CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204684Orig1s000

CHEMISTRY REVIEW(S)

NDA 204-684

Impavido® (miltefosine) Capsules, 50 mg

Paladin Therapeutics, Inc.

Maotang Zhou, Ph.D.
Anamitro Banerjee, Ph.D.

Review Chemists

Office of New Drug Quality Comments
Division of New Drug Quality Comments II
Branch V

CMC REVIEW OF NDA 204-684
For the Division of Anti-Infective Products (DAIP)

Table of Contents

CMC Review Data Sheet

1. NDA 204-684

2. REVIEW #: Addendum # 1 to Review #2

3. REVIEW DATE: 22-JAN-2014

4. REVIEWERS: Maotang Zhou, Ph.D. and Anamitro Banerjee, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original IND 105,430 submission	04-Sep-2010
Original IND 105,430 CMC review	N/A
End-of-phase-2 meeting (No CMC issues discussed)	N/A
Pre-NDA meeting	09-Feb-2012

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	DARRTS SD Number	Document Date	Stamp Date
Original NDA Submission	0000	9/27/2012	9/27/2012
Resubmission/After Refusal to File	0006	4/19/2013	4/19/2013
Quality Amendment (Response to Agency Questions)	0012	7/10/2013	7/10/2013
Quality Amendment (Response to Agency Questions)	0018	8/22/2013	8/22/2013
Quality Amendment (Response to Agency Questions)	0019	8/22/2013	8/22/2013
Quality Amendment (Response to Information Request)	0020	10/15/2013	10/15/2013
Quality Amendment (Response to Information Request)	0023	11/13/2013	11/13/2013
Quality Amendment (Response to Information Request)	0024	11/15/2013	11/15/2013

CMC Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	Paladin Therapeutics
Address:	Corporation Trust Center
	1209 Orange Street
	Wilmington, DE 19801
Representative:	Jonathan Berman, M.D., Ph.D.
	Fast Track Drugs and Biologics LLC
	Potomac Court
	North Potomac, MD 20878
Telephone:	(888) 376 7830 (x5367)

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Impavido®
b) Non-Proprietary Name: Miltefosine
c) Code Name/# (ONDQA only): D-18506
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: alkylphosphocholine
- Submission Priority: Priority

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

10. PHARMACOL. CATEGORY:

11. DOSAGE FORM: Oral capsules

12. STRENGTH/POTENCY: 50 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __√__Rx ___OTC

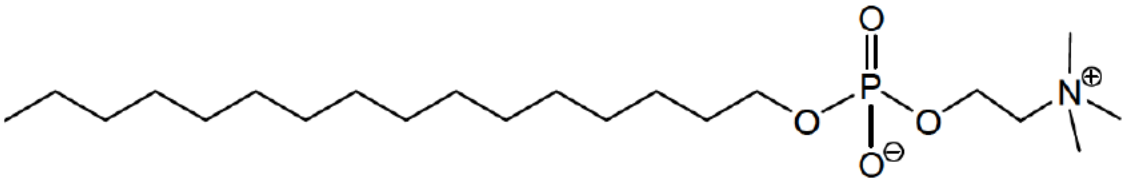
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__√___Not a SPOTS product

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

- Structure:



- Molecular formula: $C_{21}H_{46}NO_4P$
- Molecular weight: 407.6

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	IV		(b) (4)	4			
	III			4			
	III			4			
	IV			4			Included in DMF (b) (4)

[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
IND	N/A	N/A
NDA	N/A	N/A

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Review in DARRTS	9/30/2013	L Zeng
EES	Acceptable	1/17/2014	T Sharp
Pharm/Tox	N/A		
Biopharm	Adequate	8/12/2013	M Seggel
LNC	N/A		
Methods Validation	Pending		
DMEPA*	N/A		
EA	Categorical exclusion (see review)	8/27/2013	M Zhou
Microbiology	Adequate	6/5/2013	B Riley

*DMEPA: Division of Medication Error Prevention and Analysis

The CMC Review for NDA 204-684

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The NDA, as revised and coupled with the Post Marketing Commitments (PMCs), includes sufficient information on the drug substance and drug product to assure the strength, purity, and quality of the drug product through the expiration dating period. Labels and labeling contain adequate CMC information. Minor labeling comments have been conveyed to the review team.

The Office of Compliance has made an "Acceptable" overall recommendation on all the drug manufacturing facilities. Therefore, from the CMC perspective, this NDA is recommended for approval.

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

The company has agreed to conduct the following post-marketing commitments (PMC). The final PMC text and timelines will be captured in the PMC documentation in DARRTS.

1. Develop an appropriate HPLC method for release and stability testing (assay and impurities) of the drug product and the drug substance to facilitate life-cycle management of miltefosine capsules.
2. In conjunction with the development and implementation of the HPLC methodology, perform (b) (4) testing in accordance with the 2003 FDA draft guidance for stratified testing.

II. Summary of CMC Comments

A. Description of the Drug Product and Drug Substance

(1) Drug Substance

Miltefosine is a new molecular entity. Miltefosine drug substance is manufactured by (b) (4) It is a white (b) (4) with only (b) (4) as detected by (b) (4) Miltefosine is a hygroscopic (b) (4) that is freely soluble in water (b) (4) Miltefosine has (b) (4) Miltefosine melts at about (b) (4)

The synthesis of miltefosine drug substance is (b) (4)

(b) (4)

(b) (4) A typical commercial scale batch is (b) (4) Impurities in miltefosine may arise from starting materials, process or by degradation. (b) (4) are two genotoxic process impurities that may result from (b) (4) All the possible impurities resulting from the manufacturing process are controlled by the drug substance specification. The applicant has proposed that the test for the two (b) (4) impurities will be removed once sufficient data is available to show that they are not formed during the manufacturing process.

