



CBER NDA BN090067

**Isoplate Solution
Multiple electrolytes injection type 1, USP**

B. Braun Medical Inc.

Minerva Hughes, PhD, RAC
Review Chemist

**CDER/Office of New Drug Quality Assessment
Division of New Drug Quality Assessment II
Branch IV**

**CONSULT REVIEW OF NDA BN090067
For the Center for Biologics Evaluation and Research, Division of
Blood Applications**

Table of Contents

Table of Contents	2
CMC Review Data Sheet	4
The Executive Summary	8
I. Recommendations	8
A. Recommendation and Conclusion on Approvability	8
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable	8
II. Summary of CMC Assessments	8
A. Description of the Drug Product(s) and Drug Substance(s)	8
B. Description of How the Drug Product is Intended to be Used	9
C. Basis for Approvability or Not-Approval Recommendation	10
III. Administrative	10
CMC Assessment	11
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data	11
S DRUG SUBSTANCE	11
S.1 General Information	11
S.2 Manufacture	13
S.3 Characterization	15
S.4 Control of Drug Substance	16
S.5 Reference Standards or Materials	16
S.6 Container Closure System	16
S.7 Stability	17
P DRUG PRODUCT	19
P.1 Description and Composition of the Drug Product	19
P.2 Pharmaceutical Development	19
P.3 Manufacture	20
P.4 Control of Excipients	23
P.5 Control of Drug Product	25
P.6 Reference Standards or Materials	28
P.7 Container Closure System	28
A APPENDICES	29
A.1 Facilities and Equipment (---(b)(4)---only)	29
A.2 Adventitious Agents Safety Evaluation	29
A.3 Novel Excipients	29
R REGIONAL INFORMATION	29
R1 Executed Batch Records	29
R2 Comparability Protocols	29
R3 Methods Validation Package	29

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	31
A. Labeling & Package Insert.....	31
B. Environmental Assessment Or Claim Of Categorical Exclusion	37
III. List Of Deficiencies to be Communicated.....	37
IV. Attachments	38

CMC Review Data Sheet

CMC Review Data Sheet

1. NDA BN090067
2. REVIEW #: 1
3. REVIEW DATE: 10 Feb 2011
4. REVIEWER: Minerva Hughes
5. PREVIOUS DOCUMENTS: Not applicable.
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Submission	9 June 2010
Amendment (BC) – <i>Response to Day74 Quality Comments</i>	11 Nov 2010
Amendment (BC) – <i>Quality Information Update</i>	16 Nov 2010

7. NAME & ADDRESS OF APPLICANT:

Name: B. Braun Medical Inc
Address: 901 Marcon Blvd
Allentown, PA 18109
Representative: Susan K. Olinger
Telephone: 610-596-2517

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Isoplate Solution (proposed)
- b) Non-Proprietary Name: Multiple electrolytes injection type 1
- c) Code Name/# (ONDQA only): N/A
- d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: New indication (6)
 - Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

CMC Review Data Sheet

- 10. PHARMACOL. CATEGORY: Platelet Storage
- 11. DOSAGE FORM: injection (solution)
- 12. STRENGTH/POTENCY: not applicable
- 13. ROUTE OF ADMINISTRATION: intravenous/platelet storage solution
- 14. Rx/OTC DISPENSED: Rx OTC
- 15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)
 SPOTS product – Form Completed
 Not a SPOTS product

1. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Drug Substance	Molecular Formula	Molecular Weight	CAS Registry Nos.
Sodium Chloride USP	NaCl	58.44	7647-14-5
Sodium Acetate Trihydrate USP	C ₂ H ₃ NaO ₂ ·3H ₂ O	136.08	6131-90-4
Potassium Chloride USP	KCl	74.55	7447-40-7
Magnesium Chloride Hexahydrate USP	MgCl ₂ ·6H ₂ O	203.30	7791-18-6
Sodium Phosphate Dibasic Heptahydrate USP	Na ₂ HPO ₄ ·7H ₂ O	268.07	7782-85-6
Potassium Phosphate Monobasic NF	K ₂ HPO ₄	136.09	7778-77-0
Sodium Gluconate USP	C ₆ H ₁₁ NaO ₇	218.14	527-07-1

Table is as submitted by applicant. NDA BN090067 Section 2.3.S.1. Structures are considered common knowledge based on the molecular formula and substance name and are not illustrated above. Additional structural information is summarized in Section S.1.2 of this review.

CMC Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE¹	STATUS²	DATE REVIEW COMPLETE D	COMMENTS
(b)(4)	II	---(b)(4)-----	---(b)(4)----- -----	1	Adequate	8 Dec 2010	Reviewed by M. Hughes
(b)(4)	III	-(b)(4)----- ----- ---	---(b)(4)----- ----- ----- -----	7	N/A	Review is handled by CBER Product Quality Reviewer and is not covered in this CMC Review.	
(b)(4)	III	---(b)(4)-----	---(b)(4)----- ----- ----- -----	7	N/A		
(b)(4)	III	---(b)(4)----- ---	---(b)(4)----- ----- ----- -----	7	N/A		
(b)(4)	III	---(b)(4)-----	---(b)(4)----- ----- -----	7	N/A		
(b)(4)	III	---(b)(4)----- ----- --	---(b)(4)----- ----- -----	7	N/A		
(b)(4)	III	B. Braun Medical	Qualified Component Vendors	7	N/A		
(b)(4)	III	B. Braun Medical	EXCEL® Plastic Container Sterilization Program	7	N/A		
(b)(4)	III	B. Braun Medical	Material Qualification for the EXCEL® Plastic	7	N/A		
(b)(4)	III	B. Braun Medical	Chemistry, Manufacturing and Controls for the EXCEL® Plastic Container	7	N/A		
(b)(4)	III	B. Braun Medical	Vapor Transmission Studies for the EXCEL® Plastic Container	7	N/A		
(b)(4)	III	B. Braun Medical	Ink Qualification Studies for the EXCEL® Plastic Container	7	N/A		
(b)(4)	III	B. Braun Medical	Accelerated Studies for the EXCEL® Plastic Container	7	N/A		

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

CMC Review Data Sheet

- 3 – Reviewed previously and no revision since last review
- 4 – Sufficient information in application
- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	APPLICATION HOLDER	DESCRIPTION
ANDA	019696	B. Braun Medical	Active ANDA for initially approved indication of electrolyte restoration. The drug product is the same between the ANDA and this submission.

