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: Chiang Syin, Ph.D. Branch Chief, OCBQ, DMPQ, MRBII, HFM-676
Joseph (David) Doleski, OCBQ, DMPQ, MRB II, HFM-676

Subject: **Mid Cycle 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: June 4, 2009

Summary / History

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

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.

Letter Ready comments

1. To address safety and compatibility, please provide any risk assessment or testing data for leachables that was performed.
2. Please provide information about the bioburden of the container or port as well as the acceptance criteria and the action and alert limits for the bioburden for the container closure.
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.
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.
5. Please present documentation to support the Endotoxin limit -(b)(4)- EU/mL for InterSol solution.
6. There is no description or reference to depyrogenation of the container or closure in -(b)(4)---------- section 5 or the NDA submission. Please provide information about the acceptance criteria and validation studies done to ensure the container and closure are depyrogenated.
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).

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 lnformation

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 Terminal Sterilization Processes: --(b)(4)------ of TOP Closure
4.2.6.10 Evidence of Formal, Written Procedures

My review covers
Container Closure – integrity and sterility
Sterilization

DESCRIPTION OF THE PRODUCT AND PROCESS

Drug Product and Container Closure System

The container closure system for InterSol Platelet Additive Solution is comprised of a PL 2411 -(b)(4)- plastic container with a -(b)(4)- co-extruded port and a -----(b)(4)---------- Twist-off Protector (TOP) closure which is solvent bonded to the --(b)(4)---- co-extruded port after the container has been filled. Both container and TOP are supplied by ---(b)(4)----------. Fenwal referred in the submission to BB-MF section 5 for description of the container and closure system.

In --(b)(4)------- Section 5, -(b)(4)- provides the general composition for --(b)(4)--- plastics (---(b)(4)----------). However Fenwal states the container material is PL 2411, the port material is --(b)(4)--, and the Closure is ----(b)(4)----------

To address safety and compatibility, Fenwal should provide any risk assessment or testing data for leachable substances that was performed..

Fenwal states that --(b)(4)-------- sterilization validation studies and qualification studies were performed to validate the 500 mL InterSol solution in an investigational configuration container with ----(b)(4)---------- Results in all studies met the acceptance criteria.

Because of the change in the container closure system, -(b)(4)- consecutive re-qualification cycles using the same 500 mL container with TOP for the InterSol configuration were performed with the following modifications: The --(b)(4)---------- was eliminated and the --(b)(4)---------- was replaced with a ----------(b)(4)---------- (sterile) Twist-Off -Protector (TOP) closure. The TOP container configuration, which has the same container and port materials, is less of a challenge to the --(b)(4)---- sterilization process because of the pre-sterilized TOP closure.

Sterilization Process: Autoclave

Fenwal states that their autoclave design, cycle parameters, and routine process control and validation procedures are in accordance with the current ----(b)(4)----------. Cycles are developed and validated to provide a minimum Sterility Assurance Level of at least -(b)(4)-

InterSol solution is sterilized in a --(b)(4)---------- in order to maintain the integrity of the --(b)(4)--- assemblies. --(b)(4)-- is ---(b)(4)----------. Key sterilization parameters are provided in **Table 1.**

Table 1 **Key Sterilization Parameters** (Protocol 29791)

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

Product cooling is achieved by ----(b)(4)---------- This specific method of cooling has a Fenwal -(b)(4)----------designation.

Each sterilization cycle is monitored continuously for temperature, pressure, and cycle events. All cycle records are reviewed for each sterilizer load prior to acceptance. All instrumentation for temperature and pressure measurement is a part of calibration and routine maintenance.

Loading patterns and quantities of product on sterilization --(b)(4)------ are specified in controlled procedures to assure conformance to vessel qualification.
When --(b)(4)-- loading is changed, possibly affecting load density; load distribution or maximum loading, a --(b)(4)---------- is required, unless supported by approved technical justification.

THERMAL QUALIFICATION OF THE CYCLE

Process Qualification

Fenwal states that the final product qualification study consists of three parts: temperature distribution, heat penetration and biological challenge.

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

Fenwal states that for every sterilization process, they perform
--(b)(4)---------- Sterilization

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

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

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

Fenwal states that they use a spore suspension of --*(b)(4)*---------- as the biological indicator challenge organism for sterilization processes for validations of all solution drug products manufactured at the Maricao, PR plant, including InterSol solution.

A microbial suspension is prepared to contain approximately --(b)(4)----------, and each unit of product to be tested is inoculated with approximately --(b)(4)---------.
Fenwal states that they placed the -(b)(4)- inoculated units to be tested adjacent to -(b)(4)- of the units containing heat penetration probes. After sterilization, the inoculated test units are sterility tested by ---(b)(4)----------.