The specifications for miltefosine drug substance includes tests for description, identity, water, assay, impurities. (b) (4) heavy metals, and residual solvents. The HPTLC method used to analyze some of the impurities is now an interim method as it is to be replaced with an HPLC method developed under a PMC. The deficiencies in the HPTLC method were reasonably addressed by the applicant to permit its use as an interim method.

The applicant provided 12 month stability data under long term conditions and 6 month stability data under accelerated data for close to commercial scale batches of the drug substance. The data show no discernable trends or degradation of the drug substance when stored in the proposed container closure system (b) (4) . The (b) (4) retest period for miltefosine drug substance proposed by the applicant is acceptable based on the additional stability data of up to 60 months for the drug substance batches manufactured at lab and pilot scale.

(2) Drug Product

The drug product, Impavido®, is an oral capsule that contains the drug substance miltefosine (50 mg/capsule) and the excipients, Colloidal Silicon Dioxide NF, Microcrystalline Cellulose NF (b) (4), Lactose Monohydrate NF, Talc NF and Magnesium Stearate NF; the capsule shell consists of Gelatin NF, Titanium Dioxide USP, Ferric Oxide NF Red and Purified Water USP. All the excipients are of compendial grade (USP/NF). The finished capsules are packaged in (b) (4) blisters (7 blisters/strip) in a (b) (4) peel/push-through carton (2 strips/carton).

The drug product is manufactured, packaged in blister cards and tested for water content and microbial limits (b) (4) The (b) (4) outer carton is applied over the blister cards (b) (4) All other release tests are performed (b) (4)

The drug product manufacturing process is straightforward and consists of (b) (4) (b) (4)

The applicant did not discuss their control strategy in the NDA. Based on this reviewer's

evaluation of the NDA information, the following conventional control strategies are used for product quality assurance by the applicant:

- Use of excipients commonly used in ophthalmic products with excipient quality controlled by adherence to compendial specifications
- Use of critical process parameter ranges and in-process testing specification to control the manufacturing process
- Maintaining a low humidity environment (b) (4) to avoid moisture uptake.
- Release testing of final drug product for critical product attributes such as description, identity, water content, assay, degradants, weight variation, dissolution, and microbial limits.

The biopharmaceutics review dated August 12, 2013 recommended that NDA 204684 for Impavido® be approved with the proposed regulatory dissolution method and the revised dissolution acceptance criteria (Q= (b) (4) at 15 min). The product quality microbiology review has found the microbiology aspects acceptable and has recommended approval of the NDA.

By the time of its original GRMP due date, this NDA was recommended for approval by the CMC review team in CMC Review #1 dated 9/6/2013 due to several outstanding CMC deficiencies. The applicant's subsequent responses to these deficiencies were reviewed by the CMC review team and found adequate. Consequently, the CMC team recommended approval for the NDA on 11/21/2013 in Addendum #1 to CMC Review #1, pending an overall "acceptable" site recommendation from the Office of Compliance. On January 17, 2014, the Office of Compliance (OC) has made an "Acceptable" overall site recommendation (Please refer to the EES Summary Report in the appendix of this review). As a result, the CMC information provided in the NDA is now considered adequate to assure identity, strength, purity, and quality of the drug product.

The applicant has submitted up to 18-month long-term and 6-month accelerated stability data for the three primary stability batches. The stability testing of these batches is expected to continue to 36 months. In addition, up to 48-month long term and 6 month accelerated stability data for several earlier batches were also provided. The supportive stability batches were manufactured using an earlier manufacturing process that was slightly different from the proposed commercial process. While the applicant has requested a (b) (4) shelf life, from the CMC perspective, only a 24-month expiration dating period can be granted at this time based on the totality of the stability data provided. The applicant has agreed to an expiration dating period of 24 months for the drug product, when stored at 20-25 °C (68-77 °F); excursions permitted to 15-30 °C (59-86 °F) [see USP controlled room temperature].

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

Miltefosine is an alkylphosphocholine with activity against visceral, mucosal and cutaneous leishmaniasis. It was originally developed as a topical antineoplastic, but has found use as an oral antiprotozoal drug. Impavido (miltefosine) capsules are available as

10 mg and 50 mg miltefosine capsules; however under NDA 204684, Paladin is currently seeking USFDA approval of only the 50 mg strength. The proposed treatment regimen is one capsule taken two or three times a day, for 28 days. Because of its emetogenic effect, the product is taken with food.

C. Basis for Approvability or Not-Approval Recommendation

This NDA, as revised and coupled with two PMCs, has provided sufficient information on raw material controls, manufacturing processes and process controls, specifications for assuring consistent product quality of the drug substance and drug product. Sufficient stability information on the drug product is also provided to assure the strength, purity, and quality of the drug product during the expiration dating period. Labels and labeling contain adequate CMC information. Minor labeling comments have been conveyed to the review team. The Office of Compliance (OC) has made an "Acceptable" overall site recommendation. Therefore, from the CMC perspective, this NDA is now recommended for approval.

III. Administrative

A. Reviewer's Signature:

(See appended electronic signature page)

Maotang Zhou, Ph.D., Reviewer, ONDQA
Anamitro Banerjee, Ph.D., Reviewer, ONDQA

B. Endorsement Block:

(See appended electronic signature page)

Rapti Madurawe, Ph.D., Branch Chief, Branch V, Division of New Drug Quality Comments II, ONDQA

C. CC Block: entered electronically in DARRTS

2 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

MAOTANG ZHOU
01/23/2014

ANAMITRO BANERJEE
01/23/2014

RAPTI D MADURAWE
01/23/2014

NDA 204-684

Impavido® (miltefosine) Capsules, 50 mg

Paladin Therapeutics, Inc.