18. STATUS/ONDQA Consults:

This NDA is managed by CBER. ONDQA was consulted to review the CMC information on the drug substance and drug product, excluding process sterilization and container closure systems for the drug product, which are reviewed by CBER. Facility inspections, methods validation and labeling are also managed by CBER. The status of these non CDER activities are not tracked in this consult review, as the information is not readily accessible to this reviewer.

Executive Summary Section

The CMC Review for NDA BN090067

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 090067 has provided sufficient information to assure the identity, strength, purity, and quality of the drug product. However, the labels do not have adequate information as required. Therefore, the NDA is not recommended for approval until all pending labeling issues are resolved.

This recommendation is based on the CMC information covered by this consult review and excludes critical aspects such as process sterilization, container closure system, and manufacturing facility compliance, which were reviewed by Nawab Siddiqui, CBER's Product Quality Reviewer.

Reference is made to Nawab Siddiqui's (CBER) Quality Review for final conclusions on approvability from the perspective of CMC.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

There are no Phase 4 commitments from the CMC perspective.

II. Summary of CMC Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Substance

Drug substances used in the manufacture of drug product were as follows: sodium chloride USP, sodium acetate USP, potassium chloride USP, magnesium chloride hexahydrate USP, dibasic sodium phosphate heptahydrate USP, and monobasic potassium phosphate NF. Each drug substance was manufactured using standard manufacturing processes and controls to assure the quality of the material was in compliance with USP/NF standards as purported.

Reference was made to DMF (b)(4) for the chemistry, manufacturing, and controls information for sodium gluconate. An adequate letter of authorization was submitted to permit a review of DMF (b)(4) in support of NDA 090067. The DMF was reviewed and deemed adequate.

Executive Summary Section

The drug substances and suppliers used for NDA 090067 have been approved previously for use in the manufacture of Isolyte S, pH 7.4, which is the same product marketed under ANDA 19696 for a different indication.

(2) Drug Product

The drug product is a sterile, nonpyrogenic, 500 mL electrolyte solution contained in B. Braun’s proprietary EXCEL container. Each 100 mL of solution contains sodium chloride USP 0.53 g, sodium gluconate USP 0.5 g, sodium acetate trihydrate USP 0.37 g, potassium chloride USP 0.037 g, magnesium chloride hexahydrate USP 0.03 g, dibasic sodium phosphate heptahydrate USP 0.012 g, monobasic potassium phosphate NF 0.00082 g, and water for injection USP.

Isoplate Solution is intended to be used to store platelets collected from the CaridianBCT’s Trima Accel® System (device clearance was pending at the time of this review). The platelets are stored in a mixture of 65% Isoplate Solution and 35% plasma for up to 5 days at 20-24°C. This drug product is the same as previously approved Isolyte S, pH 7.4 (ANDA 19696) by the same applicant. There were no proposed changes to the drug product, with the exception of the indication statement. All chemistry, manufacturing, and controls information relevant to this consult review were reviewed for consistency with ANDA 19696 and compliance with current regulatory standards.

Isoplate Solution is manufactured by using a ----(b)(4)----- process. -----
----- (b)(4) -----
steps to assure product quality. The drug product specification includes adequate tests for identity, strength, and chemical purity. Product sterility and the container closure system are not covered by this review. Stability data support the applicant’s request for an expiration dating period of 24 months, from a chemical perspective (i.e., no degradation of actives or changes in pH); however, conclusions on product expiry is deferred to CBER because sterility must be considered.

The only deficiencies noted pertain to labeling. The proposed product labeling does not comply with the requirements for drug product label and labeling in 21 CFR 201. Revisions are requested to account for the established name, dosage form, bar code and location of the NDC number. Reference is made to Section III of this report for a list of deficiencies to be communicated to the applicant.

B. Description of How the Drug Product is Intended to be Used

Isoplate Solution is intended to be used 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. Platelets are stored in a mix of 65% Isoplate Solution and 35% plasma.

Executive Summary Section

C. Basis for Approvability or Not-Approval Recommendation

NDA 090067 is not recommended for approval because the label and labeling do not comply with the requirements of 21 CFR 201, from the CMC perspective.

III. Administrative

A. Reviewer's Signature:

Minerva Hughes, Ph.D., R.A.C., Chemist, Branch IV, ONDQA

B. Endorsement Block:

Terrance Ocheltree, Ph.D., R.Ph., Division Director, ONDQA

C. CC Block: Iliana Valencia, CBER Regulatory Project Manager

CMC Assessment Section

CMC Assessment**I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2:
Body Of Data****S DRUG SUBSTANCE**

There are seven drug substances in the drug product formulation: sodium chloride USP, sodium acetate trihydrate USP, potassium chloride USP, magnesium chloride hexahydrate USP, sodium phosphate dibasic heptahydrate USP, potassium phosphate monobasic NF, and sodium gluconate USP.

S.1 General Information**S.1.1 Nomenclature**

The table below summarizes the name, molecular formula, molecular weight, and CAS numbers for each ingredient.

