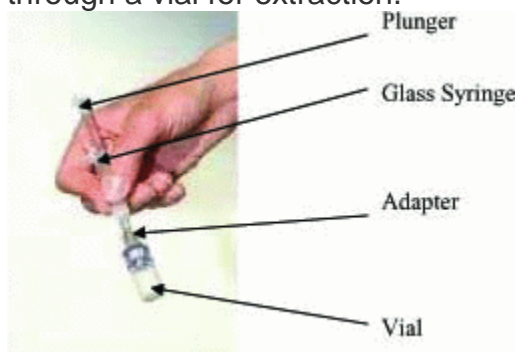
DATE: Thursday January 17th, 2008

SUBJECT: Review (CON076106) of Transfer Device in STN 125265/0 Rotarix Vaccine Response 1

**General description of device:**

The vaccine diluent is filled in a clean, sterile syringe. To transfer the vaccine into the syringe, a transfer adapter device is used. According to the sponsor, the reconstitution of the HRV vaccine with the diluent suspension requires the use of a transfer adapter. The transfer system consists of two plastic parts moulded together: a rigid ----- vial adapter whose spike pierces the vial stopper, and a ----- Elastomer) hose which fits tightly on the syringe tip. For the manufacturing of this transfer system based on -----

The transfer system is used for HRV lyophilised vaccine reconstitution prior to its oral administration. The sponsor states that this material is not sterilized due to the oral route of the vaccine administration and the short time of contact of the vaccine with the device. Picture below shows the syringe connected to the adapter that has pierced through a vial for extraction.



***Consultant's comments analyzing the sponsor's responses:***

The sponsor has provided the list of materials and their manufacturers. However, their claim that biocompatibility and sterilization on certain devices is unnecessary is not correct. These devices come into contact with the mucosal membrane hence need to be sterilized and assured that they meet biocompatibility criteria identified in ISO 10993. The analysis of the sponsor's response to the deficiencies is provided below. Since, manufacturer has not sufficiently answered all the questions, additional deficiencies are stated as well.

**Response to the Deficiencies from the Sponsor:**

1. In section 2 of Container Closure System you have stated that "Raw materials used in the transfer device are of pharmacopeia quality in compliance with -- pharmacopeia and ISO 10993 guidelines." Certain materials such as ----- are mentioned in the description of the Transfer Adapter. We believe that generic class alone (e.g. -----) is not adequate because there are many formulations of material composition. Please provide a complete listing of all device materials (trade name and chemical formula) and manufacturer. Please also provide the list of materials, name of the manufacturer for glass syringes, syringe plunger stoppers, plunger rods for the syringes and the backstops for the syringes. Please also include the exact name, composition, manufacturer of the ----- used on the syringe.

**Sponsor's Response (January 22nd, 2008):** The sponsor has provided the exact name of the material, manufacturer, and referred to the chemical formulation of the materials. According to the sponsor, the transfer adaptor is supplied to GSK (sponsor) from ----- located in ----- . A reference to the ----- is made for the details regarding the chemical formula and manufacture of this device. The sponsor states that the vial adapter is ----- material -----, -----, especially developed for medical devices. The adapter is compliant with requirements of ISO 10993-1 (biocompatibility tests for medical devices), ----- . Also, the material used for the tube is a -----), with trade name of -----, suitable for medical device applications. This material was tested up to 2001 by the manufacturer according to ----- guidelines, and is now tested according to ISO 10993 Biological Reactivity Tests. Other materials such as ----- is a well characterized material made of rigid and flexible ----- (e.g. for ----- systems). This material is stated as reference material in FDA Guidance document on ----- . A Certificate of Compliance with ----- ensuring compliance of the transfer adapter with ----- is available. The sponsor has purchased the glass syringes from ----- and has referenced ----- document for details regarding the chemical formula and manufacture of the glass syringe. (A Letter of Authorization for FDA to refer to this ----- on behalf of the sponsor is provided in m1.4.1). According to the sponsor, the glass syringes are supplied by ----- . A list of the materials and manufacturers for the syringe components is as follows:

Article	Material	Manufacturer
Syringe 1.75 ml	Glass -----	-----

<b>Article</b>	<b>Material</b>	<b>Manufacturer</b>
-----	----- -----	-----
Plunger stopper	-----	-----
Plunger rod	-----	-----
Backstop	-----	-----

**Consultant's Comment:** The sponsor has provided sufficient information and references to support that appropriate testing on the individual materials was conducted and the materials have been used previously in medical devices. ---  
**Response Acceptable.**

- The description, tests, specifications you have provided of the Container Closure System do not state that any biocompatibility was performed according to the ISO 10993 or an equivalent standard. Even though the syringe and the adapter may not be touching the patient, they are contacting the vaccine. Hence untested devices and their materials such as the ----- may contaminate the vaccine being administered to the patient. Please provide biocompatibility test results obtained by testing representative samples of final finished product (including the syringe and the adapter). Please also identify lot number tested and date of manufacture. Please also provide us with testing protocols with end points: Cytotoxicity, Sensitization, Irritation or Intracutaneous reactivity. The Agency recommends that you conduct biocompatibility testing as described in the guidance, Use of International Standard ISO-10993, Biological Evaluation of Medical Devices Part-1: Evaluation and Testing, <http://www.fda.gov/cdrh/g951.html>.