Maotang Zhou, Ph.D.
Anamitro Banerjee, Ph.D.

Review Chemists

Office of New Drug Quality Comments
Division of New Drug Quality Comments II
Branch V

CMC REVIEW OF NDA 204-684
For the Division of Anti-Infective Products (DAIP)

Table of Contents

CMC Review Data Sheet

1. NDA 204-684

2. REVIEW #: Addendum # 1 to Review #1

3. REVIEW DATE: 21-Nov-2013

4. REVIEWERS: Maotang Zhou, Ph.D. and Anamitro Banerjee, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original IND 105,430 submission	04-Sep-2010
Original IND 105,430 CMC review	N/A
End-of-phase-2 meeting (No CMC issues discussed)	N/A
Pre-NDA meeting	09-Feb-2012

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	DARRTS SD Number	Document Date	Stamp Date
Original NDA Submission	0000	9/27/2012	9/27/2012
Resubmission/After Refusal to File	0006	4/19/2013	4/19/2013
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Quality Amendment (Response to Agency Questions)	0019	8/22/2013	8/22/2013
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Quality Amendment (Response to Information Request)	0023	11/13/2013	11/13/2013
Quality Amendment (Response to Information Request)	0024	11/15/2013	11/15/2013

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7. NAME & ADDRESS OF APPLICANT:

Name:	Paladin Therapeutics
Address:	Corporation Trust Center
	1209 Orange Street
	Wilmington, DE 19801
Representative:	Jonathan Berman, M.D., Ph.D.
	Fast Track Drugs and Biologics LLC
	Potomac Court
	North Potomac, MD 20878
Telephone:	(888) 376 7830 (x5367)

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Impavido®
b) Non-Proprietary Name: Miltefosine
c) Code Name/# (ONDQA only): D-18506
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: alkylphosphocholine
- Submission Priority: Priority

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

10. PHARMACOL. CATEGORY:

11. DOSAGE FORM: Oral capsules

12. STRENGTH/POTENCY: 50 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __√__Rx ___OTC

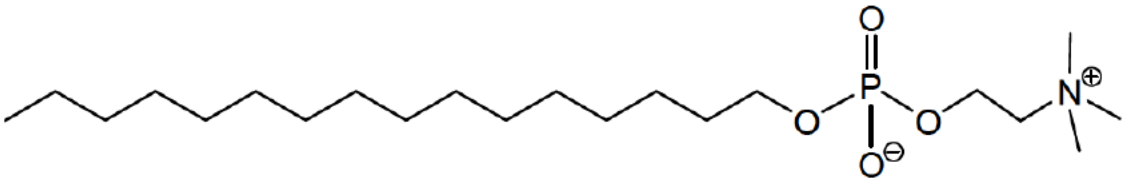
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__√___Not a SPOTS product

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

- Structure:



- Molecular formula: $C_{21}H_{46}NO_4P$
- Molecular weight: 407.6

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	IV		(b) (4)	4			
	III			4			
	III			4			
	IV			4			Included in DMF (b) (4)

[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
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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
IND	N/A	N/A
NDA	N/A	N/A

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Review in DARRTS	9/30/2013	L Zeng
EES	Pending		
Pharm/Tox	N/A		
Biopharm	Adequate	8/12/2013	M Seggel
LNC	N/A		
Methods Validation	Pending		
DMEPA*	N/A		
EA	Categorical exclusion (see review)	8/27/2013	M Zhou
Microbiology	Adequate	6/5/2013	B Riley

*DMEPA: Division of Medication Error Prevention and Analysis

The CMC Review for NDA 204-684

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The NDA, as revised and coupled with the Post Marketing Commitments (PMCs), includes sufficient information on the drug substance and drug product to assure the strength, purity, and quality of the drug product through the expiration dating period. Labels and labeling contain adequate CMC information. Minor labeling comments have been conveyed to the review team. As of the date of this review, the Office of Compliance has not made a recommendation on the overall site acceptability. From the CMC perspective, this NDA may be recommended for approval once the overall site acceptability is established by the Office of Compliance.

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

The company has agreed to conduct the following post-marketing commitments (PMC). The final PMC text and timelines will be captured in the PMC documentation in DARRTS.

1. Develop an appropriate HPLC method for release and stability testing (assay and impurities) of the drug product and the drug substance to facilitate life-cycle management of miltefosine capsules.
2. In conjunction with the development and implementation of the HPLC methodology, perform (b) (4) testing in accordance with the 2003 FDA draft guidance for stratified testing.

II. Summary of CMC Comments

A. Description of the Drug Product and Drug Substance

(1) Drug Substance

Miltefosine is a new molecular entity. Miltefosine drug substance is manufactured by (b) (4). It is a white (b) (4) with only (b) (4) as detected by (b) (4) Miltefosine is a hygroscopic (b) (4) that is freely soluble in water at (b) (4) Miltefosine has (b) (4) Miltefosine melts at about (b) (4)

The synthesis of miltefosine drug substance is (b) (4)

[redacted] A typical commercial scale batch is [redacted]. Impurities in miltefosine may arise from starting materials, process or by degradation. [redacted] are two genotoxic process impurities that may result from [redacted] All the possible impurities resulting from the manufacturing process are controlled by the drug substance specification. The applicant has proposed that the test for the two [redacted] impurities will be removed once sufficient data is available to show that they are not formed during the manufacturing process.

The specifications for miltefosine drug substance includes tests for description, identity, water, assay, impurities, [redacted], heavy metals, and residual solvents. The HPTLC method used to analyze some of the impurities is now an interim method as it is to be replaced with an HPLC method developed under a PMC. The deficiencies in the HPTLC method were reasonably addressed by the applicant to permit its use as an interim method..