Drug Substance	Molecular Formula	Molecular Weight	CAS Registry Nos.
Sodium Chloride USP	NaCl	58.44	7647-14-5
Sodium Acetate Trihydrate USP	C ₂ H ₃ NaO ₂ ·3H ₂ O	136.08	6131-90-4
Potassium Chloride USP	KCl	74.55	7447-40-7
Magnesium Chloride Hexahydrate USP	MgCl ₂ ·6H ₂ O	203.30	7791-18-6
Sodium Phosphate Dibasic Heptahydrate USP	Na ₂ HPO ₄ ·7H ₂ O	268.07	7782-85-6
Potassium Phosphate Monobasic NF	K ₂ HPO ₄	136.09	7778-77-0
Sodium Gluconate USP	C ₆ H ₁₁ NaO ₇	218.14	527-07-1

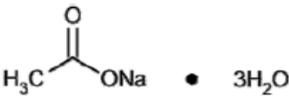
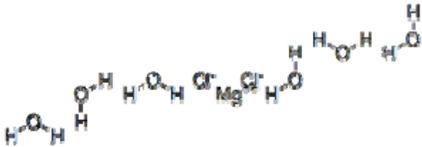
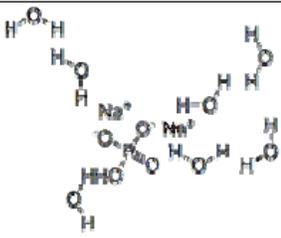
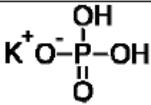
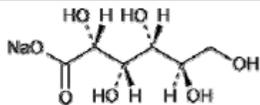
Source: NDA BN090067 Section 2.3.S.1.

USP = United States Pharmacopeia.

S.1.2 Structure

Structural information for the drug substances is provided in the table below, as submitted by the applicant in NDA BN090067.

CMC Assessment Section

Drug Substance	Chemical Formula
Sodium Chloride USP MW = 58.44	NaCl
Sodium Acetate Trihydrate USP MW = 136.08	
Potassium Chloride USP MW = 74.55	KCl
Magnesium Chloride Hexahydrate USP MW = 203.30	
Sodium Phosphate Dibasic Heptahydrate USP MW = 268.07	
Potassium Phosphate Monobasic NF MW = 136.09	
Sodium Gluconate USP MW = 218.14	

Source: NDA BN090067 Section 2.3.S.1.

USP = United States Pharmacopeia.

S.1.3 General Properties

Drug substances are of compendial quality (USP or NF). General properties summarized in the application is as follows:

- Sodium chloride – colorless, cubic crystals or white crystalline powder
- Sodium acetate trihydrate – colorless, transparent crystals, or white granular crystalline powder, or white flakes.
- Potassium chloride – colorless, elongated, prismatic, or cubical crystal, or white, granular powder
- Magnesium chloride hexahydrate – white to colorless, odorless, deliquescent flakes or crystals
- Sodium phosphate dibasic heptahydrate – colorless or white, granular salt.

CMC Assessment Section

Drug Substance	Manufacture	References
	----- ----- (b)(4) ----- -----	
Monobasic potassium phosphate, NF	----- ----- ----- (b)(4) ----- ----- -----	No DMF

*B. Braun did not include a Letter of Authorization with valid DMF numbers in the initial submission. In response to the 27 Aug 2010 information request (NDA amendment 11 Nov 2010), B. Braun stated that the supplier no longer had active DMFs and references were removed.

S.2.2 Description of Manufacturing Process and Process Controls

A brief summary of the manufacturing process and controls was described for each active. The applicant stated that the manufacturing process and controls were the same as those for ANDA 19-696.

Drug Substance	Process	References
Sodium Chloride, USP	----- ----- ----- (b)(4) ----- ----- -----	ANDA 19-696
Sodium acetate trihydrate, USP	----- (b)(4) -----	ANDA 19-696
Potassium chloride, USP	----- (b)(4) ----- -----	ANDA 19-696
Magnesium chloride, USP	----- (b)(4) ----- -----	ANDA 19-696
Sodium phosphate dibasic heptahydrate, USP	----- ----- (b)(4) ----- -----	ANDA 19-696
Sodium gluconate, USP	Not described in NDA	DMF (b)(4), ANDA 19-696
Monobasic potassium phosphate, NF	----- ----- ----- (b)(4) ----- -----	ANDA 19-696

CMC Assessment Section

Evaluation: Acceptable. The drug substance manufacturing information was reviewed for completeness and consistency with approved ANDA 19-696. The information was deemed sufficient to support the pending application for all drug substances.

Of note, the initial NDA did not provide a valid right of reference to –(b)(4)-- DMFs for sodium chloride and potassium chloride for review. Therefore, the application was deficient with respect to information on the method of synthesis for these drug substances per 21 CFR 314.50 (d)(1)(i).

In response to the 27 Aug 2010 quality information request, the applicant submitted details on the manufacture of the sodium chloride and potassium chloride drug substances (i.e., NDA amendment 16 Nov 2010). The manufacturing process information was deemed sufficient to support approval for the proposed change in indication.

S.2.3 Control of Materials

All drug substances are tested for compliance with USP and NF monographs. Analytical methods used for the control of raw materials are the same as those in approved ANDA 19-696.

S.2.4 Controls of Critical Steps and Intermediates

Manufacturing process information submitted in the NDA were reviewed. There were no changes proposed to approved sources of raw materials. Referenced DMFs were reviewed, where applicable.

S.2.5 Process Validation and/or Evaluation

Not applicable. Methods are described in the current USP/NF, without modification.

S.2.6 Manufacturing Process Development

Not applicable.

S.3 Characterization

S.3.1 Elucidation of Structure and other Characteristics

The drug substances are widely used in pharmaceutical and chemical preparations, and the physical and chemical properties are well-understood

S.3.2 Impurities

The drug substances are widely used in pharmaceutical and chemical preparations, and the physical and chemical properties are well-understood

CMC Assessment Section

S.4 Control of Drug Substance

S.4.1 Specification

All drug substances are tested for compliance with USP and NF monographs.

S.4.2 Analytical Procedures

Analytical methods used for the control of the drug substance are described in the relevant USP/NF monographs. These are the same methods as those in approved ANDA 19-696, with appropriate updates for monograph changes.

S.4.3 Validation of Analytical Procedures

Not applicable.

S.4.4 Batch Analyses

Evaluation: The applicant obtains representative samples from every lot of drug substance received for commercial use. All manufacturer certificate of analyses (COAs) are reviewed for every lot received. For commercial lot release, the applicant either fully tests each lot of material according to their specification or utilizes a vendor COA program. The program includes sampling lots, reviewing COAs, and performing routine tests per the applicants internal SOPs. A minimum of (b)(4) lot of each material is evaluated annually. Batch data were submitted for 3 annual requalification runs. There were no noticeable trends in changes in drug substance quality. All qualification data were in compliance with USP/NF quality limits.

