CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200582Orig1s000

CHEMISTRY REVIEW(S)

ONDQA MEMO: CMC ASSESSMENT OF NDA 200582

Date:	25-Jan-2011
To:	NDA 200582
From:	Debasis Ghosh, M. Pharm., Ph.D., CMC Reviewer
Through:	Sarah Pope Miksinski, Ph.D., Branch Chief
Subject:	Final CMC recommendation
Documents Reviewed:	SD 16 (03-Dec-2010) and SD 17 (18-Jan-2011)

Background:

The application (NDA 200582) was submitted under 505(b)(2) by Hospira Pharmaceuticals on 29-Oct-2009 to the Division of Drug Oncology Products for the commercialization of Topotecan Injection 4 mg/4 mL (1mg/mL) for the treatment of cancer. The reference listed drug, Hycamtin (topotecan hydrochloride) for injection, was approved on 28-May-2006 under NDA 20671. In a letter dated 26-NOV-2010, the Agency took a "Complete Response" action for the current NDA. The Applicant submitted a 03-Dec-2010 resubmission (SD 16) to address the Agency's Complete Response letter. The Agency subsequently classified the resubmission as a Class 1 resubmission.

GlaxoSmithKline's Hycamtin is supplied as a sterile lyophilized powder. Each vial contains topotecan hydrochloride equivalent to 4 mg of topotecan free base. Upon reconstitution with 4 mL of diluent, the concentration of topotecan free base in the reconstituted solution is 1 mg/mL.

Each vial of the proposed (NDA 200582) Topotecan Injection contains topotecan hydrochloride equivalent to 4 mg of topotecan free base in 4 mL solution with a concentration of 1 mg/mL.

The CMC section of NDA 200582 application was reviewed by this reviewer. Review # 1 (09-Jul-2010), Review # 2 (30-Jul-2010) and Review #3 (19-Nov-2010) are available in DARRTS.

Purpose:
This objective of this memo is to provide:

- A description of the unresolved issues
- Recent response from the applicant and Evaluation by the Agency
- Recommendations and final conclusion

Unresolved Issues:

- Whether an inspection is required for (b) (4)
- Finished dosage packager, Hospira Worldwide Inc, Rocky Mount, NC, had received WITHOLD recommendation from the Office of Compliance on 11-Aug-

2010. This was issued as a deficiency in the Agency's previous Complete Response letter.

- Container, Carton and PI Labels need revision.

Description of the Response and Evaluation:

- The applicant updated Sec 2.1 *Manufacturers* on 06-Oct-2010 as an amendment (SD 013) to include (b) (4) was not listed in the original submission. A recommendation from the Office of Compliance (OC) will be needed to accept this facility.

  Evaluation: Satisfactory
  The application received an updated overall acceptable recommendation from the Office of Compliance on 04-Jan-2011.

- Hospira Worldwide Inc, Rocky Mount NC facility received WITHOLD recommendation from the Office of Compliance on 11-Aug-2011. In a response (SD 16) submitted to the Agency on 03-Dec-2010, the Applicant amended the establishment information and deleted NC facility from the updated list of establishment information. Hospira indicated that all packaging and labeling needs can be completed at Zydus Hospira Oncology Pvt. Ltd. (ZHOPL), India.

  Evaluation: Satisfactory

- The Applicant provided updated container and carton labels in SD 16 (03-Dec-2010).

  Evaluation: Unsatisfactory.
  From CMC perspective, Carton and Container labels are satisfactory. PI label should be updated as per two recommendations issued in the DARRTS Memo (11/19/2010). Based on a discussion with PM (Internal meeting, 18-Jan-2010), the PI changes will be communicated to the Applicant once we receive the updated PI with clinical carve-out information. All other labeling is acceptable, save for the two pending recommendations.

Overall CMC Recommendation and Conclusion:

From the perspective of Chemistry, Manufacturing and Controls (CMC), this NDA is recommended for approval pending satisfactory resolution of labeling (PI) issues.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DEBASIS GHOSH
01/25/2011

SARAH P MIKSINSKI
01/25/2011

ONDQA MEMO: CMC ASSESSMENT OF NDA 200582

Date: 12-Nov-2010
To: NDA 200582
From: Debasis Ghosh, M. Pharm., Ph.D., CMC Reviewer
Through: Sarah Pope Miksinski, Ph.D., Branch Chief
Subject: Final CMC recommendation
Documents Reviewed: SD009, SD013

Background:

The application (NDA 200582) was submitted under 505(b)(2) by Hospira Pharmaceuticals on 29-Oct-2009 to the Division of Drug Oncology Products for the commercialization of Topotecan Injection 4 mg/4 mL (1mg/mL) for the treatment of cancer. The reference listed drug, Hycamtin (topotecan hydrochloride) for injection, was approved on 28-May-2006 under NDA 20671.

GlaxoSmithKline's Hycamtin is supplied as a sterile lyophilized powder. Each vial contains topotecan hydrochloride equivalent to 4 mg of topotecan free base. Upon reconstitution with 4 mL of diluent, the concentration of topotecan free base in the reconstituted solution is 1 mg/mL.

