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

Through: David Doleski, Acting Branch Chief, OCBQ, DMPQ, MRBII, HFM-676

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

Action Due: December 12, 2009

Action Recommended

The described sterilization process and the container closure integrity and sterility studies demonstrate that these processes are acceptable for approval.

Summary / History

InterSol solution is an isotonic solution designed to replace a proportion of the plasma used in the storage of platelets. It does not have a pharmacological effect in vivo, but rather acts to provide the appropriate environment and nutrients in lieu of a portion of the plasma normally used for storage. InterSol is a platelet storage solution to be used with the AMICUS separator only. The solution should never be infused directly to a patient.

InterSol solution is currently marketed by Fenwal, Inc. in the European Union (EU) and other Eastern European countries. InterSol solution has been sold with AMICUS apheresis kits for use as part of the INTERCEPT Blood System (IBS) since 2003. Marketing approval in Europe was received for stand-alone InterSol solution in February 2007.

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. This new platelet product is intended for treatment of patients with low platelet counts or to decrease bleeding.

Submission Content

Fenwal, Inc. submitted this NDA on July 31, 2008. The information in the NDA includes:

- Cover Letter
- FDA forms 356h and 3674
- NDA Executive Summary
- Chemistry, Manufacturing and Controls
- Clinical Data including Integrated Summaries
- Draft Labeling
- Other Info and References
- Patent Information and Certification
- Debarment Certification
- Financial Disclosure Information

Submission Review

4. CHEMISTRY, MANUFACTURING AND CONTROLS

4.2.6 Sterilization

4.2.6.1 Description of the Product and Process
4.2.6.2 Thermal Qualification of the Cycle
4.2.6.3 Microbiological Efficacy of the Cycle
4.2.6.4 Microbiological Monitoring of the Environment
4.2.6.5 Container-Closure and Package Integrity
4.2.6.6 Integrity over the Product Shelf Life
4.2.6.7 Bacterial Endotoxin Test and Method
4.2.6.8 Final Product Release Criteria
4.2.6.9 Other ---b(4)--- Sterilization Processes: ---b(4)------- TOP Closure
4.2.6.10 Evidence of Formal, Written Procedures

This review covers the information presented in the NDA submission (BN080041/0) and the responses to the information requests presented in seven amendments: BN080041-009 (March 10, 2009), BN080041-015 (May 14, 2009), BN080041-020 (July 31, 2009), BN080041-026 (September 15, 2009), BN080041-032 (October 9, 2009), BN080041-033 (October 29, 2009) and BN080041- 034 (November 4, 2009) pertaining to

- Container Closure – integrity and sterility
- Sterilization

As well as amendment BN080041-030 submitted on September 30, 2009 to describe a change in the ---b(4)---------- packaging of InterSol.

DESCRIPTION OF THE PRODUCT AND PROCESS

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

10 Pages determined to be not releasable; (b)(4)

FINAL PRODUCT RELEASE CRITERIA

Fenwal states that their sterilization cycle parameters are validated, and thus InterSol solution product will be parametrically released during commercial production. They affirm that the (b)(4) Test of Sterility Compendial method, ----(b)(4)---------- (-(b)(4)----------), was performed on the solution and verified total lethality at the determined cycle parameters.

OTHER TERMINAL STERILIZATION PROCESSES: ------(b)(4)------- OF TOP CLOSURE

InterSol solution is filled into PL 2411 ----(b)(4)----- plastic container with a --(b)(4)-- co-extruded port. A ---(b)(4)--- Twist-off Protector (TOP) closure is ----(b)(4)---------- co-extruded port after the container has been filled. The TOPs are ----(b)(4)---------- .

The (TOP), ----------(b)(4)----------(b)(4)----------.

Fenwal states that, a (b)(4)----- audit is performed, at minimum, every –(b)(4)- months, per ----(b)(4)----------, to ascertain the continued validity of the sterilization dose.