The applicant provided 12 month stability data under long term conditions and 6 month stability data under accelerated data for close to commercial scale batches of the drug substance. The data show no discernable trends or degradation of the drug substance when stored in the proposed container closure system [redacted] The [redacted] retest period for miltefosine drug substance proposed by the applicant is acceptable based on the additional stability data of up to 60 months for the drug substance batches manufactured at lab and pilot scale, but will need to be confirmed upon review of the response to the analytical method deficiencies.

(2) Drug Product

The drug product, Impavido®, is an oral capsule that contains the drug substance miltefosine (50 mg/capsule) and the excipients, Colloidal Silicon Dioxide NF, Microcrystalline Cellulose NF [redacted] Lactose Monohydrate NF, Talc NF and Magnesium Stearate NF; the capsule shell consists of Gelatin NF, Titanium Dioxide USP, Ferric Oxide NF Red and Purified Water USP. All the excipients are of compendial grade (USP/NF). The finished capsules are packaged in [redacted] blisters (7 blisters/strip) in a [redacted] peel/push-through carton (2 strips/carton).

The drug product is manufactured, packaged in blister cards and tested for water content and microbial limits [redacted] The [redacted] outer carton is applied over the blister cards [redacted] All other release tests are performed [redacted]

The drug product manufacturing process is straightforward and consists of [redacted]

The applicant did not discuss their control strategy in the NDA. Based on this reviewer's

evaluation of the NDA information, the following conventional control strategies are used for product quality assurance by the applicant:

- Use of excipients commonly used in ophthalmic products with excipient quality controlled by adherence to compendial specifications
- Use of critical process parameter ranges and in-process testing specification to control the manufacturing process
- Maintaining a low humidity environment (b) (4) to avoid moisture uptake.
- Release testing of final drug product for critical product attributes such as description, identity, water content, assay, degradants, weight variation, dissolution, and microbial limits.

The biopharmaceutics review dated August 12, 2013 recommended that NDA 204684 for Impavido® be approved with the proposed regulatory dissolution method and the revised dissolution acceptance criteria (Q= (b) (4) at 15 min). The product quality microbiology review has found the microbiology aspects acceptable and has recommended approval of the NDA.

CMC review #1 did not recommend approval of the NDA as the applicant had failed provide adequate method validation information by the GRMP date to support the proposed HPTLC analytical methods for identity, assay, purity, and dissolution tests. On October 15, 2013, the applicant provided complete responses to all outstanding CMC deficiencies communicated in Agency letters dated June 20, 2013 and Aug 2, 2013. The applicant agreed to develop HPLC methods within one year of the current PDUFA date and to perform (b) (4) tests using the newly developed HPLC methodology under two PMCs. Additionally, the applicant provided sufficient information on the HPTLC methods to permit its use as an interim method until the HPLC method is implemented. CMC information provided in the NDA is now considered adequate to assure identity, strength, purity, and quality of the drug product.

The applicant has submitted up to 18-month long-term and 6-month accelerated stability data for the three primary stability batches. The stability testing of these batches is expected to continue to 36 months. In addition, up to 48-month long term and 6 month accelerated stability data for several earlier batches were also provided. The supportive stability batches were manufactured using an earlier manufacturing process that was slightly different from the proposed commercial process. While the applicant has requested a (b) (4) shelf life, from the CMC perspective, only a 24-month expiration dating period can be granted at this time based on the totality of the stability data provided. The applicant has agreed to an expiration dating period of 24 months for the drug product, when stored at 20-25 °C (68-77 °F); excursions permitted to 15-30 °C (59-86 °F) [see USP controlled room temperature].

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

Miltefosine is an alkylphosphocholine with activity against visceral, mucosal and cutaneous leishmaniasis. It was originally developed as a topical antineoplastic, but has

found use as an oral antiprotozoal drug. Impavido (miltefosine) capsules are available as 10 mg and 50 mg miltefosine capsules; however under NDA 204684, Paladin is currently seeking USFDA approval of only the 50 mg strength. The proposed treatment regimen is one capsule taken two or three times a day, for 28 days. Because of its emetogenic effect, the product is taken with food.

C. Basis for Approvability or Not-Approval Recommendation

This NDA, as revised and coupled with two PMCs, has provided sufficient information on raw material controls, manufacturing processes and process controls, specifications for assuring consistent product quality of the drug substance and drug product. Sufficient stability information on the drug product is also provided to assure the strength, purity, and quality of the drug product during the expiration dating period. Labels and labeling contain adequate CMC information. Minor labeling comments have been conveyed to the review team. However, some facility inspections are currently pending as of the date of this review and the Office of Compliance has not determined the overall site acceptability .

From the CMC perspective, this NDA may be recommended for approval once the overall site acceptability is established by the Office of Compliance.

III. Administrative

A. Reviewer's Signature:

(See appended electronic signature page)

Maotang Zhou, Ph.D., Reviewer, ONDQA
Anamitro Banerjee, Ph.D., Reviewer, ONDQA

B. Endorsement Block:

(See appended electronic signature page)

Rapti Madurawe, Ph.D., Branch Chief, Branch V, Division of New Drug Quality Comments II, ONDQA

C. CC Block: entered electronically in DARRTS

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/s/

MAOTANG ZHOU
11/21/2013

ANAMITRO BANERJEE
11/21/2013

RAPTI D MADURAWE
11/21/2013

NDA 204-684

Impavido® (miltefosine) Capsules, 50 mg

Paladin Therapeutics, Inc.

Maotang Zhou, Ph.D.
Anamitro Banerjee, Ph.D.