Each vial of the proposed (NDA 200582) Topotecan Injection contains topotecan hydrochloride equivalent to 4 mg of topotecan free base in 4 mL solution with a concentration of 1 mg/mL.

The CMC section of NDA 200582 application was reviewed by this reviewer. Review # 1 (09-Jul-2010) and Review # 2 (30-Jul-2010) are available in DARRTS. Per Review # 2, the CMC Team recommended a not approvable ("Complete Response") status due to unresolved DMF issues.

Purpose:
This objective of this memo is to provide:

- A description of the unresolved issues
- A description of the recent response from the applicant
- Evaluation of the current status of the application
- Recommendations and conclusion

Unresolved Issues:
The CMC information of the drug substance is provided in DMF (b) (4). At the time of the completion of Review # 2 on 27-Jul-2010, the status of DMF (b) (4) was inadequate. Since drug substance, drug product, and labeling issues are all related to the information contained in the DMF (b) (4), the satisfactory resolution of DMF issues was necessary to address outstanding CMC deficiencies in the NDA.

Response from the DMF holder:
(b) (4) the DMF holder, provided a response on 24-Sep-2010 to the Agency to address the deficiencies identified during the DMF review process.

Evaluation of the Response received from the DMF holder:
On 09-Nov-2010, Ann Marie Russell, Ph.D. of ONDQA completed her evaluation of the response from (b) (4) and concluded that the DMF (b) (4) is adequate to support NDA (b) (4). Since the formulations of NDA (b) (4) and NDA 200582 are similar except for the inclusion of tartaric acid as a buffering agent in NDA 200582, DMF (b) (4) is also adequate for the purpose of supporting NDA 200582.

Current Status of the NDA 200582:

- As stated in Sec S.1 *General Information* of Review # 2, the CAS number and IUPAC name of the drug substance were not related to the proposed drug substance manufactured (b) (4) Therefore, the review distinguishes this section as "unsatisfactory". In the DMF (b) (4) provided a new CAS number and IUPAC name.

  Current Evaluation: Satisfactory.

  Based on the updated information from the DMF holder, the CAS number and IUPAC name of the drug are available. The applicant referenced drug substance information to DMF (b) (4). No update of NDA is necessary. For specific information on CAS and IUPAC name, see the 09-NOV-2010 DMF review in DARRTS.

- As stated in Sec S.1.2 *Structure* of Review # 2, the chemical structure, molecular formula, molecular weight (b) (4) The applicant referenced the chemical structure information in DMF (b) (4).

  Current Evaluation: Satisfactory.

  Based on the information received form the DMF holder, the chemical structure of the drug substance is now established. See the 09-NOV-2010 DMF review.

- The applicant updated Sec 2.1 *Manufacturers* on 06-Oct-2010 as an amendment (SD 013) to include (b) (4)

  Evaluation: Unsatisfactory

(b) (4) was not listed in the original submission. A recommendation from compliance will be needed to accept this facility. Due to the overall withhold already issued for this application by the Office of Compliance, this site will not be entered into EES during this review cycle. However, subsequent CMC reviews should confirm that this site is (or is not) proposed as part of a resubmission or response.

- In Sec S. 4.1 *Specification* of Review # 2, the specification for drug substance is related to DMF information. Based on the new information received from the DMF holder, the specification of drug substance needed to be updated. The applicant provided the updated information on 06-Oct-2010 as an amendment to NDA (SD 013).

  Current Evaluation: Satisfactory.

  See Appendix II for the updated specification for topotecan hydrochloride. Two changes have been noted. (b) (4)

- As stated in Sec 4.5 *Justification of Specification* of Review # 2, the chloride content information needed to be based on the new information received form the DMF holder. The applicant provided the updated information on 06-Oct-2010 as an amendment to NDA (SD 013).

  Current Evaluation: Satisfactory.

  The applicant updated chloride content information based on the molar ratio of HCl used to produce topotecan hydrochloride salt as per the manufacturing process of the supplier.

- As stated in Sec 7.3 *Stability Data* of Review # 2, the stability information should be updated based on the new information received from the DMF holder. The applicant referenced the stability information in the DMF (b) (4) (b) (4)

  Evaluation: Satisfactory.

  (b) (4)

- In Sec P.3.3 *Description of Manufacturing Process and Process Controls* of Review # 2, the drug substance information should be updated based on the

new information received from the DMF holder. The applicant referenced drug substance information in DMF (b) (4).

Evaluation: Satisfactory.

Since applicant indicated that the amount of drug substance (topotecan hydrochloride) to be charged for the manufacturing process is calculated based on the assay of topotecan in the supplied drug substance as well as the amount of (b) (4) present in that particular batch. Hence the change of specification for (b) (4) will not affect the protocol for the manufacturing procedure.

Labeling and Package Insert:

- See Appendix III for the proposed changes for Section 11.
- See Appendix IV for other minor changes in PI.