Fenwal states that packaging remains intact with -b(4)---- processing; moreover, as there is no requirement for pressure or vacuum, the seals are not stressed.

EVIDENCE OF FORMAL, WRITTEN PROCEDURES

Fenwal provides a list of Final Reports and Reference documents.

INFORMATION REQUEST

Additional information was requested from Fenwal, and the firm submitted their response in Amendments BN080041-009 (March 10, 2009), BN080041-015 (May 140, 2009), BN080041-020 (July 31, 2009), BN080041-026 (September 15, 2009), and BN080041-032 (October 9, 2009), BN080041-033 (October 29, 2009), BN080041-034 (November 9, 2009). Review of the amendments is presented below.

Fenwal reports a change in the secondary and tertiary packaging of InterSol. They provided the information in Amendment BN080041-030 (September 30, 2009), which is reviewed below.

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

Amendment BN080041-009 (March 10, 2009)

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)-----, Hemolysis testing under --(b)(4)---------, and physicochemical testing under ----(b)(4)-----. The leachables profile for –(b)(4)---- was also provided.

   I requested that a toxicologist on the review team should evaluate the toxicological 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)--- of product -(b)(4)--- for ---(b)(4)--- ---------. The testing may be discontinued if the testing shows that the component is under the limit for a –(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 washing steps for the bags.

Fenwal stated that no washing steps are performed in the manufacture of InterSol solution or during the production of the container or container closure. They stated the water for Injection (WFI), tested according to the requirements described in the USP, is used to ----------(b)(4)---------- of InterSol solution.

Additional information is required.

In the submission section 4.2.6.4.2.1, Fenwal provides 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 sampling sites, frequency and acceptance criteria for sampling of WFI.

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)------ are enumerated using an ----------(b)(4)----------. 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 particle counts of all modules within a room are within Class (b)(4) for a continuous (b)(4) months period. The shut-down limit is “Not to exceed (b)(4) particles of size ----------(b)(4)----------.

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 visual and sub-visual particulate matter.

Procedures for Visible Particulate Matter Evaluation:
Inspection of the final device assembly for evidence of visible particulate matter in the fluid path 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 'accept number', a 100% 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 Large Volume Injections using a ---(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.

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. Additional information was requested.

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 -(b)(4)- of InterSol platelets per hour into a (b)(4) subject. For InterSol Additive Solution, the dose is calculated as

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

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

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

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 plastic sheeting, tubing and molded 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 routinely monitored for integrity and air flow according to established procedures.

Fenwal affirms that the **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)----------

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

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

Additional information about qualification of the autoclave and the sterilization process is needed.

Note: Seventeen questions were sent to the firm as part of a CR letter.

Amendment BN080041-015 (May 14, 2009) – Response to CR Letter

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)------ system 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(b)(4) loops and the storage tank. Microbiological samples are taken at random sites on production days using a randomization method that assures that all sites are sampled at (b)(4)---- . The acceptance criterion is ---------(b)(4)---------- for the total count test. Additionally, a (b)(4)- sample for coliforms is required for all (b)(4) 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 coliform count ----(b)(4)----------. On a production day basis, all sample sites used for ---b(4)----------t are tested for the -(b)(4)-- test using the -----(b)(4)----- Method 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 USP per the limits described in **Q1a** above. Fenwal states that there are--- (b)(4)-- WFI loops in Amendments BN080041-020.

   Response is acceptable

2. **In amendment BN080041- 009, you state in response to question 4 that Laminar flow hoods (class** (b)(4)**), are monitored** ---(b)(4)---- **weeks.**

   a. Is the testing done under static or dynamic conditions?

   Fenwal confirms that the monitoring is performed under -b(4)---- conditions, and that ----------(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)---, 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)------- Particle counter instrument. This particle counter uses a ----------(b)(4)----------. 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 two sample sites locations are monitored within the LFH areas that have a floor area of ----------(b)(4)---- . Additional sample sites are tested for larger areas according to standard procedure. All test manipulations are performed at least --b(4)---------- 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)-- for (b)(4)-- . Each sampling count is taken----------(b)(4)---------.