Review Chemists

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment II
Branch V

CMC REVIEW OF NDA 204-684
For the Division of Anti-Infective Products (DAIP)

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1. NDA 204-684

2. REVIEW #: 1

3. REVIEW DATE: 06-SEP-2013

4. REVIEWERS: Maotang Zhou, Ph.D. and Anamitro Banerjee, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original IND 105,430 submission	04-Sep-2010
Original IND 105,430 CMC review	N/A
End-of-phase-2 meeting (No CMC issues discussed)	N/A
Pre-NDA meeting	09-Feb-2012

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	DARRTS SD Number	Document Date	Stamp Date
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Quality Amendment (Response to Agency Questions)	0012	7/10/2013	7/10/2013
Quality Amendment (Response to Agency Questions)	0018	8/22/2013	8/22/2013
Quality Amendment (Response to Agency Questions)	0019	8/22/2013	8/22/2013
Quality Amendment (Response to Information Request)			
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CMC Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	Paladin Therapeutics
Address:	Corporation Trust Center 1209 Orange Street Wilmington, DE 19801
Representative:	Jonathan Berman, M.D., Ph.D. Fast Track Drugs and Biologics LLC Potomac Court North Potomac, MD 20878
Telephone:	(888) 376 7830 (x5367)

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Impavido®
b) Non-Proprietary Name: Miltefosine
c) Code Name/# (ONDQA only): D-18506
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: alkylphosphocholine
- Submission Priority: Priority

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

10. PHARMACOL. CATEGORY:

11. DOSAGE FORM: Oral capsules

12. STRENGTH/POTENCY: 50 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __√__Rx ___OTC

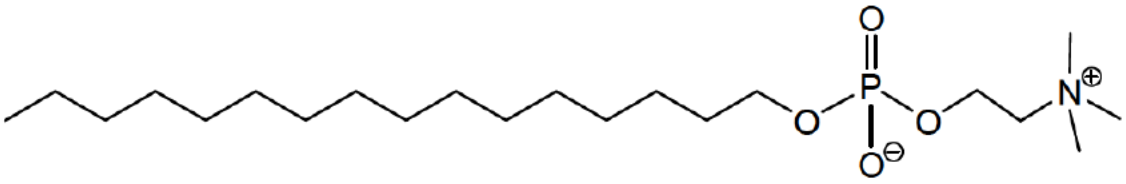
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__√___Not a SPOTS product

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

- Structure:



- Molecular formula: $C_{21}H_{46}NO_4P$
- Molecular weight: 407.6

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	IV		(b) (4)	4			
	III			4			
	III			4			
	IV			4			Included in DMF (b) (4)

[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
IND	N/A	N/A
NDA	N/A	N/A

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending		
Pharm/Tox	N/A		
Biopharm	Adequate	8/12/2013	M Seggel
LNC	N/A		
Methods Validation	Pending		
DMEPA*	N/A		
EA	Categorical exclusion (see review)	8/27/2013	M Zhou
Microbiology	Adequate	6/5/2013	B Riley

*DMEPA: Division of Medication Error Prevention and Analysis

The CMC Review for NDA 204-684

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has not provided sufficient information to assure identity, strength, purity, and quality of the drug product as there are outstanding deficiencies relating to the analytical methods while the rest of the CMC information in the NDA is adequate. The labeling issues are still pending and a site recommendation from the Office of Compliance has not been made as of the date of this review. Therefore, from the CMC perspective, this NDA is not recommended for approval until all pending issues are satisfactorily resolved.

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

None at this time.

II. Summary of CMC Assessments

A. Description of the Drug Product and Drug Substance

(1) Drug Substance

Miltefosine is a new molecular entity. Miltefosine drug substance is manufactured by (b) (4) It is a white (b) (4) with only (b) (4) as detected by (b) (4) Miltefosine is a hygroscopic (b) (4) that is freely soluble in water at (b) (4) Miltefosine has (b) (4). Miltefosine melts at about (b) (4)

The synthesis of miltefosine drug substance is (b) (4) (b) (4) (b) (4) A typical commercial scale batch is (b) (4) Impurities in miltefosine may arise from starting materials, process or by degradation. (b) (4) are two genotoxic process impurities that may result from (b) (4) All the possible impurities resulting from the manufacturing process are controlled by the drug substance specification. The applicant has proposed that the test for the two (b) (4) impurities will be removed once

sufficient data is available to show that they are not formed during the manufacturing process.

The specifications for miltefosine drug substance includes tests for description, identity, water, assay, impurities, (b) (4) heavy metals, and residual solvents. The HPTLC method used to analyze some of the impurities was found to be deficient. The stress conditions employed by the applicant were mild. The applicant was asked to repeat stress studies using appropriate conditions in Agency letter date June 20, 2013. No response has been received to date. Other analytical methods are acceptable.

The applicant provided 12 month stability data under long term conditions and 6 month stability data under accelerated data for close to commercial scale batches of the drug substance. The data show no discernable trends or degradation of the drug substance when stored in the proposed container closure system (b) (4) The (b) (4) retest period for miltefosine drug substance proposed by the applicant is acceptable based on the additional stability data of up to 60 months for the drug substance batches manufactured at lab and pilot scale, but will need to be confirmed upon review of the response to the analytical method deficiencies.

(2) Drug Product

The drug product, Impavido®, is an oral capsule that contains the drug substance miltefosine (50 mg/capsule) and the excipients, Colloidal Silicon Dioxide NF, Microcrystalline Cellulose NF (b) (4), Lactose Monohydrate NF, Talc NF and Magnesium Stearate NF; the capsule shell consists of Gelatin NF, Titanium Dioxide USP, Ferric Oxide NF Red and Purified Water USP. All the excipients are of compendial grade (USP/NF). The finished capsules are packaged in (b) (4) blisters (7 blisters/strip) in a (b) (4) peel/push-through carton (2 strips/carton).