Overall CMC Recommendation and Conclusion:

From the perspective of Chemistry, Manufacturing and Controls (CMC), this NDA is recommended for a "CR" action due to an overall withhold recommendation issued 11-AUG-2010 from the Office of Compliance.

APPENDIX I

Updated (06-Oct-2010) Drug Substance Sec 2.1.

Site Name	Site Address	Telephone Number	Site Contact	Registration Number (CFN)	Drug Master File Number (DMF)	Manufacturing Steps and/or Type of Testing (i.e., Final dosage form, Stability Testing)	Ready for Inspection (Yes or No*)
(b) (4)							
Zydus Hospira Oncology Private Ltd (ZHOPL)	Pharmez, Special Economic Zone Plot No. 3, Matoda, Sarkhej Bavla Hwy., Taluka Sanand, District Ahmedabad – 382213 Gujarat, India	Tel: +91 (0) 2717 663300 Cell: +91 (0) 9974 051838 Fax: +91 (0) 2717 663100 Email: vikramshukla@zydushospira.com	Vikram B Shukla	3007869619	NA	Acceptance testing	Yes
(b) (4)							

APPENDIX II

Updated (06-Oct-2010) Sec S.4.1 *Specification* for topotecan hydrochloride

Test	Acceptance Criteria	Regulatory Analytical Procedure
(b) (4)		

APPENDIX III

NDA 200582

Current PI Version (SD 009, Aug-11-2010)

11 DESCRIPTION

(b) (4)

Proposed Changes in RED: (as of 09-Nov-2010)

11. Description

(b) (4)

Appendix IV

In addition to changes in Sec 11, following changes are to be made in PI to harmonize all Topotecan PIs..

- From 'HIGHLIGHTS OF PRESCRIBING INFORMATION' **cut** the following sentence (b) (4)

- From Sec 16 How Supplied Storage and Handling **cut** the following sentence (b) (4)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DEBASIS GHOSH
11/19/2010

SARAH P MIKSINSKI
11/19/2010

NDA 200582

Topotecan Injection
4mg/4 mL
(1 mg/mL)

Hospira, Inc

Debasis Ghosh, M. Pharm., Ph.D.

Review Chemist

Office of New Drug Quality Assessment
Division I
Branch II

CMC REVIEW # 2 OF NDA 200582
For the Division of Drug Oncology Products

CMC Review Data Sheet

1. NDA 200582

2. REVIEW #: 2

3. REVIEW DATE: 27-Jul-2010

4. REVIEWER: Debasis Ghosh, M. Pharm., Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
RTF Letter (NDA (b) (4))	21-Aug-2010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original NDA Submission	29-OCT-2009
Amendment SD 001	11-FEB-2010
Amendment SD 003	22-MAR-2010
Amendment SD 005	30-APR-2010
Amendment SD 006	01-JUN-2010
Amendment SD 007	19-JUL-2010

7. NAME & ADDRESS OF APPLICANT:

Name:	Hospira, Inc
Address:	275 North Field Drive, Dept 0389, Bldg H2-2, Lake Forest, IL 60045, USA
Representative:	Wendy Tian
Telephone:	224-212-6163

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name: Topotecan Injection
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 5 (new formulation)

- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2);
   - The Reference Listed Drug (RLD) is Hycamtin (topotecan hydrochloride) for Injection - NDA 20671 was approved on 28-May-2006.
   - GlaxoSmithKline's Hycamtin is supplied as a sterile lyophilized powder. Each vial contains topotecan hydrochloride equivalent to 4 mg of topotecan base. Upon reconstitution with 4 mL of diluent, the concentration of reconstituted solution is 1 mg/mL.
   - Each vial of the proposed Topotecan Injection contains 4 mg topotecan hydrochloride equivalent to 4 mg of topotecan base in 4 mL solution with a concentration of 1 mg/mL.

10. PHARMACOL. CATEGORY: Anticancer

11. DOSAGE FORM: injection, solution

12. STRENGTH/POTENCY: 4 mg/4 mL (1 mg/mL) (The drug product strength is based on the equivalent amount of topotecan free base)