**Sponsor's Response (January 22nd, 2008):** The sponsor has stated that the closure system does not include biocompatibility tests specified in ISO 10993 (ISO 10993-4:2002 provides general requirements for evaluating the interactions of medical devices with blood) because neither the final drug product nor the applicator device come into contact with blood.

**Consultant's Comment:** We believe that although the transfer device does not contact blood but it does contact Mucosal Membrane as a surface device. The ISO 10993 states that a surface device coming into contact with the mucosal membrane for less than 24 hours needs to be tested for Cytotoxicity, Sensitization, irritation or intracutaneous reactivity. This fact was confirmed by Dr. Lana Shiu who stated that the device will be touching the mouth. Hence, the sponsor needs to perform the biocompatibility according to the ISO 10993. --- **Additional Information Required.**

- The description, tests, specifications you have provided of the Container Closure System do not describe the labeling and instructions that would be on the packages of these devices (syringe and adapter). A user should be provided sufficient information about the devices and instructions on how to use them on the packaging of the devices. The labeling on the packaging of these devices should identify if they are single-use, sterile, pyrogen-free, etc. Please provide us with the

labeling and instructions of use that would be present on the packaging of your devices (syringe and the adapter).

**Consultant's Comment:** *The response is not present in the document provided. I believe that the sponsor provided the instructions of use in a separate document previously. Lead reviewer should verify this issue. --- **Needs verification.***

4. In the Container Closure System section you state, "Both tip caps and plunger rubber contains dry natural latex. The transfer adapter is latex-free." A user or a patient can have an allergic reaction to products containing latex. Therefore in order for your device to be latex-free, please certify that your product does not contain latex, is manufactured in a latex free environment, and that the raw materials used to make your product have not been exposed to latex proteins. For devices containing natural latex, please refer to 21 CFR 801.437 User Labeling for devices that contain natural rubber.

**Sponsor's Response (January 22nd, 2008):** *The sponsor states that the sentences quoted from Module 3.2.P.7 - Diluent are indeed factual. However, these statements should not be considered in isolation, i.e. there is no intent to claim that all components in the product--the HRV vaccine component, the diluent syringe, and the transfer adapter--are latex free. The sponsor points to the language in the draft PI (m1.14.1.3): "The tip cap and the rubber plunger of the oral applicator contain dry natural latex rubber that may cause allergic reactions in latex sensitive individuals. The vial stopper and transfer adapter are latex-free." The sponsor admits that a statement warning of the latex-containing components was inadvertently left off the draft carton label (m1.14.1.1). The cartons need the following language: "The tip cap and the rubber plunger of the oral applicator contain dry natural latex rubber that may cause allergic reactions in latex sensitive individuals."*

**Consultant's Comment:** *The sponsor has identified that their device is not latex free. Hence, they have stated in the response that they will update their labeling to notify the user that the latex in device can have an allergic reaction to latex sensitive individuals. --- **Response Acceptable.***

5. In section 2 of the Container Closure System section you have provided tables containing the tests and specifications for glass syringes. FDA recommends conformance to FDA recognized standard(s) to ensure that the device has been tested according to the international consensus tests outlined in the standards. Please confirm if the glass syringe conforms to: ISO 7886-1:1993 Sterile hypodermic syringes for single use -- Part 1: Syringes for manual use, ISO 594-1 Conical fittings with a 6 % (Luer) taper for syringes, needles and certain other medical equipment -- Part 1: General requirements, and / or ISO 594-2 Conical Fittings with a 6% (Luer) Taper for Syringes, Needles, and Certain other Medical Equipment. Please also verify if the Enteral Transfer Adapter conforms to any FDA recognized standards.