S.4.5 Justification of Specification

Not applicable.

S.5 Reference Standards or Materials

Not applicable.

S.6 Container Closure System

Submitted data on container closure systems for each drug substance is summarized in the table below.

Drug Substance	Container Closure System	References
Sodium Chloride, USP	---(b)(4)---	ANDA 19-696
Sodium acetate trihydrate, USP	---(b)(4)---	ANDA 19-696
Potassium chloride, USP	---(b)(4)-----	ANDA 19-696

CMC Assessment Section

Drug Substance	Container Closure System	References
Magnesium chloride, USP	----(b)(4)---	ANDA 19-696
Sodium phosphate dibasic heptahydrate, USP	----(b)(4)---	ANDA 19-696
Sodium gluconate, USP	----(b)(4)---	DMF (b)(4), ANDA 19-696
Monobasic potassium phosphate, NF	----(b)(4)---	ANDA 19-696

Evaluation: NDA BN090067 did not include full details on the container closure system for each active. No information on material composition, quality control, or compliance with applicable food contact regulations is provided; however, all drug substance suppliers certify that the container closure systems for the their respective drug substance complies with USP/NF requirements and are suitable for its intended use. Reference was made to ANDA 19696 (valid letter of authorization submitted) for chemistry information. The applicant states that the manufacture and packaging of Isoplate Solution is the same as approved product Isolyte S, pH 7.4. For the ease of review, quality information was requested as noted in the Mid-Cycle Review Memo of 10 Nov 2010, captured below.

Provide complete details on the container closure system (i.e., materials of composition, suitability, and quality control) for the following drug substances: sodium chloride, sodium acetate trihydrate, potassium chloride, magnesium chloride, sodium phosphate dibasic heptahydrate, and monobasic potassium phosphate. A statement of compliance with the appropriate indirect food contact regulations may be sufficient to establish the safety of the materials used.

At the time of this report, no updates were received from the applicant for the above request. DMF (b)(4) for sodium gluconate was reviewed by this reviewer (8 Dec 2010) and found adequate to support this NDA. As noted previously, the applicant has included a reference to ANDA 19696 for manufacturing and packaging information and has stated that there are no changes from approved processes. Given this, the adequacy of the drug substance container closure information can be inferred from the Agency's previous finding of acceptability for ANDA 19696. Therefore, this deficiency is not an approvability issue.

S.7 Stability

S.7.1 Stability Summary and Conclusions

The stability of each drug substance is determined based on the supplier's certificate of analysis. Each vendor is qualified by the applicant and products are routinely tested for compliance with product specifications. The expiration/re-test period for each drug substance is as follows, as noted by the applicant.

- Sodium Chloride, USP — -----(b)(4)-----.
- Sodium acetate trihydrate, USP — --(b)(4)--
- Postassium chloride, USP — ---(b)(4)---
- Magnesium chloride, USP — ---(b)(4)---
- Sodium phosphate dibasic heptahydrate, USP — --(b)(4)---

CMC Assessment Section

- Sodium gluconate, USP — ---(b)(4)----
- Monobasic potassium phosphate, NF — --(b)(4)--

Evaluation: The drug substance re-testing periods summarized above are considered adequate based on the known chemical and physical properties of the substances. Most of the listed drug substances were deemed by the manufacturer to have “indefinite” stability on the certificates of analyses, and the retest period established by B. Braun is considered sufficient to assure the quality of the product for continued use in drug product manufacturing.

S.7.2 Postapproval Stability Protocol and Stability Commitment

Not applicable.

S 7.3 Stability Data

No stability data are submitted. The applicant relies on the supplier’s certificate of analysis with respect to product expiry. The same products are currently used for approved Isolyte S pH 7.4, ANDA 19-696, which is the same formulation.

CMC Assessment Section

P DRUG PRODUCT**P.1 Description and Composition of the Drug Product**

The drug product is a sterile, nonpyrogenic multiple electrolyte solution, packaged in B. Braun's EXCEL container. Compositional information for a 100 mL volume is summarized in the table below.

Isoplate Solution Formulation Table

Component	Compendial Status	Function	Quantity g/100mL
Sodium Chloride USP	USP	Active Pharmaceutical Ingredient	0.53
Sodium Gluconate USP	USP	Active Pharmaceutical Ingredient	0.5
Sodium Acetate Trihydrate USP	USP	Active Pharmaceutical Ingredient	0.37
Potassium Chloride USP	USP	Active Pharmaceutical Ingredient	0.037
Magnesium Chloride Hexahydrate USP	USP	Active Pharmaceutical Ingredient	0.03
Dibasic Sodium Phosphate Heptahydrate USP	USP	Active pharmaceutical ingredient	0.012
Monobasic Potassium Phosphate NF	NF	Active Pharmaceutical Ingredient	0.0082
Water for Injection USP	USP	Inactive Ingredient/Solvent ¹	q.s.
Glacial Acetic Acid USP	USP	Inactive Ingredient/pH Adjustment	As required to adjust pH
Sodium Hydroxide NF	NF	Inactive Ingredient/pH Adjustment	As required to adjust pH

Source : NDA BN090067 Section 3.2.P.1.1 Table 1.

Evaluation: Consistency of the information was verified with ANDA 19-696. The formulation is the same as marketed Isolyte S, pH 7.4 by the same applicant.

P.2 Pharmaceutical Development

The applicant states that the formulation, with target fills (overfills), specifications, analytical procedures, stability, container closure testing, manufacturing processes, including sterilization validation, have been defined and approved by FDA in ANDA 19-696. As such a pharmaceutical development section is not applicable for NDA BN090067.

Evaluation: Acceptable. No pharmaceutical development work was warranted to support the proposed new indication for Isoplate Solution.

CMC Assessment Section

P.2.1 Components of the Drug Product**P.2.1.1 Drug Substance**

Not applicable.