13. ROUTE OF ADMINISTRATION: Injection, Intravenous

14. Rx/OTC DISPENSED: __√__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

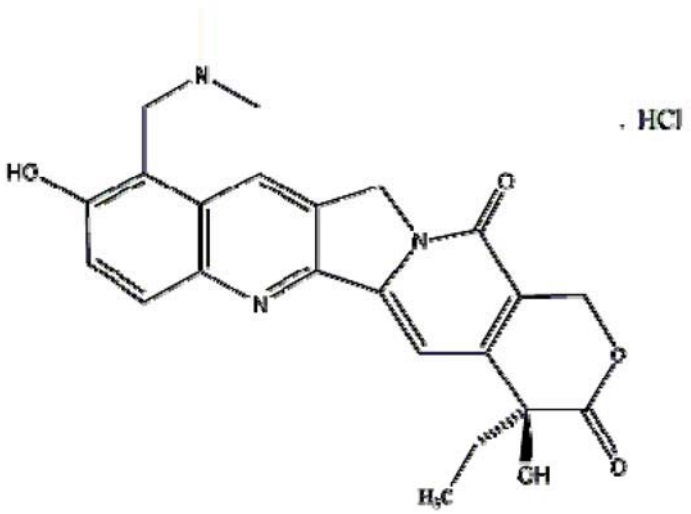
    _____SPOTS product Form Completed

    √___Not a SPOTS product

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

Chemical Name:
(*S*)-10-[(Dimethylamino)methyl]-4-ethyl-4,9-dihydroxy-1*H*-pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4*H*,12*H*)-dione monohydrochloride (reproduced from the submission)

Chemical Structure for topotecan hydrochloride is reproduced form the submission:



Molecular Formula: $C_{23}H_{23}N_3O_5.HCl$

Molecular Weight: 457.91

Molecular Weight (free base): 421.45

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		1	Inadequate	15-Jun-2010	Reviewed by Ann Marie Russell for (b) (4)
	III			1,4	Adequate	24-Jul-2008 and 19-May-2010	Reviewed by Terry Ocheltree for NDA 22234; see also this review section P.7.
	III			4	Adequate	19-May-2010	See also this review section P.7.
	III			1	Adequate	02-Sep-2009	Reviewed by Rona A LeBlanc for ANDA 60-657/S018

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
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	DESCRIPTION
NDA	(b) (4)	Submitted previously-RTF
NDA	20671	Hycamtin for injection (reference Listed Drug)
NDA	20981	Hycamtin capsules

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Overall acceptable	18-DEC-2009	Office of Compliance
Pharm/Tox	No non-clinical information to review. Pharmacology/Toxicology team provided comments on labeling issues	N/A	William D. McGuinn
Biopharm	Biowaiver request can be granted	01-JUN-2010	John Duan
LNC	N/A		
Methods Validation	N/A**		
DMEPA*	See DARRTS. Recommended several changes in the container and carton labeling	27-MAY-2010	Walter L. Fava
Environmental Assessment	Finding of No Significant Impact (FONSI)	22-Jun-2010	Emily A. McVey
Microbiology	Recommended for approval	29-APR-2010	Bryan S. Riley

*DMEPA: Division of Medication Error Prevention and Analysis
no formal review is available in DARRTS
**According to the current ONDQA policy

The CMC Review for NDA 200582

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the perspective of Chemistry, Manufacturing and Controls (CMC), this NDA is **Not Approvable** due to lack of response to a deficiency letter to the DMF holder. Therefore, CMC recommend that a Complete Response (CR) letter be issued indicating the above unresolved issue.

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

None

II. CMC Assessments

- The applicant referenced drug substance (topotecan) information in DMF (b) (4). Currently, the DMF is inadequate. The NDA applicant has been notified of the status of DMF (b) (4) on 22-Jul-2010. Based on the revised drug substance information from the DMF (b) (4) holder, comments will be conveyed to the applicant for further revision of drug substance information.

- Drug product (Topotecan Injection) is a solution containing topotecan hydrochloride, tartaric acid and water. As described above, the DMF holder will address the deficiencies with updated information on drug substance. Based on the revised drug substance information from the DMF (b) (4) holder, comments will be conveyed to the applicant for further revision of drug product information.

Basis for Approvability or Not-Approval Recommendation

- The CMC information of the drug substance is provided in DMF (b) (4). As of 27-Jul-2010, DMF is inadequate. Labeling and CMC issues are connected to the DMF information. After the satisfactory resolution of DMF (b) (4), the applicant will be notified to address the outstanding CMC issues.

III. Administrative

A. Reviewer's Signature:
(See appended electronic signature page)

Debasis Ghosh, M. Pharm., Ph.D. CMC Reviewer, Branch II, Division I, ONDQA

B. Endorsement Block:
(See appended electronic signature page)

Sarah Pope Miksinski, Ph.D. Branch Chief, Branch II, Division I, ONDQA

C. CC Block: entered electronically in DARRTS

10 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200582	ORIG-1	HOSPIRA INC	TOPOTECAN INJ

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DEBASIS GHOSH
07/30/2010

WILLIAM M ADAMS
07/30/2010
William Adams, acting for Sarah Pope Miksinski

NDA 200582

Topotecan Injection
4mg/4 mL
(1 mg/mL)

Hospira, Inc

Debasis Ghosh, M. Pharm., Ph.D.

