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

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.

I then submitted several questions as part of a CR letter sent to the firm on April 6, 2009. Fenwal submitted (paper) a complete response in amendment BN080041-015 on May 14, 2009.

In this review memo, I evaluate Fenwal's Complete Response, and request that the firm provide additional information to clarify some aspects of their complete respone.

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. **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.**

    Fenwal states that the WFI is used for the cleaning and sanitization of the ---(b)(4)----Room Areas, cleaning and sanitization of the ---(b)(4)----------equipment and in the preparation of the product solution. The WFI sampling sites are Stills and Loops and the storage tank. At the Fenwal's Maricao facility there are --(b)(4)-- stills and ---(b)(4)-- loops, which include mix, rinse loops and the storage tank. Microbiological samples are taken at --(b)(4)-- sites on production days using a ---(b)(4)--------- method that assures that all sites are sampled at ---(b)(4)------. The acceptance criterion is -(b)(4)---------- for the ---(b)(4)---- test. Additionally, a ---(b)(4)-- sample for ---(b)(4)--- is required for all distilled water systems for when a re-sample is required or for qualification testing. The samples are tested using the ---(b)(4)-------- method. The action limit for the ---(b)(4)--count test is -(b)(4)- organisms. On a production day basis, all sample sites used for the solution mixing process and cleaning of the equipment are tested for the ---(b)(4)---- using the ---(b)(4)---------- per the current ---(b)(4)--- The limit of this test is ---(b)(4)----.

Additional information is required.

Please clarify whether the WFI are hot or cold loops? If cold loops, please elaborate on sanitization of the loops.

    b. **If WFI is purchased, please provide a copy of the Certificate of Analysis with the incoming specifications.**

    Fenwal states that the WFI used in the Maricao facility is produced at the facility and is obtained from a ---(b)(4)---- Source that goes through a distillation process and is tested per -(b)(4)- per the limits described in **Q1a** above.

Response is acceptable.

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?**

Fenwal confirms that the monitoring is performed under ---(b)(4)-- conditions, and that a sampling probe is positioned into the ---(b)(4)----------.

b. Please provide the rationale and data to support the testing method and frequency.

Fenwal states that the LFHs in the Maricao manufacturing areas are currently monitored on a --(b)(4)-- basis. When a new area begins production, the LFHs on the production lines are monitored every ---(b)(4)---------. If the particle counts of all modules within a room are within class -(b)(4)- for a continuous ------(b)(4)----- period, the frequency may be changed to ---(b)(4)---.

They provided data for the LFH (where InterSol Manufacturing takes place) from 1/8/2008 to 3/5/2009, and the -(b)(4)- particle count /ft³ ranges from -(b)(4)- (which is below the limit of -(b)(4)- particle/ft³).

Fenwal uses a ---(b)(4)---------- counter instrument. This particle counter uses a ---(b)(4)---------- for particle detection. Monitoring of the airborne particle counts at the number of locations established per rooms sizes, spaced evenly over the work area of the controlled area has proven sufficient to insure product quality.

c. Please provide the sampling locations, air sample volume and duration in the Laminar Flow Hoods.

Fenwal states that ---(b)(4)--- sample sites locations are monitored within the LFH areas that have a floor area of -(b)(4)-square feet or less. Additional sample sites are tested for larger areas according to standard procedure. All test manipulations are performed at least ---(b)(4)---- inside the hood to assure that air is collected from the inside of the hood. They added that the air sampling counts are collected per cubic foot equal to a volume of air of -(b)(4)- liter for one --(b)(4)--. Each sampling count is taken individually per sample site.

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?

Maricao filling rooms are currently monitored on a ---(b)(4)----basis. When a new area begins production, the Filling rooms are monitored every ---(b)(4)---------until the particle counts for a continuous --------(b)(4)------ period have shown results below alert limits, at which time the frequency may be change to --(b)(4)--. If results of alert limits are exceed, frequency will revert to every ---(b)(4)------ until such time as ---(b)(4)---------- of acceptable data has again been achieved on the manufacturing room. The alert limits for the manufacturing filling rooms are calculated based on the room historical data over a ---(b)(4)---- period.

Responses to Q2(a-d) are acceptable.

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.

For LFH (Class -(b)(4)-)

Fenwal states that the Action limits (shut down limits) established for the Filling LFH are -(b)(4)- particles (-(b)(4)-) per cubic foot (ft^3). The alert limits for the manufacturing filling rooms are calculated based on the room historical data over a -(b)(4)- months period. The alert limit established for the InterSol Filling module (--(b)(4)--) is -(b)(4)- particles (0.5µm) per cubic foot (ft^3).

