DEPARTMENT OF HEALTH & HUMAN SERVICES

U.S. Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Manufacturing and Product Quality

To: Administrative File, BN080041/0, InterSol Solution

From: Randa Melhem, Ph.D., OCBQ, DMPQ, MRBII, HFM-676

cc: James Crim, Acting Team Lead, OCBQ, DMPQ, MRB II, HFM-676
David Doleski, Acting Branch Chief, OCBQ, DMPQ, MRB II, HFM-676

Subject: **Comments on Response to IR (NDA):** [Fenwal, Inc. – ERN 2627511]: Review of NDA submitted by Fenwal, Inc. for InterSol solution for the storage of AMICUS-derived apheresis platelets.

Action Due: June 4, 2009

Summary / History

InterSol solution is an isotonic solution designed to replace a proportion of the plasma used in the storage of platelets.

Fenwal, Inc. plans to manufacture this solution at the Maricao, Puerto Rico manufacturing plant, the same manufacturing facility used for other blood storage solutions manufactured by Fenwal.

InterSol solution will be supplied in a 500 mL PL 24ll plastic container with a nominal solution fill volume of --(b)(4)-- mL.

This NDA provides clinical data to support the use of InterSol solution for the storage of AMICUS-derived apheresis platelets in a 65% InterSol and 35% plasma solution for up to 5 days post-collection, when stored under standard blood-bank conditions with agitation.

I requested clarification and additional information regarding section 4 of the submission, and Fenwal submitted in Amendment BN080041-009, a response to the Information Request on March 10, 2009.

Evaluation of Responses to Information Request

The **questions are in bold**, Fenwal response is in plain lettering, my comments are underlined, and *additional questions to be communicated to the firm are in italics*.

1. **To address safety and compatibility, please provide any risk assessment or testing data for leachables that was performed.**

   Fenwal provided a pharmacotoxicological assessment for the PL 2411 plastic container system, which summarizes the risk analysis of container material based on data gathered for a solution contact application for this material.

   In addition they provided results of tests performed on the ---(b)(4)--- TOP closure - bioreactivity testing per ---(b)(4)----------testing under ----(b)(4)-----, and physicochemical testing under ---(b)(4)---. The leachables profile for ---(b)(4)--- was also provided.

   The response is acceptable. I will defer to the product office for a follow-up on the evaluation of leachable compounds and their toxicological profiles. I requested that the toxicologist on the review team to evaluate the l data provided by Fenwal.

2. **Please provide information about the ---(b)(4)---- of the container or port as well as the acceptance criteria and the action and alert limits for the** ---(b)(4)--- --- **for the container closure.**

   Fenwal stated that the PL 2411 plastic containers are not tested for ---(b)(4)---- prior to release at --(b)(4)--. Non-pyrogenicity is assured by control of the raw materials, components and processes used in manufacturing the container.
   They added that incoming batches of the PL 2411 plastic container will be monitored for ---(b)(4)---- through sampling of the -----(b)(4)---batches coming from the supplier, followed by testing a sample of -(b)(4)- batch of product --(b)(4)-- for at least --(b)(4)--. The testing may be discontinued if the testing shows that the component is under the limit for -b(4)-.
   Since the PL2411 containers are ---(b)(4)--- sterilized, ---(b)(4)--- containers will be sampled and tested on a --(b)(4)-- basis (if manufactured) following specification testing procedures. Per specification, the limits for this component are not to exceed -(b)(4)- organisms per component.

   As for the closure, the firm stated that the -(b)(4)--TOP is received as a (---(b)(4)----------) sterilized part from ---(b)(4)---------. The ---(b)(4)---- for the ---(b)(4)---TOP is monitored to assure that levels are within the limits qualified for the sterilization cycle. A summary of ---(b)(4)-- testing results for the TOP product family (provided from -(b)(4)-) was also included.

   Response is acceptable.

3. **Please expand on the specific uses of the different water sources in relation to product manufacturing and final product. Is WFI used in the processing and manufacturing of InterSol? In particular, please describe any final** ---(b)(4)---------- **for the bags.**

Fenwal stated that ---(b)(4)---------- are performed in the manufacture of InterSol solution or during the production of the container or closure.
They stated the water for Injection (WFI), tested according to the requirements described in the -(b)(4)-, is used to ---(b)(4)---------- of InterSol solution.

Additional information is required.
In the submission section 4.2.6.4.2.1, Fenwal provided a summary of water sampling (In-process water, incoming well water, distilled water and hand-rinsing water), yet there was no information provided about the usage of WFI, or about the sampling sites, frequency and acceptance criteria for sampling of WFI.