   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 exceeded, 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)-- ----------.

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)-- (0.5µm) 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 Manufacturing 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)------ (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) (0.5µm) per cubic foot (ft^3).

If alert limits are exceeded, a ------(b)(4)-------- 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)---------- 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)-------- (0.5µm) 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.**

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

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

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

----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)---

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

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

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

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

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 re-qualifying vessel (b)(4) , loads, and cycle parameters?

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

Fenwal provides three reports **(**Protocols 17395, 17913 and 29791) describing three 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 --b(4)--------- (-----*(b)(4)*----------) 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 three 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. ---(b)(4)--------- ---
---.

Fenwal states that the loading pattern used for every study executed for InterSol solution included ---(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 unpackaged 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.**

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---(b)(4)----------. Thus, ---(b)(4)---------- 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.

On September 30, 2009, Fenwal submitted amendment BN080041-030 to propose a change in the secondary and tertiary packaging of InterSol. The change does not impact sterilization, sterility or stability. This change is described at the end of this review memo.

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** (b)(4)**.**

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 TCs and Bis. This practice allows for coverage of the entire vessel over the course of validation studies and regularly scheduled re-qualifications. No probes are ----------(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 d---(b)(4)---------- ---------- . ---(b)(4)----- is 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 in the ---(b)(4)---------- location of the container inserted ---(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 each probe. ---(b)(4)- probe is placed adjacent to the ----------(b)(4)---------- .

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

Biological Indicators (Bis):

A total of -(b)(4)- 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) *as it is the* ---(b)(4)---------- . *Have you ever during your* ***-b(4)-*** *validation, re-qualification, or routine cycles, placed probes next to the* (b)(4)*? 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) sealed and contains one (b)(4) port tube. This container is filled with solution then ---(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 ---(b)(4)---------- . ---(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)----. The -(b)(4) contain -(b)(4)-. The InterSol containers are placed ---(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 No. (b)(4) Serial No. (b)(4) manufactured by (b)(4) . There is no model number for Vessel No. (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:

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

Response is acceptable

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) Sterilization (b)(4) is an analytical material chemical indicator used ----------(b)(4)----------.

Fenwal confirmed that each (b)(4) must have at---------(b)(4)---------- in the appropriate holder, prior to sterilization. ----------(b)(4)----------.

Fenwal states that they follow the ----------(b)(4)----------.

They stated that (b)(4) is used on Commercial loads.

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

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

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

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

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

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

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 ----(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)---------- .**

    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)------- , Section A.6.3.2 which lists --------(b)(4)----- *as an acceptable microorganism* that demonstrate --------(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 twice 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)------- in 2006.

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

Fenwal states that the D value (b)(4) are (b)(4) minutes and (b)(4) minutes for the BI, --------(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 F0 value, which represents the microbial lethality in minutes at a temperature of (b)(4) and a z value of (b)(4) .

Response is acceptable

15. Fenwal states that they use ----------(b)(4)--------- 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)----------
---

---.

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.

Fenwal states that they test --(b)(4)----- produced in the facility for the --(b)(4)---------- microbial population (bioburden) --(b)(4)----------. The number of samples per batch tested is dependent on --(b)(4)----------. The sampling must provide for the following:

---(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:

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

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

Response is acceptable

Please clarify the number of units tested from ---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)-).**

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

----------(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)---------- (also known as the ---------(b)(4)----------) with the ---------(b)(4)---------- TOP closure. 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 closure 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 ---(b)(4)----TOP ---(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)----------

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

To assure that sterility of the membrane inside the port (lumen in the TOP closure is maintained, the TOP 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

Amendment BN080041-020 (July 31, 2009)

1. **In your response to Q1 in amendment** BN080041-015, May 15, 2009**, 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 the sanitization of the loops.**

   Fenwal states that the ---(b)(4)---- WFI loops described in amendment (BN080041-015, May 15, 2009) are all (b)(4) loops. The Maricao Distilled water distribution system is a (b)(4) system (---(b)(4)----).