If an action limit is exceeded, a retest is performed to confirm the out-of-limit result. If the result is confirmed, the module is taken out of service immediately and remains out until the corrective action has been completed. An investigation will be conducted to determine the cause and correct it. Fenwal stated that because all product lots are tested for solution particulate matter and evaluated to meet the official compendia for particulate matter limits prior to release, product is not put on hold if action limits are exceeded.

After corrective actions are completed, the module is re-certified using the following testing:

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

For Manufascturing rooms:

Fenwal stated that the Action limits (shut down limits) established for the Filling -(b)(4) department in which the InterSol solution will be manufactured is --(b)(4)-- particles (0.5µm) per cubic foot (ft^3). The alert limits are established based upon the historical data over a -(b)(4)- months period. The alert limit established for the Filling -(b)(4)- department in which the InterSol solution is manufactured is ---(b)(4)--- particles -(b)(4)- per cubic foot (ft^3).

If alert limits are exceeded, a ---(b)(4)------- count test is performed at the location where instrumental count was exceeded. If the --(b)(4)---------- exceeds the action limit an out-of- limits corrective action will be taken and a report will be completed. If the --(b)(4)---------- method confirms that the alert limit has not been exceeded, no further action is required. After corrective actions are completed the out-of-limits sites are tested instrumentally to confirm that the area return to comply with the established acceptance criteria which is --(b)(4)-- particles -(b)(4)- per cubic foot (ft^3).

Response is acceptable.

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

Fenwal states that they do not reprocess or rework based on the strict definition of reprocessing or reworking per ICH Q7A. However, they stated that they validated the sterilization cycle to allow for a restart under specific conditions:

Sterilization reprocessing of the InterSol product is allowed if the sterilization cycle is aborted within the ----------(b)(4)---------- . The aborted cycle is re-started and the cycle is completed. If the cycle is aborted any time after the first --(b)(4)---------- , the product is subject to discard.

Fenwal allows for --(b)(4)---------- as described in BN080041/0 (Volume 1, Section 4.2.4.1, page 29 of 317) that may be performed after --(b)(4)---------- testing. After the solution is released for filling --(b)(4)---------- . Depending on the interpretation of the definition above, this may be considered a type of reprocessing step.

Final InterSol solution product may undergo rework or re-inspection per procedure if ----------(b)(4)----------

Response is acceptable.

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.**

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

-- -

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

-------------------------------------.

Data from qualifications show tight temperature control for each of the --(b)(4)-- temperature probes --(b)(4)-- placed throughout the vessel. As an example, average temperature probe data for the -(b)(4)- qualification cycles performed in Vessel -(b)(4)- (the vessel currently qualified for the InterSol solution cycle) show that individual probes show only a standard deviation of less than -(b)(4)- for all readings throughout the cycle on that probe. Additionally, the average temperatures between the various probes within a cycle varied less than -(b)(4)- for the -(b)(4)- cycles. Finally, for these -(b)(4)- qualification cycles, the difference between the average high and low temperature probes between cycles was only -(b)(4)-.

These show that there are no true hot or cold spots within the vessels. The maintenance of the temperature within -(b)(4)- as shown through the monitor of randomly placed probes is adequate to show that temperature is evenly distributed throughout the vessel.

Fenwal also provides diagrams of the probe locations (heat penetration probes, heat distribution probes and Biological Indicators) used during the qualification of the qualification of the InterSol solution (PAS III) cycle with TOP closure (commercial configuration).

Additional Information is required:

Have you mapped autoclave -(b)(4)- for hot and cold spots during the initial qualification of the vessel (i.e. empty chamber?) Please present data.

What is the frequency of requalifying vessel -(b)(4)-, loads, and cycle parameters?

6. Please provide protocols used and data summary for the heat distribution and penetration studies.

Fenwal provides -(b)(4)----- reports **(**---(b)(4)--------------------) describing -(b)(4)- studies performed for validating and verifying the sterilization cycle used for InterSol solution. They state that several vessels (----(b)(4)-----) were studied as part of validation and qualification studies. The distribution probe range for all probes must be -(b)(4)- (i.e. maximum temperature delta) for any given minute during the Exposure; in addition no temperature distribution probe may drop below -(b)(4)- or go above -(b)(4)-.

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

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

Fenwal presents summary of the data for all -(b)(4)- heat distribution and heat penetration studies.