Review Chemist

Office of New Drug Quality Assessment
Division I
Branch II

CMC REVIEW OF NDA 200582
For the Division of Drug Oncology Products

Table of Contents

CMC Review Data Sheet

1. NDA 200582

2. REVIEW #: 1

3. REVIEW DATE: 30-Jun-2010

4. REVIEWER: Debasis Ghosh, M. Pharm., Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
RTF Letter (NDA (b) (4))	21-Aug-2010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original NDA Submission	29-OCT-2009
Amendment SD 001	11-FEB-2010
Amendment SD 003	22-MAR-2010
Amendment SD 005	30-APR-2010
Amendment SD 006	01-JUN-2010

7. NAME & ADDRESS OF APPLICANT:

Name:	Hospira, Inc
Address:	275 North Field Drive, Dept 0389, Bldg H2-2, Lake Forest, IL 60045, USA
Representative:	Wendy Tian
Telephone:	224-212-6163

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name: Topotecan Injection
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 5 (new formulation)

- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2);
   - The Reference Listed Drug (RLD) is Hycamtin (topotecan hydrochloride) for Injection - NDA 20671 was approved on 28-May-2006.
   - GlaxoSmithKline's Hycamtin is supplied as a sterile lyophilized powder. Each vial contains topotecan hydrochloride equivalent to 4 mg of topotecan base. Upon reconstitution with 4 mL of diluent, the concentration of reconstituted solution is 1 mg/mL.
   - Each vial of the proposed Topotecan Injection contains 4 mg topotecan hydrochloride equivalent to 4 mg of topotecan base in 4 mL solution with a concentration of 1 mg/mL.

10. PHARMACOL. CATEGORY: Anticancer

11. DOSAGE FORM: injection, solution

12. STRENGTH/POTENCY: 4 mg/4 mL (1 mg/mL) (The drug product strength is based on the equivalent amount of topotecan free base.)

13. ROUTE OF ADMINISTRATION: Injection, Intravenous

14. Rx/OTC DISPENSED: __√__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product Form Completed

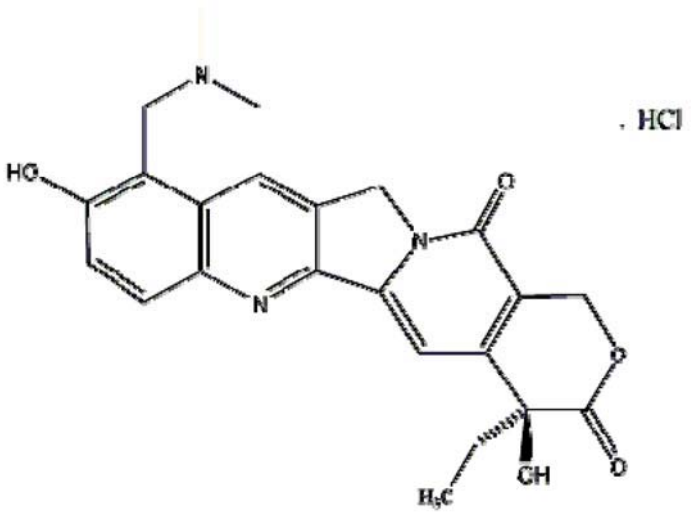
√___Not a SPOTS product

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

Chemical Name:
(*S*)-10-[(Dimethylamino)methyl]-4-ethyl-4,9-dihydroxy-1*H*-pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4*H*,12*H*)-dione monohydrochloride (reproduced from the submission)

Chemical Structure for topotecan hydrochloride is reproduced form the submission:

CMC Review Data Sheet



Molecular Formula: $C_{23}H_{23}N_3O_5.HCl$

Molecular Weight: 457.91

Molecular Weight (free base): 421.45

Comments:

- Above chemical name is based on the monohydrochloride salt form of topotecan. It has been noted that the innovator's drug substance is topotecan monohydrochloride. [redacted] (b) (4) It will be based on the information contained in the DMF [redacted]. Since DMF [redacted] is inadequate at this time of the review, no information is available to address this issue at this time.
- On 24-Jun-2010, the status of DMF [redacted] (b) (4) has been communicated to the applicant.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted] (b) (4)	II	[redacted] (b) (4)	[redacted] (b) (4)	1	Inadequate	15-Jun-2010	Reviewed by Ann Marie Russell for [redacted] (b) (4)
	III			1,4	Adequate	24-Jul-2008 and 19-May-2010	Reviewed by Terry Ocheltree for NDA

CMC Review Data Sheet

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
							22234; see also this review section P.7.
(b) (4)	III		(b) (4)	4	Adequate	19-May-2010	See also this review section P.7.
	III			1	Adequate	02-Sep-2009	Reviewed by Rona A LeBlanc for ANDA 60-657/S018

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
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	DESCRIPTION
NDA	(b) (4)	Submitted previously-RTF
NDA	20671	Hycamtin for injection (reference Listed Drug)
NDA	20981	Hycamtin capsules

CMC Review Data Sheet

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Overall acceptable	18-DEC-2009	Office of Compliance
Pharm/Tox	#	#	William D. McGuinn
Biopharm	Biowaiver request can be granted	01-JUN-2010	John Duan
LNC	N/A		
Methods Validation	N/A**		
DMEPA*	See DARRTS. Recommended several changes in the container and carton labeling	27-MAY-2010	Walter L. Fava
Environmental Assessment	Finding of No Significant Impact (FONSI)	22-Jun-2010	Emily A. McVey
Microbiology	Recommended for approval	29-APR-2010	Bryan S. Riley

*DMEPA: Division of Medication Error Prevention and Analysis
no formal review is available in DARRTS
**According to the current ONDQA policy

The CMC Review for NDA 200582

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the perspective of chemistry, manufacturing and controls (CMC), this NDA is Not Approvable due to pending CMC deficiencies, and labeling issues.