   Response is acceptable

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.**

   Fenwal states that they mapped the empty chamber of autoclave (b)(4) as part of the initial qualification of the vessel. They add that the initial qualification of vessel (b)(4) included two types of studies:

   - (b)(4) point temperature distribution using(b)(4) locations with an empty chamber

     Fenwal lists the locations of the probes and presents a schematic diagram for the empty chamber study- (b)(4)-1432 using twelve (b)(4) temperature distribution probes ----------(b)(4)---------- the empty (b)(4).

   - (b)(4) point geometric temperature distribution using a fixed pattern with full loading of the product to map the vessel throughout the load inside the----------(b)(4)---------- .

     Fenwal lists the locations of the probes and presents a schematic diagram of the Geometric Temperature Distribution Study: Worst Case Conditions -(b)(4)-1431. For the qualification of Vessel (b)(4), the load consisted of solution product with (b)(4) plastic containers containing (b)(4) mL of solution. This is considered worst case because the load ------(b)(4)---------- containers, thereby giving a greater challenge of the circulation of the (b)(4) mixture throughout the vessel.

Fenwal explains that the temperature distribution probes above are monitored and analyzed --b(4)---------- and must be within (b)(4) during the exposure for any given minute.

Additional Information is required

In a telecon with the firm, we stated that a single study is not enough and requested additional data to support the qualification of vessel(b)(4)*. The information was provided in Amendment BN080041-26.*

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

Fenwal explains that they perform two types of requalification for sterilization cycles:

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

----------.

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

----------.

Fenwal adds that cycle and process requalification may be performed using units filled with an appropriate surrogate solution. These "dummy units "consist of the product packaging filled with ---------(b)(4)---------- solution instead of the actual solution product.

Response is acceptable

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.**

Fenwal explains that initial studies performed to determine the process parameters for a new product need to be executed in an approved/certified sterilizer vessel; vessel (b)(4**)** met those requirements.

After the process for InterSol was developed, additional vessels No. (b)(4**)** were qualified for the cycle for the experimental configuration of InterSol (validation

protocol 17913). After the container design for InterSol was changed to contain a (b)(4) twist-off protector port, the cycle was validated for this commercial configuration in vessel (b)(4) (validation protocol 29791).

Fenwal states that currently, Vessel (b)(4) is the only sterilizer that is fully validated and currently qualified to run the InterSol sterilization cycle. They add that when product volume requires that additional capacity be added, a new vessel(s) will be qualified using the same process requirements as used for Vessel (b)(4) .

Fenwal states that they will follow Guidance for Industry: Changes to an Approved NDA or ANDA (April 2004), to report the addition of new qualified vessels, changes to loading pattern, or changes to validated operating parameters.

Response is acceptable

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 results in a difference of** (b)(4) **Please clarify.**

   Fenwal explains that the maximum temperature delta is determined for the greatest temperature span between probes at any given time during the cycle, not for the minimum and maximum temperatures for the whole cycle. For all temperature distribution probes the distribution probe range must be (b)(4) °F during the exposure section time. This distribution range is collected and analyzed using a (b)(4) ---- (b)(4) evaluation. It is determined by reviewing the temperature delta for each (b)(4) during the cycle to identify the maximum delta experienced during the cycle.

   Response is acceptable

6. **Traditionally, BIs and TCs are placed in the** (b)(4) **as it is the area of (b)(4). Have you ever, during your random validation, requalification, or routine cycles, placed probes next to the** (b)(4) **? Please explain.**

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

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

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

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

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

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

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

----------.

Additional Information is required

In a telecon with the firm, we requested additional information to address the following questions:

- *Did any random location address worst case locations?*
- *How can you demonstrate reproducibility with worst case locations?*

7. Please list the tests (other than (b)(4)) and acceptance criteria (critical process parameters) needed to release the InterSol loads.