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

Fenwal provides summary of the accumulated heat during the -(b)(4)- consecutive sterilization cycles for InterSol. The results presented were consistent for the -(b)(4)- lots assuring the capability/ repeatability/reproducibility of the process in the vessel tested.

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

Fenwal also provides results of Microbial Challenge test using --*(b)(4)*----

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

The study results for Process Qualification of 500 mL lnterSol Solution Container with TOP Closure using --*(b)(4)*---------- met all acceptance criteria.
• Sterilization cycle event times and processing parameters were within the specified tolerances (**Table 1**)
• All penetration thermocouple results achieved an accumulated Fo during exposure of between --(b)(4)------ minutes.
• The temperature distribution range within the sterilizer was maintained at less than or equal to --(b)(4)- during exposure.

• All recovered biological indicator solution containers demonstrated total inactivation of the indicator organism. The Spore Log Reduction (SLR) is -(b)(4)- for each of the -(b)(4)- runs.
• The ---(b)(4)---------- results for indicator color change were -(b)(4)-

Fenwal states that they re-qualify each sterilization vessel at least ---(b)(4)----------. In addition, each cycle employed in a vessel is re-qualified at least once -----(b)(4)---.

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

---(b)(4)----- is not allowed for this solution product; and --(b)(4)-------- is not applicable for this solution product.

Batch Record

Fenwal states that they include the following documentation in the Batch record for each acceptable sterilizer test:
• Cycle Recorder Charts
• Cycle Event Recorder Report
•-(b)(4)-Sterilizer Record
• Temperature acquisition system printouts (if applicable)
• Biological Indicator Loading Documentation
• Biological Indicator Sterility Test Report
• Sterilizer Qualification Summary
• Probe Calibration Documentation
• Sterilizer Evaluation
• Qualification Probe Locations
• Sterilizer Study Recap Form

MICROBIOLOGICAL EFFICACY OF THE CYCLE

Identification and Characterization of Bioburden Organisms

Fenwal uses a laboratory prepared spore suspension of --*(b)(4)*---------- as a biological indicator bioburden model for sterilization processes. Strains of this microorganism demonstrate a high resistance to --(b)(4)-------- with respect to bioburden. The cycle conditions established to kill the microbiological challenge (---(b)(4)----------) are more robust than those required to kill the bioburden. Fenwal states that they selected --*(b)(4)*-------- because it has a -(b)(4)-value greater than -(b)(4)- minutes, and no other organism with a -(b)(4)- value of more than -(b)(4)- minutes has been recovered from the product at the Maricao, PR manufacturing plant.

Fenwal states that ----------(b)(4)----------:

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

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

Finished unsterilized units are sampled --(b)(4)---------- and the --(b)(4)---------- batch for total and spore count.
Samples are tested using the --(b)(4)----------

All representative isolates, including spore isolates, from finished unsterilized units are identified to genus and species when reasonably attainable.

Fenwal set the limits for Bioburden as shown in the **Table 4**.

Table 4 Bioburden Limits

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

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

Fenwal states that they performed a –(b)(4)--------- sterilization cycles using the -(b)(4)---------- to validate their sterilization process. Their data show that sterilization for -(b)(4)- minutes was enough for both the --(b)(4)---------- and the --(b)(4)---------- to exhibit an SLR -(b)(4)- and no survivors. InterSol solution required -(b)(4)- minutes of sterilization time to be free of microorganism (0 survivors), and to attain an SLR ≥ -(b)(4)-.

As the InterSol Solution container configuration was modified, Fenwal requalified the new (commercial) container configuration and sterilization process. Microbial data generated confirmed the effectiveness and reproducibility of the sterilization process under manufacturing conditions in Maricao, Puerto Rico. All three study numbers ((b)(4)--1578 solution, (b)(4)-1582 solution and (b)(4)-1583 solution) attained an SLR -(b)(4)- and none of the containers tested positive for microbial growth.

MICROBIOLOGICAL MONITORING OF THE ENVIRONMENT

Fenwal states that they have established microbiological monitoring program (procedures and sampling plans) for production areas along with a bioburden monitoring program for product components and process water. If the limits are exceeded and out-of-action level results are confirmed by subsequent samplings, a formal investigation (procedure 2008-02-H) is initiated and the challenged site sanitized and requalified. A risk analysis for the impact to the product is performed which will determine product disposition.

InterSol solution Bioburden Testing
Fenwal states that they test samples -------(b)(4)---------- total microbial counts and spore-formers. All samples are processed using the -(b)(4)----------. Fenwal briefly describes the procedure to address excursions beyond the alert and action limits.