The drug product is manufactured, packaged in blister cards and tested for water content and microbial limits (b) (4). The (b) (4) outer carton is applied over the blister cards (b) (4)
All other release tests are performed (b) (4)

The drug product manufacturing process is straightforward and consists of (b) (4) (b) (4)

The applicant did not discuss their control strategy in the NDA. Based on this reviewer's evaluation of the NDA information, the following conventional control strategies are used for product quality assurance by the applicant:

- Use of excipients commonly used in ophthalmic products with excipient quality controlled by adherence to compendial specifications
- Use of critical process parameter ranges and in-process testing specification to control the manufacturing process
- Maintaining a low humidity environment (b) (4) to avoid moisture uptake.

- Release testing of final drug product for critical product attributes such as description, identity, water content, assay, degradants, weight variation, dissolution, and microbial limits.

These control strategies appear to be adequate for product quality assurance, except for the proposed analytical procedures, where HPTLC methods are used for identity, assay, purity, and dissolution tests. Methods validation consult request was forwarded to FDA's Division of Pharmaceutical Analysis (DPA) and the validation results from DPA are still pending. In the mean time, the method validation information provided by the applicant was found inadequate and an information request was send to the applicant on June 20, 2013. The applicant has not yet responded to the request as of the date of this review and has indicated a response will be sent sometime after the GRMP date. As a result, the CMC information provided in the NDA is considered insufficient to assure identity, strength, purity, and quality of the drug product until the HPTLC methods are adequately validated.

The biopharmaceutics review dated August 12, 2013 recommended that NDA 204684 for Impavido® be approved with the proposed regulatory dissolution method and the revised dissolution acceptance criteria (Q= (b) (4) at 15 min). The product quality microbiology review has found the microbiology aspects acceptable and has recommended approval of the NDA.

The applicant has submitted up to 18-month long-term and 6-month accelerated stability data for the three primary stability batches. The stability testing of these batches is expected to continue to 36 months. In addition, up to 48-month long term and 6 month accelerated stability data for several early batches were also provided. The supportive stability batches were manufactured using the original process instead of the proposed commercial. While the applicant has requested a (b) (4) shelf life, from the CMC perspective, only a 24-month expiration dating period can be granted at this time based on the totality of the stability data provided. The expiration date will be confirmed upon review of the response to the analytical method deficiencies.

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

Miltefosine is an alkylphosphocholine with activity against visceral, mucosal and cutaneous leishmaniasis. It was originally developed as a topical antineoplastic, but has found use as an oral antiprotozoal drug. Impavido (miltefosine) capsules are available as 10 mg and 50 mg miltefosine capsules; however under NDA 204684, Paladin is currently seeking USFDA approval of only the 50 mg strength. The proposed treatment regimen is one capsule taken two or three times a day, for 28 days. Because of its emetogenic effect, the product is taken with food.

C. Basis for Approvability or Not-Approval Recommendation

The applicant has not yet responded to deficiencies relating to the analytical methods for the drug substance and drug product. Although the NDA has provided sufficient information on raw material controls, manufacturing processes and process controls, and contains adequate specifications and stability data, without adequately validated analytical methods the product quality of the drug substance and drug product cannot be assured. Additionally, an overall recommendation of acceptability has not yet been made for the establishments. Therefore, the NDA is not recommended for approval from the CMC-perspective at this time.

The review team has not yet initiated labeling discussions with the applicant. Edits to the labels and labeling are noted in this review and will be finalized during review team labeling discussions.

Prior to approval, the following pending issues must be satisfactorily resolved.

- An adequate response to the outstanding CMC deficiencies regarding the analytical methods validation
- An overall site recommendation of acceptable in EES
- Final acceptability of the labels and labeling

III. Administrative

A. Reviewer's Signature:

(See appended electronic signature page)

Maotang Zhou, Ph.D., Reviewer, ONDQA
Anamitro Banerjee, Ph.D., Reviewer, ONDQA

B. Endorsement Block:

(See appended electronic signature page)

Rapti Madurawe, Ph.D., Branch Chief, Branch V, Division of New Drug Quality Assessment II, ONDQA

C. CC Block: entered electronically in DARRTS

83 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

MAOTANG ZHOU
09/06/2013

ANAMITRO BANERJEE
09/06/2013

RAPTI D MADURAWE
09/06/2013

Initial Quality Assessment (IQA) and Filing Review for Pre-Marketing Applications

Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: 204-684
   Submission Date: April 19, 2013
   GRMP Goal Date: September 13, 2013
   PDUFA Goal Date: December 19, 2013

2. PRODUCT PROPERTIES:

Trade or Proprietary Name:	IMPAVIDO®*
Established or Non-Proprietary Name (USAN) and strength:	Miltefosine capsules, 50 mg
Dosage Form:	Capsule

** Proposed in the NDA (under review - previously granted on 02/08/2012)*

3. NAME:

Name:	Paladin Therapeutics Inc.

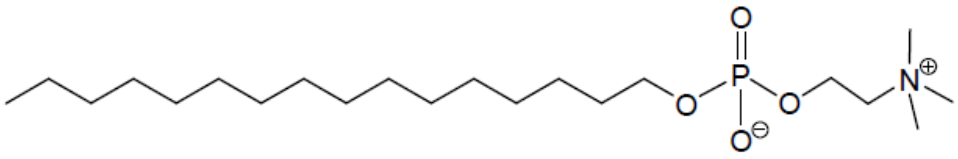
4. SUBMISSION PROPERTIES:

Review Priority :	PRIORITY
Property (Legal Basis):	505 (b)(2)
Responsible Organization:	DAIP

Review Information

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

Miltefosine: choline hydroxide, hexadecyl hydrogen phosphate, inner salt (USAN)
2-(Hexadecoxy-oxido-phosphoryl)oxyethyl-trimethyl-azanium



$C_{21}H_{46}NO_4P$
MW = 407.6

2. INDICATION: Treatment of visceral, cutaneous, and mucosal leishmaniasis

3. ROUTE OF ADMINISTRATION: Oral

4. STRENGTH/POTENCY: 50 mg

5. Rx/OTC DISPENSED: ☒Rx ☐OTC

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

Is this a SPOTS product? ☐Yes ☒No ☐ Not evaluated at time of IQA.