Additional clarification is required:

You state that vessel -(b)(4)- is the only qualified vessel for InterSol, yet you validate the sterilization process in -(b)(4)- *different vessels. Please clarify.*

For Protocol 17913, the Heat Distribution Data Table (p 19/279), you report for Study -(b)(4)- 1227 that the maximum temperature delta is -(b)(4)-, however the highest temperature is -(b)(4)- and the lowest temperature reported is -(b)(4)- which result in a difference of -(b)(4)- Please clarify.

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.**

   Fenwal states that ----(b)(4)------- terminology is a remnant from a previous program and is confusing. They provide in their response a diagram of the investigational container and the commercial container as well as the container and closure specifications such as material, volume and size. Both the investigational and the commercial configuration do not have a packaging/vapor barrier overpouch.

   Fenwal states that the loading pattern used for every study executed for InterSol solution included -(b)(4)- sterilization -(b)(4)- loaded with -(b)(4)- InterSol containers each for a total of -(b)(4)-- units per sterilizer as follows:

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

   They also provided a schematic diagram and photos of the loading pattern of the sterilization -(b)(4)-.

Response is acceptable.

8. **FDA 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)------ **. 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.

Fenwal reiterates that -----(b)(4)----- (-----(b)(4)-------) is a nomenclature that is remnant from a different program. They state that both the investigational configuration and the commercial configuration use a container made of PL2411 plastic which has -----(b)(4)----- properties. Thus, no vapor barrier pouch is needed to maintain stability. The container itself protects the product from contamination. The twist-off protector (commercial package validated in Study 29791) provides a tamper-evident seal over the membrane to be spiked, which is shown to maintain closure integrity. The solution containers are packaged 6 per corrugated box after sterilization Photo provided).

The PL 2411 plastic container and TOP closure provide the function of the primary and secondary packaging for this product configuration. The carton, which contains 6 solution containers, provides the function of secondary packaging as well as transport packaging.

Response is acceptable.

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 next to the drain.**

Fenwal provides the protocols for the -(b)(4)- studies performed to qualify the InterSol sterilization cycle.

They reiterate that they use a -(b)(4)-- distribution pattern for placement of thermocouples and biological indicators. This practice allows for coverage of the entire vessel over the course of validation studies and regularly scheduled re-qualifications. No probes are specifically placed -----(b)(4)---------- or the ----------(b)(4)----------.

Heat Distribution Probes (TCs):

A total of -(b)(4)- temperature distribution probes are used for the heat distribution study. Probes are ----(b)(4)---- located throughout the load directly -----(b)(4)----------placed adjacent to the -----(b)(4)----------. Distribution temperatures are determined at intervals of -(b)(4)----------.

Heat Penetration Probes (TCs):

A total of --(b)(4)-- temperature penetration probes are used for the heat penetration study. Heat penetration probes are positioned -----(b)(4)----------. Product temperature of the solution is determined during cycle exposure, at intervals of -----(b)(4)------- . The heat

penetration test data are used to calculate the F0 during exposure for -----(b)(4)----. ----------(b)(4)----------.

Fenwal stated that the qualification was performed with -----(b)(4)----------.

Biological Indicators (BIs):

A total of -(b)(4)- units containing BIs were -(b)(4)-- placed through the load. -(b)(4)- BI units served as control units and were not placed in the sterilizer.

Fenwal presents diagrams and locations of the probes used in the -(b)(4)- different studies used to validate the sterilization process.

Additional Information is required:

Traditionally, BIs and TCs are placed in the -----(b)(4)---------- . *Have you ever during your* -----(b)(4)---- *validation, re-qualification, or routine cycles, placed probes next to the drain? Please explain.*

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.

InterSol solution is packaged in a 500 mL PL 2411 plastic container that is --(b)(4)-- and contains one --(b)(4)-- port tube. This container is filled with solution then sealed -----(b)(4)---------- Twist-off-Protector (TOP) that is -----(b)(4)------ onto the port using

-----(b)(4)------ . This product is sterilized using -----(b)(4)---------- sterilization, and the final product is packaged in a corrugated cardboard box, 6 units per carton after sterilization.

The commercial manufacturing load is the same as the validation load in the number and placement of the InterSol containers as described in Question 7. The InterSol containers can -----(b)(4)----------. --------(b)(4)------- are not currently permitted because ----------(b)(4)----------. If and when appropriate validations for proper loads are completed, an appropriate supplementary application will be submitted.

The fully loaded autoclave contains -----(b)(4)--- with -(b)(4)- units on each for a total of -(b)(4)- units. The -(b)(4)- contain -----(b)(4)----------. The InterSol containers are placed ---(b)(4)------- and ---(b)(4)----------.