The following question should be communicated to the firm:

1. *In amendment BN080041- 009, you state in response to question 3 that WFI is used to* ---(b)(4)---------- *of InterSol solution.*
    a. *Please provide a summary of WFI usage, sampling, sampling sites, sampling frequency and acceptance criteria used in the manufacturing of InterSol at Fenwal's Maricao facility in Puerto Rico.*
    b. *If WFI is purchased, please provide a copy of the Certificate of Analysis with the incoming specifications.*

4. **Please provide the acceptance criteria for non-viable particles, and describe your program for testing non viable particles in the classified and Laminar flow hood areas.**

Fenwal stated that written procedures established for certification, recertification and monitoring of the Laminar Flow Modules classified as Class -(b)(4)-. This is to assure environmental control within this area. For the certification, recertification and routine monitoring of the Laminar flow hood areas or modules, non-viable particles greater than or equal to -(b)(4)-µm per ft^3 are enumerated using an ---(b)(4)------ counter. They stated that each Laminar Flow Hood (LFH) used in the manufacturing area is certified before use, and when HEPA filters are replaced. The LFHs are recertified when relocated or moved. Fenwal stated that LFHs are monitored every ---(b)(4)-------- , and that the monitoring frequency may be changed to ---(b)(4)------ if the ---(b)(4)-----of all modules within a room are within Class -(b)(4)- for a continuous -------(b)(4)----- period. The shut-down limit is "Not to exceed --(b)(4)-------- of size -(b)(4)- micron per cubic foot".
They also provide a summary of the tests performed, frequency and acceptance criteria for viable and non-viable particle monitoring in Class -(b)(4)- Maricao filling Rooms.
Fenwal also stated that environmental testing is also performed at -(b)(4)-- facility to ensure that the plastic components are produced in an appropriate environment, and provided a summary of the tests performed, the frequency and the limits is provided below.

In addition, Fenwal stated that after filling, ---(b)(4)---------- and sterilization, the final product is sampled for visible and sub-visible particulate matter.

Procedures for Visible Particulate Matter Evaluation:
Inspection of the final device assembly for evidence of visible particulate matter in the ----(b)(4)-- is performed during the manufacture of the device as specified in the device product control specification. The presence of visible particulate matter is classified as a --(b)(4)-- defect and is prescribed an acceptance quality level (AQL) as defined in the plant's operating procedures. If the number of defects found exceeds the , ---(b)(4)---------- inspection of the lot will be conducted. Plant Quality Assurance will identify corrective and/or preventative actions, if any, which must be implemented.

Procedures for Sub-Visible Particulate Matter Evaluation:
Sub-visible particulate matter data generated according to the release specification for the finished device is reviewed according to the approved quality procedures of the releasing facility. PAS III solution is tested for particulate matter per , ---(b)(4)----- for , ---(b)(4)----------. The specifications for particulate matter in the PAS III solution container are , --(b)(4)- counts/mL for particles ---(b)(4)-- and --(b)(4)-- counts/mL for particles --(b)(4)--. A minimum of --(b)(4)-- samples are required representing --(b)(4)- and ---(b)(4)- ----; each of the samples tested must yield particle counts within the -(b)(4)- limits.

If an out-of-trend or out-of-specification result is obtained during finished product testing or during the device quality monitoring program, a failure investigation will be initiated by the plant quality organization. Any aberrant or out-of-specification test result requires completion of an investigation and if necessary, implementation of corrective action. The findings of the investigation, including the retest/resample test results, must be interpreted to evaluate the acceptability of the batch and/or manufacturing period.

<u>The response is not adequate as it did not present rationale or supporting data to substantiate the frequency of monitoring in Class -(b)(4)- LFH. The response did not address the frequency of monitoring during manufacturing and filling operations of InterSol.</u>

The following questions should be communicated to the firm:

2. *In amendment BN080041- 009, you state in response to question 4, that Laminar flow hoods (class -(b)(4)-), are monitored every ----(b)(4)-----.*
    a. *Is the testing done under static or dynamic conditions?*
    b. *Please provide the rationale and data to support the testing method and frequency.*
    c. *Please provide the sampling locations, air sample volume and duration in the Laminar Flow Hoods.*
    d. *In addition, what is the frequency of monitoring non-viable particles during the manufacturing and filling of InterSol at Fenwal's Maricao facility, PR?*
3. *Please provide the Alert and Action limits for the non-viable particles monitoring, and describe the processes in place used to address the deviations.*

4. *Does Fenwal have a reprocessing policy? If so, please provide a detailed description of the process.*

5. Please present documentation to support the ----(b)(4)--- limit of ----(b)(4)----- for InterSol solution.

One therapeutic dose of platelets would include a maximum **-(b)(4)-** mL InterSol solution when using a ratio of 65% Intersol/35% plasma for a platelet unit. Fenwal provided the calculation for ---(b)(4)--- limit considering an aggressive platelet transfusion therapy of one unit of InterSol platelets per hour into a 70kg subject. For InterSol Additive Solution, the dose is calculated as

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---(b)(4)---

Fenwal concludes that the **----(b)(4)---** limit is consistent with the FDA, **-(b)(4)-**Test Validation guideline using the formula ----------(b)(4)----------
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Response is acceptable.