Fenwal states that release of sterile loads is accomplished by demonstrating that qualified critical and key operating parameters were met during routine sterilization cycles. They state that the following critical parametric release parameters must be met for load release.

Critical Parametric Release Parameters

[(b)(4)]

In addition, Fenwal lists the key parametric release parameters which are more indicative of a state of control. The firm states that investigations are conducted to determine the disposition of a load if any parameter is not met.

Key Parametric Release Parameters

[(b)(4)]

Response is acceptable

8. **Please list the common isolates identified at the Maricao facility. Please also state how frequently you monitor and evaluate (re-assess) the bioburden at the Maricao facility.**

   Fenwal states that every year they have a review of the normal flora and compare it to the data of the previous year. Changes in the flora are assessed and documented. They state that the purpose of the (b)(4) review of the flora is to determine:

   - The impact of the cleaning/ sanitization or disinfectants efficacy validation.
   - The types of flora common in the facility.

   Fenwal lists the most frequently recovered microorganisms at the Maricao plant over the past five years.

[(b)(4)]

Fenwal states that representative isolates from the microbiological environmental testing are identified to genus. The representative colonies are identified from all out-of-limit, out of action samples and routine monitoring samples taken on a seasonal basis (each quarter) such as microbiological surface, water, air and compressed air testing. They add that finished unsterilized units for the solution (b)(4) test are sampled from the ---(b)(4) ----------. For the solution (b)(4) test (------(b)(4)----------) all representative isolates from finished unsterilized units are identified to genus and species when reasonably attainable. For the solution (b)(4)

(b)(4)- test all isolated spores (bacilli are considered spore formers) are identified to genus and species when reasonably attainable.

Response is acceptable

9. **You state that finished unsterilized units from the** ------(b)(4)---- **batch are sampled for** ------(b)(4)---------- **. Finished unsterilized units from the** ------(b)(4)---- **batch are sampled for** ------(b)(4)---------- **. Please clarify the number of units tested from the beginning and end of every batch.**

   Fenwal states that they test ----------(b)(4)----------.

   Fenwal explains that they require a minimum of (b)(4) of solution each for the ------(b)(4)---- test and the --(b)(4)- count test. The PAS III solution final volume per unit is between ----(b)(4)---- and, therefore, one unit provides more than enough solution for the required testing.

   Response is acceptable

Amendment BN080041-026 (September 15, 2009)

1. **Please provide additional information to support the qualification of the autoclave (vessel #**(b)(4)**) used for the** -(b)(4- **sterilization of InterSol. Please present data to support worst case locations.**

   Fenwal reiterates that the *initial* qualification of vessel -(b)(4)- included two types of studies:

   - (b)(4) point temperature distribution using (b)(4) locations with an empty chamber
   - (b)(4) point geometric temperature distribution using a fixed pattern with full loading of the product

   Fenwal presented summary of the data generated from the initial studies (Study: ------(b)(4)-1432 for the (b)(4) point temperature distribution Study- Empty Vessel and Study: -(b)(4)-1431 for the (b)(4) point Geometric Temperature Distribution Study - Full Product Load).

   They explain that the temperature distribution probes above are monitored and analyzed ------(b)(4)---- and must be within the following range for any given minute:

   - Distribution Probe Range: -(b)(4)- during the Exposure

   The following excursions are permitted to the heat temperature distributions during exposure time:

   - Excursions above (b)(4), but not above (b)(4) are acceptable provided that the total number of degree minutes (number of degrees in --(b)(4)-- that probe is out of range times the time at that temperature) above (b)(4) is less than or equal to (b)(4) per probe and less than or equal to -(b)(4)- for all probes combined .