Based on the stability data provided, 18 months expiration dating period is granted for drug product when stored at 2°C-8°C (36°F-46°F) protected from light.

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

None

II. Summary of CMC Assessments

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

(1) Drug Substance

Drug substance, topotecan hydrochloride, is a yellow to orange hygroscopic powder. (b) (4) Both are stable polymorphic forms and have similar aqueous solubility and melting point profiles (both melt with decomposition at 213°C-218°C).

Particle size and hygroscopicity are not important for the proposed sterile solution formulation. Topotecan hydrochloride in aqueous solution showed a slightly higher acidic pH for (b) (4) compared to (b) (4) It has been noted that the lactone ring of drug substance is stable in acidic solution. Since the final dosage form for this NDA is a buffered (acidic) solution, the final drug product would be similar to the reconstituted solution of RLD and the solution is stable for 18 months at refrigerated conditions.

The applicant, Hospira, referenced drug substance information to DMF (b) (4). Hospira provided a Letter of Authorization (LOA) dated 26-MAR-2009 from the DMF Holder, (b) (4) authorizing the Agency to review the Type II DMF (b) (4) as filed on 22-Aug-2007, along with subsequent updates or supplements. DMF (b) (4) was reviewed by Ann Marie Russell of ONDQA on 15-Jun-2010 and found to be inadequate for similar topotecan injection formulation (NDA (b) (4)). The deficiency comments were communicated to the DMF holder on 09-Jun-2010. DMF holder provided an acknowledgement by email on 14-Jun-2010 to Debbie Mesmer of ONDQA. No additional information is available on the status of the DMF (b) (4) during the completion of this review.

Based on the response from DMF holder, the adequacy of drug substance for NDA 200582 will be determined.

(2) Drug Product

Drug product, Topotecan Injection, is a clear yellow to yellow-green sterile aqueous solution. It is supplied as a solution in a clear Type I glass vial with grey (b) (4) rubber closure and aluminum seal with plastic flip-off top. Each vial contains topotecan hydrochloride equivalent to 4.0 mg of topotecan, 20 mg tartaric acid NF, sodium hydroxide and hydrochloric acid for pH adjustment, and water for injection, USP. It has a pH of 2.6-3.2 and contains no preservatives. Drug product is intended to be diluted with a suitable intravenous solution prior to administration.

Topotecan Injection is a solution but Hycamtin (RLD) is a lyophilized powder. Each vial of topotecan injection contains topotecan hydrochloride equivalent to 4 mg of topotecan free base, tartaric acid and water. Each vial of Hycamtin contains topotecan hydrochloride equivalent to 4 mg of topotecan free base, (b) (4), and tartaric acid. Topotecan injection contains 4 mg/4 mL of topotecan free base which is exactly same as the reconstituted solution of Hycamtin except the presence of mannitol. (b) (4)

The proposed drug product is manufactured (b) (4)

The sponsor provided stability data for three drug product registration batches stored at 5°C ± 3°C (both upright and inverted) for 18 months, at 25°C ± 2°C/60%RH (both inverted and upright) for 6 months and at 15°C ± 2°C (both inverted and upright) for 12 months. It has been noted that total impurities and one individual impurity increased over six months at 25°C/60%RH (accelerated stability

conditions). The drug product was found to be stable for 18 months period during long-term condition (5°C ± 3°C) and 12 months period during intermediate conditions (15°C ± 2°C).

Based on the stability data, 18 months expiration dating period is granted for the drug product stored at 2°C to 8°C (36°F to 46°F) protected from light.

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

Drug product, topotecan injection, is indicated for the treatment of small cell lung cancer sensitive disease after failure of first line chemotherapy. The drug product is intended for dilution with 0.9% sodium chloride injection, USP, or 5% dextrose injection, USP prior to intravenous infusion. The recommended dose is 1.5 mg/m^2 by intravenous infusion over 30 minutes daily for 5 consecutive days, starting on day 1 of a 21 day course. In the absence of tumor progression, a minimum of 4 courses is recommended.