6. There is no description or reference to depyrogenation of the container or closure in BB-MF BB-MF –(b)(4)--section 5 or the NDA submission.

Fenwal stated that there is no depyrogenation step performed on the container or the closure. The **----(b)(4)----------** parts are manufactured in areas designated as a Class **-(b)(4)--**environment which is designed and qualified to meet standards for clean manufacturing. These controls for raw material processing are consistent with the operations typically carried out in clean manufacturing environments used for preparation of components for subsequent filling and **--(b)(4)--** sterilization.

They added that the environmental controls on the processing of raw materials used in -(b)(4)- manufacture of plastic components provide additional rigorous process controls which minimize the need to test the microbial quality of the components after manufacture. In addition, the manufacturing environment is controlled and routinely monitored for viable and non-viable particulate matter to assure process control of the environment. The filtration systems are **–(b)(4)---** monitored for **--(b)(4)--** and **--(b)(4)---** according to established procedures.

Fenwal affirms that the **InterSol final product is tested to be pyrogen-free** using a -(**b)(4)-** test according to the USP.

Response is acceptable.

7. **In the maximum load sterilization section (Table 4.2.6-8), please describe the process and parameters. In addition, please explain why for one study (-(b)(4)-1578), the minute value is -(b)(4)- (as compared to a value of -(b)(4)- for the other two studies).**

----------(b)(4)----------

----------(b)(4)----------

The response is inadequate.

The following questions should be communicated to the firm:

5. *Please provide the protocol used and a diagram of the cold and hot spots that were identified in the autoclave, during the qualification of the sterilization cycle.*
6. *Please provide protocols used and data summary for the heat distribution and penetration studies*
7. *Please provide a detailed description of your validation load including the number and placement of the* ----**(b)(4)**--- -------- *InterSol container in the autoclave. We recommend a picture or diagram to be provided.*
8. *The agency is concerned that the validation of sterilization using the* ----**(b)(4)**---------- *container may not represent your future manufacturing lots, as sterility cannot be maintained for the the* **-(b)(4)**-- *container. Please note that the agency requires that if changes were implemented after validation, a new validation process should be performed. Please provide additional information to address the agency's concerns.*
9. *Please provide the number of TC and BI used for maximum and minimum loads and describe using diagrams their specific locations in the autoclave. Please indicate (and present data) for the TC and BI that were placed in the product next to the -(b)(4)-.*

10. *Please provide a detailed description of your commercial manufacturing load configuration including description of packaging and load size. If different size loads are used, alternative minimum loads should also be validated.*

11. *It is not clear in the submission, the number of autoclaves that are used for InterSol sterilization. You have presented data for vessel -(b)(4)-.Validation data are required for all autoclaves that are used for the the* **-(b)(4)-** *sterilization of InterSol at the Fenwal Maricao facility. In addition, please provide the following information about all the autoclaves (sterilizers) that will be used for the* **--(b)(4)--** *sterilization of InterSol final product: Vendor, Model, Method of air removal -(b)(4)- sterilization (pre-vacuum, gravity, etc…)*

12. *We recommend that you provide the chemical indicator labeling and instructions for use. Please note that the labeling should support your intended method and intended sterilization cycle parameters. In addition, please indicate if you plan to use -(b)(4)- for your commercial lots.*

13. *. We note (4.2.6.1.2) that the sterilization process is performed in accordance with the current----------(b)(4)---------- Standard. According to the standards, spores of ----------(b)(4)---------- are used as Biological Indicators to test -(b)(4)- sterilization cycles. Please provide a scientifically valid rationale for using --(b)(4)---------- as the BI for validating the sterilization process. Alternatively, provide validation data using----------(b)(4)-----.*

14. *We also note that you use ---(b)(4)---------- sterilization cycle temperature --(b)(4)----. Please provide the Dvalue studies for ---(b)(4)----- at that temperature.*

15. *Fenwal states that they use ---(b)(4)---------- concept to assure the destruction of the actual bioburden in the product.*
    a. *Please describe the methods and results from studies used to identify and characterize bioburden organisms.*
    b. *Please describe the protocol used to routinely monitor bioburden to ensure that established and validated limits are not exceeded. Please be specific.*
    c. *Please provide the methods used to verify the microbial count and resistance of ---(b)(4)---------- (obtained from --(b)(4)--).*