Component Testing

Fenwal gets the TOP closures --(b)(4)----------, and they test them on a --(b)(4)--- basis for bioburden using the --(b)(4)---- method. --(b)(4)----------

Fenwal does not provide any information about the bioburden of the container or port. Moreover they do not provide the acceptance criteria and the action and alert limit for the bioburden for the container closure.

Environmental testing

Fenwal states that Environmental testing is the same for all drug products manufactured at the Maricao, Puerto Rico plant (---(b)(4)----------). All results are trended. If test results show a trend toward the limits indicating that a more intensive test period is required, a more frequent testing regimen is instituted by the plant.

Water Sampling

Water samples are collected, identified and sent to the laboratory for immediate plating and/or testing. All samples are tested using the --(b)(4)----------.

Fenwal samples in-process water ---(b)(4)----------

incoming well water, distilled water, hand rinsing water. They provide the frequency of sampling, sampling sites and action limits.

Fenwal does not provide information about the specific uses of the different water sources in relation to product manufacturing and final product. Fenwal does not report the use of WFI in the processing and manufacturing of InterSol.

Table 5 Summary of Water Sampling and Monitoring

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

Environmental air

Fenwal has established routine room air monitoring program for viable counts in controlled environmental areas and post-sterilization -(b)(4)-staging areas for --(b)(4)---------- products. The room air and HEPA filtered air limits are based on the class of the room or area being tested.

Fenwal states that monitoring of room air is performed per procedure 12-03-01-007. InterSol solution is filled in a Class -(b)(4)-- clean room. The limit for microorganisms is -(b)(4)-

Table 6 Sampling Sites and Frequencies

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

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

Fenwal does not provide any information about their program (and acceptance criteria) for testing non viable particles in the classified and Laminar flow hood areas.

Surface Testing

Fenwal performs surface testing for viable particles from both product contact (-(b)(4)-- area is sampled using a –(b)(4)----------), and non product contact (--(b)(4)----------) surfaces. If the established levels are exceeded in the original sample and subsequent retests, the sanitizing procedures are reviewed as part of the investigative action. Fenwal provides the testing frequency and action limits for surface testing throughout the manufacturing plant.

Table 7 Sample Frequency and Action Limit for Surfaces

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

CONTAINER CLOSURE AND PACKAGE INTEGRITY

Fenwal state that their procedure for container closure integrity testing is in compliance 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. They provide data that shows that the --(b)(4)---------- method is at least as sensitive as the -(b)(4)---- testing method.

Fenwal tested the integrity of the container/closure for InterSol solution exposed to maximum sterilization under their protocol. ----(b)(4)---------- ---------- ---------- They provide the acceptance criteria and results in Table 8.

Table 8 TOP Closure Integrity Testing for InterSol Solution

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

Fenwal states that as PL 2411 --(b)(4)------- (non-PVC) plastic container with TOP closure is the only barrier for InterSol solution, these plastic materials act as both sterility and vapor barriers, and therefore no multiple barrier testing was required.

INTEGRITY OVER THE PRODUCT SHELF LIFE

Fenwal states that they test the sterility and --(b)(4)---------- level as part of the InterSol stability program. Sterility and --(b)(4)---------- are tested at release and then again at end of shelf-life.

BACTERIAL ENDOTOXIN TEST AND METHOD

Fenwal states that they used a licensed -(b)(4)- reagent to perform the --(b)(4)---------- and the --(b)(4)---------- in their validation studies for the --(b)(4)---------- ---------- assays for bacterial endotoxins.

Fenwal presents data that validate the -(b)(4)- method test as described in -(b)(4)---------- ---------- and validated for the --(b)(4)---------- Test per --(b)(4)---------- ---------- ----------

Fenwal performed --(b)(4)---------- testing on --(b)(4)----- product batches of finished product and showed that InterSol solution has no inhibitory/enhancement effects on the -(b)(4)- testing methods used. Testing was performed for InterSol solution using the ----------(b)(4)---------- ----------

Fenwal states that the EU limit for InterSol is -(b)(4)- EU/mL.

In the NDA submission Fenwal needs to present documentation to support the Endotoxin limit of -(b)(4)- EU/mL. In addition there is no description or reference to depyrogenation of the container or closure in --(b)(4)---------- section 5. Fenwal has to provide information about the acceptance criteria and validation studies done to ensure the container and closure are depyrogenated.

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)---------- method, --(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)-------- as a bulk component.

The (TOP), -(b)(4)-, is pre-sterilized using ---------(b)(4)----------. Dose determination and dose setting are performed ---(b)(4)----------

Fenwal states that, a (b)(4) audit is performed, at minimum, --(b)(4)----------, 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 ----(b)(4)----------

EVIDENCE OF FORMAL, WRITTEN PROCEDURES

Fenwal provides a list of Final Reports and Reference documents.