Response is acceptable.

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 /steam sterilization (pre-vacuum, gravity, etc…)

Fenwal states that all validations and qualifications for InterSol solution were performed on Maricao Vessel -(b)(4)-, Serial No. -(b)(4)--, manufactured by -(b)(4)-. There is no model number for Vessel -(b)(4)-.They added that if additional vessels are to be used, those vessels will be certified and qualified according to ISO standards and regulations prior to use, and the changes reported as necessary according to Guidance for Industry: Changes to an Approved NDA or ANDA, November 1999.

They then describe the sterilization process used as follows:
InterSol solution will be ----------(b)(4)----------

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.**

The ------(b)(4)---------- used for the quality control check of the sterilization process for the InterSol solution product are purchased from ----(b)(4)----------and are the same -(b)(4)- used for Fenwal's other approved drug solution products.

Fenwal provides a release certificate for the ---(b)(4)--- used for InterSol solution sterilization dated February 27, 2009. They also provided a summary of instructions for testing and use of these -(b)(4)-.

They explain that a -------(b)(4)---------- is an analytical material chemical indicator used to assess that the load was submitted to a sterilization cycle. The -(b)(4)- is -----(b)(4)-----(the -(b)(4)-- in this case). ----------(b)(4)---------- ---------- and with ----------(b)(4)----------.

Fenwal confirmed that each -(b)(4)-- must have ----(b)(4)------ card attached to each -(b)(4)- in the appropriate holder, prior to sterilization. Each -(b)(4)-- is labeled with ---b(4)---------- for traceability. Each -(b)(4)-- is analyzed for acceptability, prior to release of product.

Fenwal states that they follow the ----------(b)(4)---------- ---------- ----------(b)(4)---------- ---- They stated that -(b)(4)- is used on Commercial loads.

Fenwal states that if the ---(b)(4)--- test fails:

- The affected sterilization load (the affected truck and its pair) are immediately placed on HOLD.
- An investigation is initiated to determine the root cause of the failure.
- If the failure is confirmed the product of the load is subject to discard.
- If a --(b)(4)-- is not available for assay the single affected -(b)(4)- is subject to discard.

Fenwal states that the ---(b)(4)--- is evaluated in conjunction with sterilization process acceptance parameters to establish cycle acceptability and product sterility.

They commit to discard all product from a sterilizer load that fails to meet **ALL** critical process parameters, including the failure of any ---(b)(4)--- to demonstrate the appropriate heat-induced change, and that they do not permit end-product sterility testing as a secondary release test.

Response is acceptable.

Please list the tests and acceptance criteria (critical process parameters) needed to release the load.

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 steam 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)----------.**

    Fenwal states that the method used for sterilization validation/qualification of the InterSol solution is the combined biological indicator/bioburden method according to ----(b)(4)---------- which lists ----(b)(4)---------- *as an acceptable microorganism* that demonstrate high -------(b)(4)---- with respect to bioburden. In addition, ----(b)(4)---------- ---------- ---------- mentions the use of ----(b)(4)----------.

    Fenwal states that bioburden is routinely monitored for spores which are resistant to ----(b)(4)------. They presented data fro 2000 to the present. ----(b)(4)---------- which has a ----(b)(4)---------- minutes is -(b)(4)-- as resistant to the ----(b)(4)--- sterilization process as the typical historical bioburden recovered in the product.

    Fenwal assures that their --(b)(4)------ sterilization process, designed to achieve a -(b)(4)- Spore Log Reduction of the biological indicator which is more resistant than

the product bioburden, provides a significant safety margin that represents a worst-case challenge.

Additional information is requested.

Please list the common isolates identified at the Maricao facility, and how frequently do you monitor and evaluate (re-assess) the bioburden at the Maricao facility.

Reviewer's comment: ----**(b)(4)**---------- was withdrawn. It has been replaced by ----**(b)(4)**----------.

14. We also note that you use ----**(b)(4)**---------- sterilization cycle temperature ----**(b)(4)**----, which corresponds to ----**(b)(4)**---. Please provide the D_{value} studies for ----**(b)(4)**-- at that temperature.

    Fenwal states that the D value at –**(b)(4)**- are -(b)(4)- minutes and -(b)(4)-minutes for the BI, ----**(b)(4)**------ lot ----**(b)(4)**------ and ----**(b)(4)**---- used in Protocol Study No. 29791 according to the following calculation:

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

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

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

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

    They went on to clarify that a reference temperature of ----**(b)(4)**---------- with a z-value of ----**(b)(4)**--- is commonly used, therefore the D value is reported as a -**(b)(4)**- value. This reference temperature is used to correlate to the Fo value, which represents the microbial lethality in minutes at a temperature of -**(b)(4)**-- and a z value of -**(b)(4)**-° F.