16. *As the investigational container is different than the commercial container, please provide the container dimensions and the lumen diameter for both.*

17. *Please provide data to support the sterility of the internal surface of the container (such as the lumen opening).*

Ready Letter comments:

1. In amendment BN080041- 009, you state in response to question 3 that WFI is used to ---*(b)(4)*---------- of InterSol solution.
    a. Please provide a summary of WFI usage, sampling, sampling sites, sampling frequency and acceptance criteria used in the manufacturing of InterSol at Fenwal's Maricao facility in Puerto Rico.
    b. If WFI is purchased, please provide a copy of the Certificate of Analysis with the incoming specifications.
2. In amendment BN080041- 009, you state in response to question 4 that Laminar flow hoods (class -(b)(4)-), are monitored every ---(b)(4)----.
    c. Is the testing done under static or dynamic conditions?
    d. Please provide the rationale and data to support the testing method and frequency.
    e. Please provide the sampling locations, air sample volume and duration in the Laminar Flow Hoods.
    f. In addition, what is the frequency of monitoring non-viable particles during the manufacturing and filling of InterSol at Fenwal's Maricao facility, PR?
3. Please provide the Alert and Action limits for the non-viable particles monitoring, and describe the processes in place used to address the deviations.
4. Does Fenwal have a reprocessing policy? If so, please provide a detailed description of the process.
5. In amendment BN080041- 009, you provide, in response to question 7, incomplete information regarding the sterilization process. Please provide the protocol used and a diagram of the cold and hot spots that were identified in the autoclave, during the qualification of the sterilization cycle.
6. Please provide protocols used and data summary for the heat distribution and penetration studies.
7. Please provide a detailed description of your validation load including the number and placement of the ---*(b)(4)*---------- InterSol container in the autoclave. We recommend a picture or diagram to be provided.
8. The agency is concerned that the validation of sterilization using ---*(b)(4)*---------- container may not represent your commercial manufacturing lots, as sterility cannot be maintained for the ---*(b)(4)*------container. Please note that the agency requires that if changes were implemented after validation, a new validation process should be performed. Please provide additional information to address the agency's concerns.
9. Please provide the number of Thermocouples (TCs) and Biological Indicators (BIs) used for maximum and minimum loads and describe using diagrams their specific locations in the autoclave. Please indicate (and present data) for the TC and BI that were placed in the product ---*(b)(4)*---------- .

10. Please provide a detailed description of your commercial manufacturing load configuration including description of packaging and load size. If different size loads are used, alternative minimum loads should also be validated.

11. It is not clear in the submission, the number of autoclaves that are used for InterSol sterilization. You have presented data for vessel -(b)(4)-. Validation data are required for all autoclaves that are used for the -(b)(4)-- sterilization of InterSol at the Fenwal Maricao facility. In addition, please provide the following information about all the autoclaves (sterilizers) that will be used for the -(b)(4)--- sterilization of InterSol final product: Vendor, Model, and Method of air removal /-(b)(4)-- sterilization (pre-vacuum, gravity, etc…)

12. We recommend that you provide the --(b)(4)---------- labeling and instructions for use. Please note that the labeling should support your intended method and intended sterilization cycle parameters. In addition, please indicate if you plan to use -(b)(4)- for your commercial lots.

13. . We note (4.2.6.1.2) that the sterilization process is performed in accordance with the current --(b)(4)---------- Standard. According to the standards, spores of --(b)(4)---------- are used as Biological Indicators to test --(b)(4)-- sterilization cycles. Please provide a scientifically valid rationale for using ----(b)(4)------ as the BI for validating the sterilization process. Alternatively, provide validation data using --(b)(4)----------

14. We also note that you use --(b)(4)---------- sterilization cycle temperature (--(b)(4)----- which corresponds to --(b)(4)---). Please provide the Dvalue studies for --(b)(4)-------- at that temperature.

15. Fenwal states that they use (--(b)(4)--- concept to assure the destruction of the actual bioburden in the product.

    d. Please describe the methods and results from studies used to identify and characterize bioburden organisms.

    e. Please describe the protocol used to routinely monitor bioburden to ensure that established and validated limits are not exceeded. Please be specific.

    f. Please provide the methods used to verify the microbial count and resistance of (--(b)(4)------ (obtained from (--(b)(4)---).

16. As the investigational container is different than the commercial container, please provide the container dimensions and the lumen diameter for both.

17. Please provide data to support the sterility of the internal surface of the container (such as the lumen opening).
