

Initial Quality Assessment
Branch IV
Division of New Drug Quality Assessment II

Division: CBER, Division of Blood Applications
NDA: 090067
Applicant: B. Braun Medical
Stamp Date: 14 June 2010
PDUFA Date: 14 April 2011
Trade Name: Isoplate Solution
Established Name: Multiple Electrolyte Solution
Dosage Form: Solution
Route of Administration: Intravenous
Indication: Platelet additive solution for the storage of leukoreduced hyper concentrated apheresis platelets

Review Chemist: Minerva Hughes, PhD
Team Lead: Moo-Jhong Rhee, PhD

	<i>Yes</i>	<i>No</i>
ONDQA Fileability:	√	
Comments for 74-Day Letter:	√	

Summary and Critical Issues:

A. Summary

Pursuant to Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act, B. Braun Medical has submitted NDA 090067 for the use of Isoplate Solution as a platelet additive solution for the storage of leukoreduced hyperconcentrated apheresis platelets collected on CaridianBCT's Trima Accel System under standard blood banking conditions. The CaridianBCT device is the subject of a pending 510(k) application.

Isoplate Solution is a sterile, nonpyrogenic, multi-electrolyte solution (pH 7.4) for intravenous use. The drug product consists of the active ingredients sodium chloride USP (0.53%), sodium acetate trihydrate USP (0.37%), potassium chloride USP (0.037%), magnesium chloride USP (0.03%), sodium phosphate dibasic heptahydrate USP (0.012%), potassium phosphate monobasic NF (0.0082%), sodium gluconate USP (0.5%), and inactive ingredients glacial acetic acid, sodium hydroxide, and water packaged in B. Braun's EXCEL Container.

Isoplate Solution is identical in formulation, packaging, sterilization and manufacturing as B. Braun's approved Isolyte S, pH 7.4 solution for injection (NDA 19-696), which has been marketed since 1989. NDA 19-696 was transferred to the Office of Generics in 1997 and is maintained as ANDA 19-696. The only difference between Isoplate Solution and Isolyte S, pH 7.4 is a change in indication.

For ease of review, complete manufacturing information is provided in Module 3, with references to DMFs where appropriate.

B. Critical Issues for Review

The applicant purports that there are no changes to approved chemistry, manufacturing, and controls (CMC) for Isolyte S, pH 7.4, with the exception of the name and indication change. The comparability of Isoplate Solution to Isolyte S, pH 7.4 should be verified and the suitability of the product for its proposed new use assessed.

C. Comments for 74-Day Letter

The following comments should be conveyed to the sponsor.

1. DMF letter of authorizations should reference the DMF number, the specific item being referenced, and the date of the submission for that item. Provide revised DMF letter of authorizations for the ---(b)(4)--- Sodium Chloride USP and Potassium Chloride USP drug substances. The Agency is unable to review the referenced DMFs in support of your NDA in the absence of an adequate letter of authorization.

D. Comments/Recommendation

From a CMC perspective, the application is fileable. All pertinent information appears to be included for review.

NDA FILING ASSESSMENT

NDA 090067

NDA Number:	Supplement Number and Type:	Established/Proper Name:
090067	N/A	Multiple Electrolyte Solution
Applicant:	Letter Date:	Stamp Date:
B. Braun Medical	9 June 2010	14 June 2010

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	√		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	√		
3.	Are all the pages in the CMC section legible?	√		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	√		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			Not applicable
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	√		

B. FACILITIES*				
8.	Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	√		
9.	Are additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	√		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	√		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	√		Request for categorical exclusion based on 21 CFR 25.31

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	PARAMETER	YES	NO	COMMENT
12.	Does the section contain a description of the DS manufacturing process?	√		There are 7 APIs, all salts of compendial grade. Information is included if available, otherwise referenced to DMFs and ANDA 019696
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	√		Same as above
14.	Does the section contain information regarding the characterization of the DS?	√		Same as above
15.	Does the section contain controls for the DS?	√		Same as above

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	PARAMETER	YES	NO	COMMENT
16.	Has stability data and analysis been provided for the drug substance?	√		Same as above
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		√	Not a filing issue
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		√	Not a filing issue

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	√		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	√		
21.	Is there a batch production record and a proposed master batch record?	√		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	√		Investigational formula is the same as approved ANDA product.
23.	Have any biowaivers been requested?		√	Not needed
24.	Does the section contain a description of the to-be-marketed container/closure system and presentations?	√		
25.	Does the section contain controls of the final drug product?	√		
26.	Has stability data and analysis been provided to support the requested expiration date?	√		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		√	Not a filing issue
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		√	Not a filing issue

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	√		

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?	√		Product sterility and validation of the sterilization process is included in appropriate DP sections. Applicant uses parametric release for product sterility control, which was recently approved for the ANDA.

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	√		

DM F #	TY PE	HOLDER	ITEM REFERENCED	LO A DA TE	COMME NTS
N/A	II	---(b)(4)---	(b)(4), Sodium Chloride USP	23 Mar 2009	LOA is not adequate. No DMF number or reference to sponsor is given in letter.
N/A	II	---(b)(4)---	(b)(4)--, Potassium Chloride USP	23 Feb 2009	LOA is not adequate. No DMF number or reference to sponsor is given in letter.
(b)(4)	II	---(b)(4)-----	(b)(4)---, Sodium Gluconate USP	9 April 2009	
(b)(4)	III	---(b)(4)----- -----.	----- (b)(4)----- ----- -	4 Feb 2009	
(b)(4)	III	---(b)(4)-----	---(b)(4)-----	23	

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4)			----- -----	Jul 200 8	
(b)(4)	III	---(b)(4)-----.	----(b)(4)----- -----	2 Mar 201 0	
(b)(4)	III	---(b)(4)-----	----(b)(4)-----	14 Jul 200 9	
(b)(4)	III	---(b)(4)----- -----	----(b)(4)-----	15 Dec 200 9	
(b)(4)	III	B. Braun Medical	Qualified Component Vendors	13 Apri l 201 0	
(b)(4)	III	B. Braun Medical	EXCEL® Plastic Container Sterilization Program	15 Dec 200 9	
(b)(4)	III	B. Braun Medical	Material Qualification for the EXCEL® Plastic	15 Dec 200 9	
(b)(4)	III	B. Braun Medical	Chemistry, Manufacturing and Controls for the EXCEL® Plastic Container	15 Dec 200 9	
(b)(4)	III	B. Braun Medical	Vapor Transmission Studies for the EXCEL® Plastic Container	15 Dec 200 9	
(b)(4)	III	B. Braun Medical	Ink Qualification Studies for the EXCEL® Plastic Container	15 Dec 200 9	
(b)(4)	III	B. Braun Medical	Accelerated Studies for the EXCEL® Plastic Container	15 Dec 200 9	

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	√		
33.	Have the immediate container and carton labels been provided?	√		

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment

J. FILING CONCLUSION				
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	√		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			Not applicable
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?	√		Updated LOA for ----(b)(4)---- DMFs.

Approval Signatures:

 Minerva Hughes, PhD, RAC
 Review Chemist, ONDQA/DNDQA II/Branch IV

 Date

 Moo-Jhong Rhee, Ph.D.
 Branch Chief, ONDQA/DNDQA II/Branch IV

 Date