7. RELATED REVIEW DOCUMENTS:

a. Drug Master Files listed on 356h form:

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	IV		(b) (4)	August 31, 2012	
	III			August 24, 2012	
	III			September 10, 2012	
	IV			Included in DMF (b) (4)	

b. Consults Recommended by CMC and Biopharmaceutics

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics	☐	☒	
Clin Pharm	☐	☐	
EES	☒	☐	Submitted (May 3, 2013)
Pharm/Tox	☒	☐	To be submitted
Methods Validation	☒	☐	To be submitted
EA	☐	☒	Categorical exclusion claim
New Drug Micro	☐	☐	TBD (*if needed*)
CDRH	☐	☐	
Other ( )	☐	☐	

c. Other Applications or Submissions to note (if any):

DOCUMENT NAME	DATE	APPLICATION NUMBER	DESCRIPTION
IND		105430	Submitted March 8, 2010

d. Previous Communications with the Applicant to note (if any):

DOCUMENT NAME	Document DATE	APPLICATION NUMBER	DESCRIPTION
STP letter	04/09/2010	105430	CMC comments included
Advice letter	6/28/201o	105430	Comments sent (meeting denied)
Pre-NDA meeting	01/11/2012	105430	Preliminary responses
Pre-NDA meeting	02/09/2012	105430	Meeting minutes
RTF Letter	11/26/2012	NDA 204684	

Overall Conclusions and Recommendations

Is the Product Quality Section of the application fileable from a CMC perspective?		
Yes	No	CMC Filing Issues
☒	☐	

Are there potential CMC review issues to be forward to the applicant with the 74 day letter?		
Yes	No	CMC Comments for 74 Day Letter
☒	☐	The following comments have been forwarded to the applicant on May 31, 2013: 1. *Please provide a sample of the drug product, miltefosine capsules, packaged in the proposed* (b) (4) *packaging configuration. Also, include a sample of a blister* (b) (4) 2. *As eight months have passed since the first NDA submission (dated September 27, 2012), please provide updated stability data for the batches listed in section 3.2.P.8, particularly for batches 1F2639, 1M3150, and batch 2C3816* (b) (4) .

Is the Product Quality Section of the application fileable from a biopharmaceutics perspective?		
Yes	No	Biopharmaceutics Filing Issues
☒	☐	

Are there potential biopharmaceutics review issues to be forward to the applicant with the 74 day letter?		
Yes	No	Biopharmaceutics Comments for 74 Day Letter
☒	☐	

CMC Summary: Critical Issues and Complexities

CMC Critical Issues or Complexities
Miltefosine is an antileishmanial drug, a new molecular entity, a relatively small synthetic molecule [redacted] (b) (4) The proposed drug product consists of an encapsulated formulation of miltefosine drug substance containing 50 mg drug substance per capsule, [redacted] (b) (4) with the formulation excipients and filled into a size 2 opaque red hard gelatin capsule with "PLB" imprinted on the capsule body and "MILT 50" imprinted on the cap using a white ink. One of the most critical review issues will be to determine if the proposed method of analysis for impurities (HPTLC) for both drug substance and drug product is adequate. Other important issues for this NDA are discussed below in the Summary section.

Does the submission contain any of the following elements?			
Nanotechnology	QbD Elements	PET	Other, please explain
☐	☐	☐	

Is a team review recommended?		
Yes	No	Suggested expertise for team
☒	☐	

Review Team Assignments (if known)	
Drug Substance	Anamitro Banerjee
Drug Product	Maotang Zhou
Biopharmaceutics	Mark Seggel
QbD	N/A
Product Quality Microbiology	TBD (*if needed*)
ONDQA PM	Althea Cuff/Navdeep Bhandari

Summary or Highlights of the Application *(not already mentioned in other sections)*

The original NDA was first submitted on September 26, 2012; however, due to several Clinical and Statistical deficiencies, it was issued a RTF letter on November 26, 2012. The following CMC comments were included in the "Additional Comments and Requests" section of the RTF letter:

> *1. Please provide a description and a validation report for the HPLC analytical procedure used for the detection of* (b) (4) *in miltefosine drug substance described in section 3.2.S.3.2. Impurities.*
>
> *2. Add tests for* (b) (4) *residual solvents in the drug substance specifications or provide justification for exclusion of these tests from the specification.*
>
> *3. For the drug substance, include the Postapproval Stability Protocol (with the testing intervals, storage conditions and tests) in section 3.2.S.7.2. Postapproval Stability Protocol and Stability Commitment.*

The NDA was submitted again on April 19, 2013 (current submission).

Changes between Clinical DP and Proposed Commercial DP

Clinical Tablets	Commercial Tablets
Changes in the manufacturing site and process are described below (in the Drug Product section).	

Miltefosine is an antileishmanial drug. The specific mode of action is unknown, but is likely to involve interaction with lipids (phospholipids and sterols) including membrane lipids. Miltefosine has been approved in the EU since 2002.

Miltefosine is to be taken daily for 28 days, with food. The number of 50 mg capsules per day is determined by bodyweight (two or three capsules daily).