P.2.1.2 Excipients

Not applicable.

P.2.2 Drug Product**P.2.2.1 Formulation Development**

Not applicable.

P.2.2.2 Overages

No overages were indicated for the manufacturing process. The fill volume for the 500 mL container is -----(b)(4)----- to compensate for water vapor loss through the container during shelf-life. The applicant notes that these fill volumes were approved by FDA on 15 August 2006 for ANDA 19696 S024.

Evaluation: Acceptable. Consistency of the information was verified with previously approved ANDA 19696 S024.

P.2.2.3 Physicochemical and Biological Properties

Not applicable.

P.2.3 Manufacturing Process Development

Not applicable.

P.2.4 Container Closure System

Not applicable.

P.2.5 Microbiological Attributes

Not applicable.

P.2.6 Compatibility

Not applicable.

P.3 Manufacture**P.3.1 Manufacturers**

CMC Assessment Section

The drug product manufacture(s) are summarized below.

Manufacturer	Registration No.	Responsibilities
B. Braun Medical Inc. 2525 McGaw Avenue Irvine, CA 92614	CFN - 2021236	Drug product manufacturing, processing, packaging, labeling, testing and stability.

Manufacturer certifies to compliance with cGMPs.

Evaluation: Facility inspections are managed by CBER and the compliance status is not captured in this review.

P.3.2 Batch Formula

Clinical trial material was manufactured using a ----(b)(4)---- and yielded a batch size of (b)(4)- units. The maximum batch size capability at B. Braun for this product is ---(b)(4)- which is proposed for commercial manufacturing. Batch formula information is summarized in the table below.

Isoplate Batch Formula Table

Ingredients	Quantity - Registration Batch J8H537 (2,000L)	Quantity - Proposed Commercial Batch (20,000L)
Sodium Chloride USP	(b)(4)	(b)(4)
Sodium Acetate Trihydrate USP		
Potassium Chloride USP		
Magnesium Chloride Hexahydrate USP		
Dibasic Sodium Phosphate Heptahydrate USP		
Monobasic Potassium Phosphate NF		
Sodium Gluconate USP		
Water for Injection		
Glacial Acetic Acid USP	pH adjustment	pH adjustment
Sodium Hydroxide NF	pH adjustment	pH adjustment

Evaluation: The applicant states that there are no changes in the batch formula for Isolate Solution compared with Isolyte S, pH 7.4 (multi-electrolyte injection). Consistency of the information with ANDA 19696 was verified. The -(b)(4)- scale is compositionally proportional to the ---(b)(4)---

P.3.3 Description of Manufacturing Process and Process Controls

Isoplate Solution is manufactured by using a ----(b)(4)----- process identical to that of marketed Isolyte S, pH 7.4 (multi-electrolyte injection). The facility, equipment, and processing controls are also the same. No reprocessing is performed on the bulk, in-process, or finished drug product that does not meet established specifications. The applicant’s submitted general schema is provided in Figure 1.

CMC Assessment Section

1 page redacted due (b)(4)

CMC Assessment Section

Evaluation: The description of the manufacturing process provided sufficient detail to understand the process and controls. Process sterilization and packaging is not covered by this review. Refer to CBER Product Quality Reviews.

P.3.4 Controls of Critical Steps and Intermediates

Critical steps controlled during the manufacturing process include:

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

Evaluation: Acceptable. Only the -----(b)(4)----- procedures were reviewed. The packing of the sterilizer and controls for the sterilization process is covered by CBER’s Product Quality Reviewer (Nawab Siddiqui).

P.3.5 Process Validation and/or Evaluation

The manufacturing process for Isoplate Solution is the same as for approved Isolyte S, pH 7.4, which has been validated in support of marketing approval for ANDA 19-796. The applicant has resubmitted all validation reports previously submitted for ANDA 19-796. The product name in the reports is Isolyte S pH 7.4. These reports were not re-reviewed by this reviewer. Given that there are no new changes, the acceptability of validation is inferred from the Agency’s action on ANDA 19-796. Ongoing validation studies throughout the product’s life cycle will be managed by CBER’s GMP compliance activities.

P.4 Control of Excipients

P.4.1 Specifications

Excipients in the drug product include water for injection USP, sodium hydroxide NF and glacial acetic acid USP.

CMC Assessment Section

Water for Injection USP: Excipient is manufactured at B. Braun by using -----
-----(b)(4)----- . Release specification conforms to current USP ---(b)(4)----
guidelines and includes tests for -----(b)(4)-----
----- . Only editorial changes were noted between the specification used for IND
studies compared with the commercial process (i.e., “passes” to “conforms”).

Sodium Hydroxide NF: Excipient is supplied by -----(b)(4)----- . Sodium
hydroxide is used for pH adjustment, which was not necessary for IND batch -(b)(4)-. B.
Braun performs annual qualification testing on all lots of sodium hydroxide according to
the NF criteria, with routine testing for identification, assay, appearance and -----
(b)(4)----- .

A copy of a representative COA was included in the NDA to verify compliance with NF
quality standards.

Glacial Acetic Acid USP: Excipient is supplied by -----(b)(4)----- . Glacial acetic
acid is used for pH adjustment, which was not necessary for IND batch (b)(4). The
manufacturer’s specification conforms to current USP ----(b)(4)---- guidelines. B. Braun
performs a minimum of ----(b)(4)----- testing on product lots, after full testing for USP
compliance according to internal sampling procedures. Of note, specification v.6 still
uses “passes” terminology, instead of conforms which is not consistent with changes
made for other specification sheets. This is just an observation and not a review issue,
however.

Evaluation: Adequate.

P.4.2 Analytical Procedures

Analytical procedures are in accordance with the applicable USP/NF monograph.

Evaluation: USP/NF analytical procedures are adequate for excipient evaluation.

P.4.3 Validation of Analytical Procedures

Not applicable since compendial methods are employed, without modification.

P.4.4 Justification of Specifications

Specifications are defined by the current USP/NF monograph, where applicable.