**Sponsor's Response (January 22nd, 2008):** *The sponsor states that the Rotarix vaccine is administered orally; hence the FDA recognized standards cited in the CBER question are not applicable for the orally-delivered Rotarix vaccine. In particular, ISO 7886-1:1993 applies to hypodermic syringes but this does not apply to Rotarix as the product is not administered subcutaneously or intramuscularly.*

*The syringe used for Rotarix is specifically designed without a Luer lock so that a needle cannot be attached thereby mitigating the risk of maladministration via subcutaneous or intramuscular administration.*

**Consultant's Comment:** *The sponsor has stated that the ISO 7886-1:1993 is not applicable to the glass, oral delivery syringe. The guidance document and the standard do not specifically state that the glass syringe orally being administered must conform to the ISO 7886-1 standard. Hence, sponsor's response is correct and they do not need to conform to the standard since it is not applicable. ---*

**Response Acceptable.**

6. In section 1.2 of the Container Closure System, you have stated that the vaccine is filled in a sterile syringe; however the syringe plunger rod is not sterilized. The FDA expects that the syringe, plunger stoppers, plunger rods, backstops, enteral transfer adapter (ETA) will all be sterilized since there is a possibility of contamination of the vaccine if these components are not sterile. Also the sterilization must be performed on final finished products (entire syringe and its components, and ETA). Therefore please provide us with the following:
  - a. Sterilization method description (e.g. -----)
  - b. ---, for ----- (e.g., -----)
  - c. Sterilant residuals remaining on the device. (For --, the maximum levels of residuals of ----- that remain on the device (note: not to include ----- residual level because the recognized standard, -----  
-----  
-----  
-----)  
-----)
  - d. A description of the Validation Method for the sterilization cycle (not data). For example, -----cycle method, bioburden method, combination method
  - e. Sterility assurance level (SAL). (e.g.,  $10^{-6}$  for all devices.)
  - f. If you have labeled your devices as "Pyrogen Free". Please provide a description of the method used and bench testing to support your claim.

**Sponsor's Response (January 22nd, 2008):** *According to the sponsor, the sterilization was performed on the stoppers. The syringes are supplied ----- from their manufacturer. However, the sponsor states that they do not have to perform sterilization on the transfer device since it does not come into contact for long enough time.*

**Consultant's Comment:** *Firstly, the sponsor has not clearly identified what type of sterilization was performed on which device (syringe, plunger, etc). Secondly, the sponsor claims that they do not need to perform sterilization on the transfer device, which we believe is not acceptable since the device does come into contact with the mouth of a patient. Regardless of time of contact, the device must be sterile. ---*

**Additional Information Required.**

**Deficiencies that require Additional Information from the Sponsor:**

1. In your January 15th, 2008 response you have stated that the closure system does not include biocompatibility tests since the vaccine is administered orally and ISO 10993 provides general requirements for evaluating the interactions of medical devices with blood. The Agency believes the closure system is a surface device that comes into contact with the mucosal membrane of a patient. The ISO 10993

clearly identifies that such a device coming into contact for less than 24 hours should be tested for Cytotoxicity, Sensitization and Irritation or intracutaneous reactivity. Therefore, please provide us with biocompatibility test results obtained by testing representative samples of final finished product (including the syringe and the adapter). Please also identify lot number tested and date of manufacture. Please provide us with testing protocols with end points: Cytotoxicity, Sensitization, Irritation or Intracutaneous reactivity. The Agency recommends that you conduct biocompatibility testing as described in the guidance, Use of International Standard ISO-10993, Biological Evaluation of Medical Devices Part-1: Evaluation and Testing, <http://www.fda.gov/cdrh/g951.html>.

2. In your January 21st, 2008 response you have provided us with the sterilization information pertaining to the system. You have stated that the *"plungers stoppers are supplied ----- are -----"*. In addition, you have listed ---- and ----- residuals but not identified the part of the system (plunger, syringe) where these levels are derived from. We are unsure what system part was sterilized via which method and their corresponding residual values. Please clearly state for us the sterilization method, dose, residuals, validation method, Sterility Assurance Level, and labeling for each part (syringe, plunger stopper, transfer device).
3. In your January 21st, 2008 response you have stated that *"the ETA transfer device for administering this oral product is not sterilized. Considering the oral route of the vaccine administration and the short time of contact of the vaccine with the device, the Company believes that sterilization of the transfer system is not required. Using a non-sterile transfer device to transfer the vaccine to the infant's mouth is analogous to using a spoon or dropper to administer an oral product"*. The Agency believes that even a limited contact with an unsterilized transfer device can introduce bacteria, germs into the patient. Second, an unsterilized transfer device can contaminate the vaccine itself. Hence, please perform sterilization on ETA (transfer device) as well and provide us with the following information:
  - a. Sterilization method description (e.g. -----)
  - b. ----- for ----- (e.g., -----)
  - c. Sterilant residuals remaining on the device. (For --, the maximum levels of residuals of -- and ----- that remain on the device (note: not to include ----- residual level because the recognized standard, "-----  
-----  
-----  
---)
  - d. A description of the Validation Method for the sterilization cycle (not data). For example, ----- method, bioburden method, combination method
  - e. Sterility assurance level (SAL). (e.g.,  $10^{-6}$  for all devices.)
  - f. If you have labeled your devices as "Pyrogen Free". Please provide a description of the method used and bench testing to support your claim.