• Excursions below (b)(4), but not below -(b)(4)- are acceptable provided that the total number of degree minutes (number of degrees in tenths that probe is out of range times the time at that temperature) below (b)(4)- is less than or equal to (b)(4) per probe and less than or equal to (b)(4) for all probes combined.

Fenwal states that they performed additional studies to demonstrate repeatability of the b(4) point empty chamber temperature data and the b(4) point full chamber temperature data locations for InterSol.

They performed (b)(4) new(b)(4) empty chamber temperature studies (----------(b)(4)----------). The studies used the same probe placement as was used in the previously submitted (b)(4) empty chamber study (------(b)(4)--------1432) to show reproducibility. An additional probe was added at the product position nearest to the (b)(4) of the vessel and is designated as Probe No. (b)(4). Fenwal provides a schematic diagram and the data generated for all three studies.

In addition to the empty Chamber study, Fenwal conducted (b)(4) additional (b)(4)point full load geometric temperature distribution studies (------(b)(4)---- ----------) and presented a schematic diagram for the positioning of the probes as well as the summary of the data generated.
Fenwal concludes that the additional probe near the (b)(4) of the vessel added as part of the empty vessel study shows that there is no cold spot near the (b)(4) given the design of Fenwal's sterilization vessels. Both the (b)(4)-point empty vessel studies and the (b)(4)-point geometric studies showed that although there are probe positions that may tend to be slightly hotter or cooler than others within the vessel, temperatures at all probes reproducibly meet specification. The variation between probe readings is very small. These studies verify that there are no true hot or cold spots within the vessel, consistent with the data obtained using random probing patterns as part of validation and qualification procedures.

<u>The numbering of the location of the probes in the qualification studies do not match the numbering of the probes for the validation studies of InterSol both in the investigation and the commercial configuration. In addition, there are areas of the load which are not covered the TC mapping.</u>

Please provide clarification/ additional information to assure that the conventional worst case locations of the load are represented in the heat distribution/ penetration studies. Fenwal provided data of (b)(4) *additional runs for amicus (worst case) in amendment BN080041- 033.*

<u>Amendment BN080041-032 (October 9, 2009)</u>

1. **Please provide additional information/clarification about the Container closure integrity testing using the --b(4)-- method.**

Fenwal reiterated that per ------(b)(4)---------- ------ test for confirmation of packaging integrity provided that correlation between the procedures is demonstrated showing that the (b)(4) test is at least as sensitive as the -(b)(4) test. They provide a comparison of the detection sensitivity of the -b(4)- test to the ---(b)(4)-- test as shown in the following table:

[(b)(4)]

They conclude that the ---(b)(4)-- ---------- Integrity test is more sensitive in detecting breaches of integrity than a standard ----(b)(4)--- test using (b)(4).

Response is acceptable

Amendment BN080041-033(October 29, 2009)

1. **The numbering of the location of the probes in the qualification studies does not match the numbering of the probes for the validation studies of InterSol. In addition, due to the nature of** ---(b)(4)-- **distribution, some areas of the load are not represented in the qualification/validation studies. Please provide clarification/ additional information to assure that the conventional worst case locations of the load are represented in the heat distribution/ penetration studies.**

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

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

[(b)(4)]

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

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

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

--- ---

Fenwal presents additional data to add support to their (b)(4) Distribution" locations for the thermocouples and biological indicators for validation of Vessel (b)(4) They provided summary data for (b)(4) Amicus Cycle Qualification studies----(b)(4)---------- -- which contained distribution probes, penetration probes and biological indicators. The data presented shows that all studies met the acceptance criteria.

Response is acceptable. The location of the probes for these studies (---(b)(4)------------ ---, along with the previous data submitted for InterSol (studies--- (b)(4)--- ---------------------------- and Amicus (------------(b)(4)-- -------------------) provide an adequate coverage of the load.

