

CMC Review Addendum, February 24, 2011 - Isoplate Solution

CONSULT REVIEW OF NDA BN090067

Class 2 Resubmission

For the Center for Biologics Evaluation and Research, Division of Blood Applications
(Review Addendum)

Date: 24 February 2011

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Office of New Drugs Quality Assessment/CDER

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To: BN090067 Administrative Record

Application: NDA BN090067

Sec. 505(b)(1)

Type 4,6 - Combination Product/New Indication

Class 2 Resubmission of 7 Nov 2011

Product: Isoplate Solution (multiple electrolyte injection type 1, platelet additive solution)

Applicant: B. Braun Medical

SUMMARY

Reference is made to CMC Review dated 10 Feb 2011 for full details on the chemistry, manufacturing, and controls information reviewed by CDER/ONDQA under the collaborative consult request of 22 June 2010. CMC Review #1 recommended a not approval action for NDA BN090067 on the basis of inadequate information as required by 21 CFR 201. In parallel, the CBER labeling team also issued labeling deficiencies in accordance with 21 CFR 606 and CBER policy. The revised labeling created areas of ambiguity, which were discussed at the Mid-Cycle meeting held on 15 February 2012. At the meeting, the team agreed that CBER, as the product lead division, will handle all areas of the product labeling to ensure clarity and consistency of labeling within this product. Therefore, all outstanding CMC labeling issues no longer serve a basis for a recommendation on approvability.

RECOMMENDATION AND CONCLUSION ON APPROVABILITY

NDA 090067 provided sufficient information to assure the identity, strength, purity, and quality of the drug product. Product labeling will be reviewed by CBER. Therefore, the NDA is recommended for **Approval** from the chemistry, manufacturing, and controls perspective.

Review Comments for CBER Labeling Team's Consideration

The following is a list of labeling deficiencies identified by CDER/ONDQA as per the 21 CFR 201 drug labeling regulations for CBER's consideration. As agreed to at the 15 February 2012 meeting, these deficiencies no longer serve the basis of CDER/ONDQA's approval recommendation. However, the labeling issues are noted in

the administrative record as labeling comments for the CBER review team to consider in their evaluation of the product's labeling.

1. Highlights Section:

- "500 mL bag" is not a recognized dosage form per FDA's Standards Manual and we recommend that the Applicant revise the section to include the proper dosage form. (*As per the Mid-Cycle meeting decisions, CBER will define the dosage form which is recommended as "injection" by CDER/ONDQA. At the Mid-Cycle meeting, CBER indicated they planned to designate the dosage form as "solution" to be consistent with another approved product in the same product class. The section should be revised with CBER's final decision on dosage form.*)

- Additionally, 21 CFR 201 requires that each strength of drug substance is listed in this section (i.e., all salt components).

2. Full Prescribing Information – Dosage Forms and Strengths Section:

- 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.
- The section should properly indicate the designated dosage form and strength of each drug substance.

3. Full Prescribing Information – Description Section:

- The established name, multiple electrolyte injection, should be listed adjacent to the proprietary name. (*As per the Mid-Cycle meeting, CBER plans to use only the proper name Platelet Additive Solution in the labeling as per ISBT and not the established name as per USP*)

4. Full Prescribing Information – How Supplied/Storage and Handling Section:

- The dosage form and strength are not properly displayed.

5. The Rx only statement on the immediate container should be more prominently displayed. CDER/ONDQA recommends that the Applicant increase the font size or consider bolded text.

6. Recommend removing "REF L7771" from the label's header information.

7. The Applicant did not furnish a copy of the labels intended for the case used for packaging and distributing the finished product. We recommend that you request and review this labeling information as well for acceptability.

Any labeling requirement listed above may be waived as per 21 CFR 201.58, if the 201 regulations are applicable and the CBER Review Division deems a waiver appropriate.

REVIEWER'S NOTES (ADDENDUM)

I. REGULATORY BACKGROUND

NDA BN090067 was initially submitted on 9 June 2010 in accordance with Section 505(b) of the FDC Act 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. Isoplate Solution is a sterile, nonpyrogenic, multiple electrolyte solution approved under the trade name Isolyte S, pH 7.4, ANDA 19-796 for use in adults as a source of electrolytes, calories and water for hydration. There were no major changes to the chemistry, manufacturing, and controls processes approved under ANDA 19-796 for the manufacture of Isoplate Solution.

A complete response action was issued on 4 February 2011. The complete response letter was issued in advance of the final CDER/CMC consult review of 10 February 2011. As a result, only CDER/CMC review deficiencies from the mid-cycle review memo of 10 November 2010 were included in the Action letter, which did not include all review comments related to product labeling.

CMC Deficiencies from Action Letter of 4 February 2011.

- Item 8. Provide complete container/closure information for each drug substance.
- Item 9. Update labeling to include the established name as per 21 CFR 201.10.

II. SUMMARY OF CMC ASSESSMENTS

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. In response to the CMC deficiency (Complete Response Letter Item 8), the Applicant provided additional details on the container/closure and safety compliance status for review. All actives, except sodium and potassium chloride, are ----b(4)-----

Each drug substance manufacturer included appropriate statements of compliance with applicable guidelines and regulations for safety. There are no additional CMC review issues regarding the drug substance quality data.

Drug Product: There were no outstanding review issues from review cycle 1 regarding the drug product CMC information reviewed by CDER. Drug product manufacturing and sterility was reviewed primarily by CBER.

Labeling: Revised labeling was submitted in response to CDER/CMC comments on the established name (Complete Response Letter Item 9) and other CBER labeling issues. The revised information was reviewed from CDER/CMC's perspective for compliance with the requirements of 21 CFR 201, which were approvability issues noted in the final CDER/CMC consult review. These deficiencies were discussed with the CBER review team on 15 February 2012. During the meeting, it was decided that CBER will assume the lead review on all aspects of labeling to ensure consistency with other approved products in this drug product class. Therefore, CMC labeling issues are no longer covered under this consult review request and do not form a basis for a recommendation on approvability.

III. REVIEW COMMENTS TO BE COMMUNICATED TO APPLICANT

There are no outstanding CMC review issues. The application is recommended for approval.