C. Basis for Approvability or Not-Approval Recommendation

- The CMC information of the drug substance is provided in DMF (b) (4). Based on the recent (15-Jun-2010) review by Ann Marie Russell, the DMF is inadequate. According to DARRTS, DMF deficiency comments were communicated to the DMF holder on 09-Jun-2010. The status of DMF has been communicated to the applicant on 24-Jun-2010: Unresolved

- Drug product information including the quality of inactive ingredients is satisfactory. Microbiology reviewer has provided an 'acceptable' recommendation from microbiology perspective: Resolved

- No proposal for proprietary name has been submitted. The CMC revisions of package inserts and carton and vial labels are pending. In association with DMEPA, clinical and Pharmacology/Toxicology, the list labeling comments are being finalized: Unresolved

- The inspection for the drug product manufacturing facility received 'acceptable' recommendation from the Office of Compliance (see EES Report Summary in Sec IIC): Resolved

- Environmental Assessment recommendation is 'FONSI' (Finding Of No Significant Impact): Resolved

III. Administrative

A. Reviewer's Signature:
(See appended electronic signature page)

Debasis Ghosh, M. Pharm., Ph.D. CMC Reviewer, Branch II, Division I, ONDQA

B. Endorsement Block:
(See appended electronic signature page)

Sarah Pope Miksinski, Ph.D. Branch Chief, Branch II, Division I, ONDQA

C. CC Block: entered electronically in DARRTS

78 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200582	ORIG-1	HOSPIRA INC	TOPOTECAN INJ

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DEBASIS GHOSH
07/08/2010

WILLIAM M ADAMS
07/09/2010
William Adams, acting for Sarah Pope Miksinski

Initial Quality Assessment
Branch V
Pre-Marketing Assessment Division III

OND Division:	Division of Drug Oncology Products
NDA:	200-582
Applicant:	Hospira, Inc.
Letter Date:	29 October, 2009
Stamp Date:	29 October, 2009
PDUFA Goal Date:	28 August, 2010 (standard)
Trade name:	Not proposed
Established Name:	Topotecan Injection
Dosage Form:	Injection -- 1 mg/mL
Route of Administration:	IV
Indication:	Treatment of small cell lung cancer sensitive disease after failure of first-line chemotherapy

Application format	Electronic format with non-eCTD
Regulatory Filing	For 505 (b) (2)
Related ~~IND~~/NDA	NDA (b) (4) (resubmission)
Assessed by:	Haripada Sarker

	Yes	No
ONDQA Fileability:	x	
Comments for 74-Day Letter:	x	

Summary

The application introduces Topotecan Injection (1 mg base/mL) by Hospira, Inc. Reference is made to the Refuse to File letter issued on 8/21/09 to the previously submitted application for Topotecan Injection, under application # NDA (b) (4) submitted by Hospira, Inc. The NDA (b) (4) was refused to file for insufficient data to support a commercially viable shelf-life (see CMC memo issued by Dr. Pope Miksinski dated 8/21/2009) data.

The reference listed drug for this submission is Hycamtin® (topotecan hydrochloride) for Injection, NDA 20-671, held by GlaxoSmithKline as RLD (reference listed drug). The proposed drug product Topotecan Injection is an aqueous injectable dosage form, at a concentration of 1 mg/mL topotecan, containing a total of drug content of 4 mg in a 5 mL sterile, single-use glass vial. The proposed drug product is in the same dosage form containing the same active ingredient at the same concentration as

the RLD, Hycamtin®, after reconstitution, and is intended for administration by intravenous infusion. The inactive ingredients in the proposed product are qualitatively and quantitatively the same as the inactive ingredients contained in the RLD, except that mannitol is removed. (b) (4)

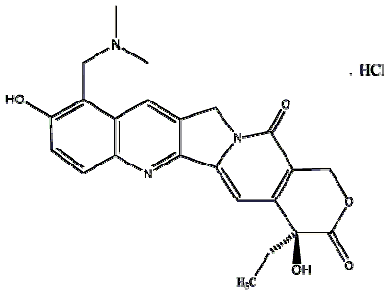
No Pre-NDA meeting is indicated for this new application NDA 200-582. Applicant indicated that this new application NDA 200-582 address the issues related to refuse to file letter issued on 8/21/09. The CMC information of the NDA is submitted as non-eCTDQ format since a waiver was submitted to justify the format.

Drug Substance (DS)

Hospira referred all the CMC information for Topotecan Hydrochloride DS to Type II DMF (b) (4) No significant new information for DS is indicated in this submission (b) (4) The summary of DS information is provided as following.

Topotecan Hydrochloride is derived from naturally occurring starting material (b) (4) (b) (4)

The Structure of Topotecan HCl DS is as following:



DS Critical Issues

- DMF (b) (4) is recently reviewed for generic drugs dated November 18, 2009, and is found to be inadequate for inappropriate control of HCl in DS. Verify the acceptability of DMF (b) (4).
- Closer examination of impurities at release and stability of DS is essential to set the retest period.
- Appropriate control on DS starting material is required, (b) (4)

Drug Product (DP)

In this NDA submission applicant updated stability data up to 12 months to secure the commercially viable shelf-life of DP.

The DP, Topotecan Hydrochloride is an injectable sterile solution manufactured and controlled by Zydus Hospira Oncology, India. It is available in one single-dose size: 4 mL fill in a 5-mL glass vial. Each mL of the product solution contains Topotecan Hydrochloride (equivalent to 1 mg Topotecan free base), 5 mg of tartaric acid, NF. The pH of the drug product is adjusted to pH 2.2 (range 2.0 to 2.5) with sodium hydroxide or hydrochloric acid. All the excipients used in drug product manufacture have standard compendial monograph. The DP finished product is diluted with normal saline or 5% dextrose prior to administration. Following Table depicts the comparison.