2. In the Original lnterSol NDA (BN080041/0), you state that all penetration thermocouple results must achieve an accumulated F_0 during exposure between –

(b)(4)------ minutes. Please provide data to support the lower acceptance limit of (b)(4) **for the sterilization of InterSol in vessel** (b)(4)**.**

Fenwal presents data for the fractional study (17395) conducted using the Investigational Configuration of InterSol container/closure in Vessel (b)(4). These data which were presented in the Original NDA show that there was total inactivation of the biological indicator in the solution container at (b)(4) minutes exposure. Fenwal also presented the ranked F_0 for exposure time based on the heat penetration probe data.

A summary of the fractional Studies is presented below:

[(b)(4)]

They conclude that the data from study 17395 show that there is total inactivation of the biological indicator in the solution container when the accumulated F_0 is (b)(4) , thereby supporting the lower limit of (b)(4) used for this cycle.

The data presented is for the sterilization cycle of InterSol in Vessel (b)(4) . In addition, the data presented indicate that at the end of cycle ((b)(4) minutes), mean F_0 = (b)(4) , which is one (1) minute less than F_0 data presented for the sterilization of InterSol in Vessel (b)(4) (studies --------(b)(4)--------).

Please provide clarification/ additional information to support the minimum F_0 of 6.1 for the sterilization cycle if InterSol in Vessel (b)(4) .

Amendment BN080041- 034 (November 4, 2009)

1. **The F_0 data provided are for F_0 studies performed in vessel** (b)(4) **. Please provide the data for F_0 studies for InterSol in vessel** (b)(4) **to support F_0 =** (b)(4) **? Alternatively, the acceptance criteria for the min F_0 have to be in the range of the data provided in Tables 4.2.6-6 and 4.2.6-7 (vol1, p. 47/317) of the submission.**

   In a telecon with the firm on November 3, 2009, Fenwal stated that the fractional studies are not vessel specific. However, they agreed to modify the range based on the limits of the acceptable temperature ranges for the process. As such, Fenwal committed to change the lower limit for F_0 from (b)(4) to (b)(4) at the end of exposure.

   Fenwal explains that fractional studies are done to biologically validate the efficacy of the sterilization cycle for the specific product configuration, and can be done in any vessel qualified to be running properly at those parameters. They report that Study 17395 was run to validate the cycle parameters to be used for the InterSol product.

   They state that addition of new qualified vessels is a change to the manufacturing process that uses the same sterilization method, uses the same loading configuration, and meets the same process parameters. This change is considered a minor change to

an approved NDA that would be required to be reported via annual report according to the *Guidance for Industry: Changes to an Approved NDA or ANDA (April 2004).* Fenwal states that they understand that, according to this guidance, a change from one qualified sterilization chamber to another that results in changes to validated operating parameters would require a CSE-30 supplement. Additionally, validation of loading patterns outside the currently validated range requires a a prior approval supplement submission.

To determine the sterilization process capability of the InterSol Cycle, Fenwal calculated the accumulated F_0 for the cycle according to the ----------(b)(4)---------- ---------- Based on these calculations, they provide an amended Key Sterilization Process Parameters for the InterSol Cycle as follows:

[(b)(4)]

Response is acceptable

CHANGE TO THE (B)(4) PACKAGING

Amendment BN080041-030 (September 30, 2009)

In their response to Q8 of CR letter, Fenwal states that the PL 2411 plastic container and TOP closure provide the function of the ---b(4)---------- packaging for this product configuration. The carton, which holds six solution containers, provides the function of --b(4)------- packaging as well as --b(4)-------- packaging.

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

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

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

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

Reviewer's comment: In a telecon with the Fenwal on October 1, 2009, we requested that the firm explain the reason(s) for changing the packaging. They explained that during a telecon with FDA in May 2009 - DMPQ asked whether Fenwal uses an -------(b)(4)---------- to protect the InterSol container. At the time they stated that an -------(b)(4)--- is not needed. However, they started to think about what they wanted to do after obtaining US approval (e.g. international shipments, etc…) and decided that they wanted a more (b)(4) packaging.

Response is acceptable.