Evaluation: References to the current USP/NF monographs, where applicable, are
considered adequate for the proposed drug product components.

P.4.5 Excipients of Human or Animal Origin

All raw materials were certified as not being from human or animal origin.

CMC Assessment Section

P.4.6 Novel Excipients

There are no novel excipients in the formulation.

P.5 Control of Drug Product

P.5.1 Specification

The proposed drug product regulatory specification is summarized below.

Drug Product Specification				
Test	Method	Acceptance Criteria		
		(b)(4)	----(b)(4)----- -	-----(b)(4)----- --
Physical	----- ---(b)(4)----- -			--(b)(4)----
Label	----- ---(b)(4)-----		----(b)(4)-----	
Total Chloride, %w/v	----- ---(b)(4)-----	----- ---(b)(4)---- ----	----- ---(b)(4)---- ----	----- ---(b)(4)---- ----- ----- --
Sodium, mEq/L	----- ---(b)(4)-----			----- ---(b)(4)--- ----- ---(b)(4)---
	----- ---(b)(4)-----	----- ---(b)(4)---- ----		
Potassium, mEq/L	----- ---(b)(4)-----			----- ---(b)(4)---- ----- ---(b)(4)---
	----- ---(b)(4)-----	----- ---(b)(4)---- ----		
Magnesium, ppm	----- ---(b)(4)----- ----	----- ---(b)(4)---- ----		----- ---(b)(4)---- ----- ---(b)(4)---
Phosphate, % w/v	----- ---(b)(4)----- -----	----- ---(b)(4)---- ----		----- ---(b)(4)---- ----- ---(b)(4)---
Acetate, mEq/L	(b)(4)			----- ---(b)(4)---- ----- ---(b)(4)---
Gluconate, mEq/L	(b)(4)			----- ---(b)(4)---- ----- ---(b)(4)---
Heavy Metals, Pb, ppm	---(b)(4)---			(b)(4)
pH	---(b)(4)---	----- ---(b)(4)---- ---		----- ---(b)(4)----
Identification	---(b)(4)---- --- (b)(4)---- --- (b)(4)----	---(b)(4)----		-(b)(4)- -(b)(4)- ----(b)(4)-----
Acetate	---(b)(4)----			-(b)(4)-
Gluconate	---(b)(4)----			-(b)(4)-
Dextrose	---(b)(4)----			-(b)(4)-
Phosphate	---(b)(4)----			-(b)(4)-

CMC Assessment Section

Evaluation: Adequate. -----(b)(4)----- was revised in 2008. The applicant has not commented on any modifications which may impact the current sampling methodology; however, the guideline indicates that the 2008 edition was a reaffirmation of 2003, so there were no major changes. The proposed drug product specification and analytical methods were not changed from those used for clinical studies or those approved for Isolyte S, pH 7.4. The sampling size was --(b)(4)--- for -----(b)(4)----- test and editorial changes for product names or obsolete tests highlight the main reasons for the revising the Isolyte S, pH 7.4 specification.

Drug product specifications are adequate from the perspective of ensuring the identity, strength, and chemical purity of the finished product. Overall acceptability is under the purview of CBER, as sterility assurance, extractables and leachables must be accounted for. The adequacy of the sampling plan, and product integrity testing is also handled by CBER.

P.5.2 Analytical Procedures

Evaluation: Adequate descriptions were provided.

P.5.3 Validation of Analytical Procedures

Evaluation: Analytical procedures for Isoplate Solution are the same as for approved Isolyte S, pH 7.4, which has been validated in support of the marketing approval. The validated methods were used for the quality control of clinical trial material. The applicant has resubmitted all validation reports previously submitted for ANDA 19-796. The product name in the reports is Isolyte S pH 7.4. These reports were not re-reviewed by this reviewer. Given that there are no new changes, the acceptability of validation is inferred from the Agency's approval action on ANDA 19-796.

P.5.4 Batch Analyses

Evaluation: Only (b)(4) of Isoplate Solution, 500 mL, was manufactured for IND studies. The certificate of analysis for this ----(b)(4)--- was submitted. To support the applicant's proposal for a 24 month expiration dating period, stability data from annual stability lots for Isolyte S, pH 7.4 (500 mL size) were also submitted.

P.5.5 Characterization of Impurities

Not applicable.

P.5.6 Justification of Specification

Evaluation: Specifications were justified based on the available data for approved Isolyte S, pH 7.4., which is the same product.

CMC Assessment Section

P.6 Reference Standards or Materials

Evaluation: Adequate descriptions were provided.

P.7 Container Closure System

The acceptability of the container closure system is assessed by CBER and is not covered in this review. Compositional information is excerpted below only for reference.

CMC Assessment Section

Table 12. EXCEL® Plastic Container Composition Overview*

Primary Bag film:	(b)(4)
Saddle:	
Set Port Cover:	
Medication Stopper:	
Overwrap Film:	

*Material Qualification for EXCEL® Plastic Container components is located in B. Braun DMF (b)(4) A letter of authorization to DMF(b)(4) is located in Module 1.4.1.

Evaluation: Not evaluated by this reviewer.

P.8 Stability

P.8.1 Stability Summary and Conclusion

Stability data were submitted for IND lot -----(b)(4)-----, and (b)(4) other commercial lots (Isolyte S, pH 7.4). There were no trends in any stability parameter through 24 months storage at room temperature. Of note, stability studies are performed in the inverted position as this represents the worst case scenario for the product. Quality parameters monitored on stability include -----(b)(4)----- pH, -----(b)(4)-----.

Evaluation: Stability data support the proposed expiration dating period of 24 months, from a chemical perspective (i.e., no degradation of actives or changes in pH); however, final recommendations on product stability is deferred to CBER because sterility and container integrity must be considered.

P.8.2 Postapproval Stability Protocol and Stability Commitment

The applicant plans to continue with the ongoing post approval stability protocol for Isolyte S, pH 7.4. As such, only (b)(4) representative lot of either Isoplate Solution or Isolyte S, pH 7.4, 500 mL will be placed on commercial stability each year. If no production lots covered by this NDA are manufactured in a given year, then a production lot will not be manufactured for the stability program in that year.