Response is acceptable.

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.

Fenwal states that the procedures used to determine the ----**(b)(4)**----- microbial population (bioburden) on ---**(b)(4)**--- sterilized solution are the ----**(b)(4)**--- test, ----**(b)(4)**----- test and the ---**(b)(4)**--- test. They explain that ----**(b)(4)**---------- -------(b)(4)------is the culture media used to plate the counts of the ----**(b)(4)**---------- counts tests and ----**(b)(4)**---------- for the ----**(b)(4)**---------- test. They add that ----**(b)(4)**---- is made from all representative colonies recovered on these tests and representative isolates from ----**(b)(4)**---------- plates are identified to genus and species when reasonably attainable.

Response is acceptable.

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

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

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

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

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

If the action limit is exceeded, an investigation is initiated to determine the cause of the condition. The following actions are taken but are not limited to:

Issue a notification to the appropriate manufacturing and quality management.

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

Response is acceptable.

Please clarify the number of units tested from the -(b)(4)- and -(b)(4)- of every batch.

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

---**(b)(4)**------- vials are certified by -----**(b)(4)**--------. A certificate is received with each lot.

The Maricao, PR plant confirms the population and purity of the ---**(b)(4)**------- vials --------**(b)(4)**------- . To confirm the population, ----------
----------(b)(4)----------

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

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

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

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

Response is acceptable.

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

Fenwal states that the InterSol commercial configuration replaces the ----------(b)(4)----------. The container itself was produced under the same specification for all -(b)(4)- sterilization studies. Therefore, the investigational container is NOT different than the commercial container, only the --(b)(4)-- used on the container is different.

They provided a drawing of the container (also provided in the NDA), and the nominal dimensions:

Port tube length:	38 mm
Port tube inner diameter:	0.247 in
Container length:	216 mm
Container width:	132 mm

Response is acceptable

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

Fenwal states that the container is filled with InterSol Platelet Additive Solution and the -------(b)(4)---- TOP is ---(b)(4)---- to the filled container. The entire finished product (Commercial Configuration) is then sterilized by ---(b)(4)--. The ---(b)(4)---- sterilization cycles are developed and validated per the ----------(b)(4)----------

----------(b)(4)---------- to provide a minimum Sterility Assurance Level (SAL) of -(b)(4)-.

To assure that sterility of the membrane inside the port (lumen) in the -(b)(4)- closure is maintained, the -(b)(4)- closure was tested after being exposed to the maximum sterilization cycles. This container and closure system integrity testing complies with FDA's Guidance for Industry, *Container and Closure System Integrity Testing in lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products, February 2008.*

Response is acceptable

Ready Letter comments:

1. *You state that there are------(b)(4)------ WFI loops at the Maricao facility. Please clarify whether they are hot or cold loops? If cold loops, please elaborate on sanitization of the loops.*
2. *Have you mapped autoclave -(b)(4)- for hot and cold spots during the initial qualification of the vessel (i.e. empty chamber?). Please present data.*
3. *What is the frequency of requalifying vessel -(b)(4)-, loads, and cycle parameters?*
4. *You state that vessel -(b)(4)- is the only qualified vessel for InterSol, yet you validate the sterilization process of InterSol in -(b)(4)- different vessels. Please clarify.*
5. *For Protocol 17913, the Heat Distribution Data Table (p 19/279), you report for Study -(b)(4)- 1227 that the maximum temperature delta is -(b)(4)- however the highest temperature is -(b)(4)- and the lowest temperature reported is -(b)(4)- which result in a difference of -(b)(4)-. Please clarify.*
6. *Traditionally, BIs and TCs are placed in the -----(b)(4)----------. Have you ever during your -(b)(4)- validation, re-qualification, or routine cycles, placed probes -(b)(4)---? Please explain.*
7. *Please list the tests (other the -(b)(4)-) and acceptance criteria (critical process parameters) needed to release the InterSol Loads.*
8. *Please list the common isolates identified at the Maricao facility; and how frequently do you monitor and evaluate (re-assess) the bioburden at the Maricao facility.*
9. *You state that finished unsterilized units from the ----(b)(4)--- of every batch are sampled for ----(b)(4)----------. Finished unsterilized units from the -(b)(4)- of each batch are sampled for ------(b)(4)----------. Please clarify the number of units tested from the --------(b)(4)----------.*