Comparison between Generic Drug and Reference Listed Drug

	Reference Listed Drug	**Generic Equivalent**
	GlaxoSmithKline Hycamtin®	Hospira, Inc. Topotecan Injection
Conditions of Use	*Ovarian Cancer*: Is indicated for the treatment of metastatic carcinoma of the ovary after failure of initial or subsequent chemotherapy.[1] *Small Lung Cancer*: Is indicated for the treatment of small cell lung cancer sensitive disease after failure of first-line chemotherapy. *In combination with cisplatin*: Is indicated for the treatment of stage IV-B, recurrent, or persistent carcinoma of the cervix which is not amenable to curative treatment with surgery and/or radiation therapy.	*Small Lung Cancer*: Is indicated for the treatment of small cell lung cancer sensitive disease after failure of first-line chemotherapy.
Active Ingredient(s)	Topotecan Hydrochloride	Topotecan Hydrochloride
Inactive Ingredient(s)	Mannitol Tartaric Acid Hydrochloric Acid Sodium Hydroxide	Water for Injection Tartaric Acid Hydrochloric Acid Sodium Hydroxide
Route of Administration	Injection (Intravenous)	Injection (Intravenous)
Dosage Form	Injectable	Injectable
Strength	Hycamtin® Freeze-Dried product: EQ 4 mg/vial (free base) Concentration after reconstitution: 4 mg/4 mL	Toptecan Injection solution: 4 mg/ 4 mL Concentration: 4 mg/4 mL (1 mg/ mL) *NO RECONSTITUTION REQUIRED*

1. See Section 1.3.5 regarding method of use patent certification. Per 21 CFR 314.50(i)(1)(iii)(A), Hospira Inc., is **not** seeking approval for and will **not** make reference to these labeled indications for which patent 5674872 and 5674872*PED method of use U-910 is applicable.

No CMC pre-NDA meeting is indicated for this NDA; however, several CMC issues were discussed in pre-NDA meeting of NDA (b) (4), dated November 14, 2008. (b) (4) In the pre-NDA meeting of NDA (b) (4), applicant indicated that it would be difficult to obtain API from the RLD supplier. The agency acknowledged and suggested that the sponsor provide any additional information on impurity profiles of drug substance and drug product ICHQ3 guidelines. FDA confirmed that the overall acceptability of the impurity profile of the drug substance is a review issue.

(b) (4)

[redacted] DP stability specification is found to be same as the corresponding release specification. Since Topotecan Injection is being submitted as a New Drug Application, the applicant requested categorical exclusions as per 21 CFR 25.31.

DP Critical Issues

- [redacted]
- [redacted]
- DP impurity profile should be justified as per ICHQ3B.
- Verify the EES for accuracy.
- Justification of waiver for eCTD format for NDA submission.
- Justification of waiver for categorical exclusions.

Fileability Template

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	√		
2	Is the section indexed and paginated adequately?	√		
3	On its face, is the section legible?	√		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	√		
5	Is a statement provided that all facilities are ready for GMP inspection?	√		
6	Has an environmental assessment report or categorical exclusion been provided?	√		
7	Does the section contain controls for the drug substance?	√		
8	Does the section contain controls for the drug product?	√		
9	Has stability data and analysis been provided to support the requested expiration date?		√	[redacted]
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		
11	Have draft container labels been provided?	√		
12	Has the draft package insert been provided?	√		
13	Has a section been provided on pharmaceutical development/ investigational formulations section?	√		
14	Is there a Methods Validation package?	√		
15	Is a separate microbiological section included?	√		
16	Have all consults been identified and initiated?			

	(bolded items to be handled by ONDQA PM)	√ √ √ √ √		Microbiology Pharm/Tox Biopharm Statistics (stability) OCP/CDRH/CB ER LNC DMETS/ODS **EER**

Have all DMF References been identified? Yes (√) No ( )

DMF Number	Holder	Description	LOA Included
(b) (4)			

Comments and Recommendations
The application is fileable. However, the following comments need to be communicated to the applicant in the 74-day letter. Facilities have been entered into EES for inspection. A single reviewer is recommended for this NDA, since the manufacturing process is not particularly complex.

Comment for 74-days letter:

1. Based on your NDA submission, an environmental assessment is required. Submit an environmental assessment as soon as possible.
2. DMF (b) (4) is currently inadequate to support this NDA.

Haripada Sarker — December 14, 2009
Pharmaceutical Assessment Lead (PAL) — Date

Sarah Pope Miksinski, Ph.D. — December 14, 2009
Branch Chief — Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200582	ORIG-1	HOSPIRA INC	TOPOTECAN INJ

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HARIPADA SARKER
12/14/2009

Sarah Pope Miksinski
12/14/2009