Evaluation: The applicant’s proposal is acceptable.

CMC Assessment Section

P.8.3 Stability Data

Adequate data summaries were provided to support the long term stability of the product.

A APPENDICES**A.1 Facilities and Equipment (---(b)(4)-----only)**

Not applicable.

A.2 Adventitious Agents Safety Evaluation

There were no substances of animal origin used in the drug substance manufacturing process.

A.3 Novel Excipients

There are no novel excipients in the formulation.

R REGIONAL INFORMATION**R1 Executed Batch Records**

Executed batch records were submitted in compliance with regulatory requirements; however, an assessment of these records is not covered in this review.

R2 Comparability Protocols

Not applicable.

R3 Methods Validation Package

Comments on analytical methods were included in previous sections, as appropriate. An FDA lab evaluation of analytical methods was not performed since the application's analytical methods do not meet the criteria for evaluation per current Office of New Drug Quality Assessment policy.



CMC Assessment Section

CMC Assessment Section

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling was reviewed from ONDQA’s chemistry, manufacturing, and controls perspective; however, final labeling is managed by CBER’s review team. Versions reviewed, 9 June 2010, SN000.

A. Labeling & Package Insert

1. Package Insert

(a) Highlights of Prescribing Information Section

Title Section:

Isoplate Solution

Initial U.S. Approval: 2010

Dosage Forms and Strengths:

500 mL bag (3)

Evaluation: This section is not satisfactory, see below.

Item	Comments on the Information Provided in NDA
Drug name (201.57(a)(2))	
Proprietary name and established name	Established name Multiple Electrolytes Injection Type 1 is not in the title. Not Satisfactory. Isoplate Solution should be revised to “Isoplate Solution (multiple electrolyte injection type 1)” or similar format
Dosage form, route of administration	Not indicated in the title section. Not Satisfactory. Information stated above should be added.
Controlled drug substance symbol (if applicable)	Not applicable
Dosage Forms and Strengths (201.57(a)(8))	
Whether the drug product is scored	Not applicable
Dosage form and strength	Dosage form is listed as 500 mL bag, which is not correct. The dosage form “injection” and strength of active ingredients should be specified. Not Satisfactory.

Note: The following comment was communicated in mid-cycle review memo of 11 Nov 10 for communication to the sponsor.

The draft labels and labeling do not comply with the established name requirements as per 21 CFR 201.10. Submit revised labels and labeling that

CMC Assessment Section

include the drug’s established name, multiple electrolytes injection type I, as defined by the USP monograph.

No response was received from the applicant at the time of this report.

(b) “Full Prescribing Information” Section

3: Dosage Forms and Strengths

Isoplate Solution in the EXCEL Container

<i>NDC</i>	<i>Cat. No.</i>	<i>Volume</i>
0264-7771-10	L7771	500 mL

Evaluation: This section is not satisfactory, see below.

Item	Comments on the Information Provided in NDA
Available dosage forms	Proper dosage form and strength is not listed. Applicant should also add (multiple electrolyte injection type 1) next to proprietary name unless in running text to satisfy the requirements of 21 CFR 201.10(g)(1) and 21 CFR 201.57(c)(4)(i). Not satisfactory.
Strengths: in metric system	Not Satisfactory. See comment above.
Active moiety expression of strength with equivalence statement (if applicable)	Not applicable.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Proprietary name notes that product is a solution in a Excel container, which is an acceptable description. However, this section includes the NDC code, which is not acceptable per 21 CFR 201.57(c)(4)(ii). The catalog number should also be removed. Not satisfactory. Applicant should delete NDC and catalog numbers.

The Dosage Forms and Strength Section does not satisfy the regulatory requirements for content and format.

#11: Description

Isoplate Solution is sterile, nonpyrogenic, and contains no bacteriostatic or antimicrobial agents. Isoplate Solution is indicated as a platelet additive solution for the storage of hyperconcentrated leukoreduced apheresis platelets collected on CaridianBCT’s Trima Accel® System under standard blood banking conditions. The formulas of the active ingredients are provided in Table 1.

Table 1: Active Ingredients		
Ingredients	Molecular Formula	Molecular Weight
<i>Sodium Chloride USP</i>	<i>NaCl</i>	58.44

CMC Assessment Section

Table 1: Active Ingredients		
Ingredients	Molecular Formula	Molecular Weight
Sodium Acetate Trihydrate USP	$CH_3COONa \cdot 3H_2O$	136.08
Potassium Chloride USP	KCl	74.55
Magnesium Chloride Hexahydrate USP	$MgCl_2 \cdot 6H_2O$	203.30
Dibasic Sodium Phosphate Heptahydrate USP	$Na_2HPO_4 \cdot 7H_2O$	268.07
Monobasic Potassium Phosphate NF	KH_2PO_4	136.09
Sodium Gluconate USP		218.14

Each 100 mL of Isoplate Solution contains: Sodium Chloride USP 0.53 g; Sodium Gluconate USP 0.5 g; Sodium Acetate Trihydrate USP 0.37 g; Potassium Chloride USP 0.037 g; Magnesium Chloride Hexahydrate USP 0.03 g; Dibasic Sodium Phosphate Heptahydrate USP 0.012 g; Monobasic Potassium Phosphate NF 0.00082 g; Water for Injection USP qs

pH may be adjusted with Glacial Acetic Acid USP or Sodium Hydroxide NF
 pH: 7.4 (7.0-7.8)

Calculated Osmolarity: 295 mOsmol/liter

Concentration of Electrolytes (mEq/liter): Sodium 141; Potassium 5; Magnesium 3; Chloride 98; Phosphate (HPO_4^-) 1 (0.5 mmole P/liter); Acetate (CH_3COO^-) 27; Gluconate ($HOCH_2(CHOH)_4COO^-$) 23

The EXCEL Container is.....additional text on the container following has been omitted from this review.
 Review Note: The description section of this label pertaining to the EXCEL Container is deferred to CBER because product packaging was not covered by this reviewer.

Evaluation: The Description Section is not satisfactory, see below.

Item	Comments on Information Provided in NDA
Proprietary name and established name	Proprietary name Isoplate Solution is listed; however, the established name is not listed. Not Satisfactory. Established name is required per 21 CFR 201.57(c)(12)(A). Applicant should revise to include “multiple electrolyte injection”
Dosage form and route of administration	Labeling indicates that the product is for platelet storage, but it does not reference the end use of the processed product which is intravenous. Revision of this section to include the established name as required (multiple electrolyte injection type 1) will satisfy this requirement.

CMC Assessment Section

Item	Comments on Information Provided in NDA
	Not satisfactory.
Active moiety expression of strength with equivalence statement (if applicable)	Not applicable.
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names (if any) in alphabetical order (USP (b)(4))	Water is the principal excipient and is listed. The product may also contain glacial acetic acid or sodium hydroxide for pH adjustments. Satisfactory.
Statement of being sterile (if applicable)	Sterile statement is included. Satisfactory.
Pharmacological/ therapeutic class	Listed as platelet storage Satisfactory.
Chemical name, structural formula, molecular weight	Structural and chemical information on the drug substances is provided as required. Satisfactory.
If radioactive, statement of important nuclear characteristics.	Not applicable
Other important chemical or physical properties (such as pKa or pH)	Osmolarity and electrolyte information, as required per USP, is also in the labeling. Satisfactory.

#16: How Supplied/Storage and Handling

Isoplate Solution is supplied sterile and nonpyrogenic In EXCEL Containers. The 500 mL containers are packaged 24 per case.

Storage

Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (between 59°F and 86°F). [See USP Controlled Room Temperature.]

Rx only

Issued: January 2010

EXCEL is a registered trademark and Isoplate is a trademark of B. Braun Medical Inc. Trima Accel is a registered trademark of CaridianBCT Inc.

B. Braun Medical Inc.

Irvine, CA 92614-5895 USA

Made in USA

Evaluation: This section is not satisfactory, see below.

Item	Comments on Information Provided in NDA
Strength of dosage form	Strength should be expressed in terms of the drug substance and not container volume. Not Satisfactory.
Available units (e.g., bottles of 100 tablets)	500 mL bag/ 24 per case. Satisfactory.

CMC Assessment Section

Item	Comments on Information Provided in NDA
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	<p>Dosage form is not properly identified. Volume and container is specified. NDC numbers, if used, should be included in this section.</p> <p>Not Satisfactory. The established name should be specified after the proprietary name. Other identifying information such as the NDC number and catalog number should be listed here.</p>
Special handling (e.g., protect from light)	Not applicable.
Storage conditions	<p>Store under USP Controlled Temperatures. Storage conditions listed are supported by product stability data.</p> <p>Satisfactory.</p>
Manufacturer/distributor name (21 CFR 201.1(h)(5))	<p>Manufacturer's name is listed.</p> <p>Satisfactory.</p>

CMC Assessment Section

Item	Comments on Information Provided in NDA
Lot number and expiration date (21 CFR 201.17 and 21 CFR 211.137)	<p>Satisfactory.</p> <p>Location is not stated above; however, the executed batch record was referenced for a copy of a completed label. The record shows that an expiration date and lot number is stamped at the bottom of the display panel during manufacture.</p> <p>The applicant will be recommended to include the location of the lot number and expiration date in label proofs.</p> <p>Satisfactory.</p>
Storage conditions	<p>Storage conditions specified are supported by NDA data. USP controlled room temperature.</p> <p>Satisfactory.</p>
Bar code (21CFR 201.25)	<p>Not addressed in label submitted.</p> <p>Not Satisfactory.</p>
Name of manufacturer/distributor	<p>B. Braun's information is listed.</p> <p>Satisfactory.</p>
And others, if space is available	-

3. Carton labeling

The product is not packed in individual cartons. Twenty-four 500 mL containers are packaged in a single case. No labeling was submitting for the case. The product's case labeling should be submitted for review.

B. Environmental Assessment Or Claim Of Categorical Exclusion

Not addressed in this review. Refer to CBER's quality assessment.

III. List Of Deficiencies to be Communicated

NDA 090067 has provided sufficient information to assure identity, strength, purity, and quality of the drug product with respect to the chemistry, manufacturing, and controls sections covered by ONDQA's consult review. However, the product labeling and labels do not have adequate information as required.

The following labeling comments should be conveyed to the applicant.

1. The draft labels and labeling do not comply with the requirements of 21 CFR 201. Submit revised labeling that include the following revisions:
 - a. Highlights Section:

CMC Assessment Section

- i. Add the drug's established name, multiple electrolytes injection type 1 USP, as defined by the USP monograph, to the title.
 - ii. "500 mL bag" should be revised to include the proper dosage form, which is injection, and strength of each drug substance.
- b. Full Prescribing Information – Dosage Forms and Strengths Section:
 - i. The NDC and catalog number should be deleted as per 21 CFR 201.57(c)(4). This information is more appropriate for the How Supplied/Storage and Handling Section.
 - ii. Revise this section to properly indicate the proper dosage form, which is injection, and strength of each drug substance.
- c. Full Prescribing Information – Description Section:
 - i. The established name should be listed adjacent to the proprietary name.
- d. Full Prescribing Information – How Supplied/Storage and Handling Section:
 - i. The dosage form and strength are not properly displayed. Revise this section to properly indicate the proper dosage form, which is injection, and strength of each drug substance.
- e. Established name should be added to the immediate container label, immediately following the proprietary name. The font size should be at least 50% of the proprietary name.
- f. The Rx only statement on the immediate container should be more prominently displayed. We recommend that you either increase the font size or consider bolded text.
- g. Indicate the location of the lot number and expiration date on the draft label.
- h. Remove "REF L7771" from the label's header information.
- i. Submit information on how you plan to satisfy the bar code label requirements for the immediate container.
- j. Provide a copy of the labels intended for the case used for packaging and distributing the finished product.

IV. Attachments

None.