Drug Substance

The miltefosine drug substance is a new molecular entity, a relatively small synthetic molecule (b) (4) It is freely soluble in water, 0.1N hydrochloric acid, 0.1N sodium hydroxide, methanol, ethanol and (b) (4) and insoluble in (b) (4) and it is quite hygroscopic. The scheme of the proposed manufacturing process described as route (b) (4) is attached below miltefosine (Appendix 1). The applicant reports that only (b) (4) has been observed by (b) (4) for miltefosine (b) (4) according to the proposed commercial synthesis. <u>*Comment*</u>*: It is not clear if any formal* (b) (4) *studies were performed.*

The applicant states that prior to manufacture at the proposed commercial site (b) (4) the drug

substance was manufactured at various development sites (b) (4) The first few batches were manufactured using earlier versions of the synthesis, (b) (4) There are no (b) (4) in the miltefosine synthesis. (b) (4) The proposed commercial synthesis route (b) (4) was introduced at (b) (4) in 1989, and all subsequent batches were manufactured by this route, with drug substance manufacture transferred to the proposed commercial (b) (4) site in 2001. *Comments: The applicant states that the impurity profile is similar for all batches manufactured at different facilities using previous and current routes of synthesis. This needs to be verified. As stated above, The proposed route of synthesis does not include any* (b) (4)*. The proposed synthetic process will need to be evaluated in detail; some operational parameters are described but is there a justification for ranges?*

Batch analysis includes data for several initial batches (b) (4) followed by three production at about (b) (4) and three validation batches at (b) (4) (proposed commercial scale about (b) (4)

The impurities include organic impurities related to miltefosine and relevant to the proposed commercial synthesis and the applicant states the levels are very low - below the qualification level of ICH Q3A (R2). (b) (4) (starting material) and (b) (4) (potential degradant) are controlled using HPTLC method .*Comment: Is the proposed method sensitive enough? Some discussion regarding the method of analysis took place at the pre-IND and pre-NDA (meeting minutes are available in DARRTS).* Also, a discussion on drug substance impurities includes data on (b) (4) – the applicant states that they were below (b) (4) *Comment: Validation data of this analytical procedure do not seem to be provided in the NDA and they may need to be requested. Also, adequacy of the proposed impurity levels and proposed limits may need to be discussed with the pharm/tox reviewer of this application.*

Drug substance specification is attached as Appendix 2 (below), and includes description, identity, chromatographic purity, assay, heavy metals, (b) (4) and residual solvents. There are several tests, which are not proposed to be included in the drug substance specification (b) (4) (b) (4) – justified by the applicant by the (b) (4) solubility of the drug substance across the physiological pH range (b) (4) and the (b) (4) during drug product manufacture. *Comment: No microbial limits are proposed for drug substance (however, some* (b) (4) *observed during drug substance stability testing?).*

The container closure system used to package bulk drug substance at the manufacturing site consists of (b) (4)

The drug substance stability data generated in accordance with ICH Q1A(R2) guidelines are provided in Section 3.2.S.7.3 for batches manufactured by (b) (4) (the proposed commercial

manufacturer) according to synthesis route (b) (4) (the proposed commercial process) in (b) (4) (the proposed commercial packaging contact surface):

- 1 batch (1079609) stored for 60 months at 25°C/60%RH
- 3 batches (813015, 813016, 813017) stored for 36 months at 25°C/60%RH
- 3 batches (5198309, 5198310, 5198311) stored for 12 months at 25°C/60% RH (ongoing) and 6 months at 40°C/75% RH

Based on these data, a retest period of (b) (4) is proposed for drug substance manufactured by (b) (4) using the proposed commercial route and stored at the proposed commercial drug product manufacturing facility in the proposed commercial bulk container closure system at warehouse conditions. *Comment: As noted by the drug substance reviewer, Dr. Banerjee, a formal stability protocol for commercial batches of the drug substance has not been included in section 3.2.S.7.2. (it will be requested via 74-day letter).*

Comments: Almost no change in chromatographic impurity profile is observed during storage under accelerated and long term conditions up to 36 months (or 60 months for one small batch 1079609). (b) (4) (b) (4) *Some results of stress studies on the proposed drug substance are provided in section P.5.*

Drug Product

The proposed drug product consists of an encapsulated formulation of miltefosine drug substance containing 50 mg drug substance per capsule, (b) (4) with the formulation excipients and filled into a size 2 opaque red hard gelatin capsule with "PLB" imprinted on the capsule body and "MILT 50" imprinted on the cap using a white ink.

Miltefosine capsules, 50 mg, contain standard compendial excipients (qualitative and quantitative composition provided in the table in Appendix 3, below). The capsule imprinting ink consists of (b) (4) The finished capsules will be packaged in (b) (4) blisters each containing seven (7) blisters per strip with two blister strips in a (b) (4) peel/push-through carton. *Comment: The applicant states that "other configurations may be possible." This statement is not clear and should be explained.*

The drug product manufacturing process consists of (b) (4) (b) (4)

(b) (4)

(b) (4) *Comment: Comparative dissolution study was conducted* (b) (4) *between batch 1F2639 and the last prechange batch (1C2130) and data provided. These data will need to be reviewed from the biopharmaceutics perspective.*

Pharmaceutical Development section describes the drug product formulation and process development issues. *Comment: No "QbD elements" were identified upon this initial assessment.*

Drug product specification is attached as Appendix 4 (below), and includes description, identification (*only by HPTLC*), assay, degradants, uniformity of dosage forms (*weight variation*), dissolution, water content, and microbiological limits. *Comment: HPTLC method is used for ID, assay and impurities. This method will need to be sent to the FDA laboratories for validation.*

The proposed commercial container closure system consists of (b) (4) blisters, made of an (b) (4) with two (2) blister cards enclosed in a (b) (4) configuration containing two (2) peel/push-through (b) (4) blister cards (b) (4) The secondary packaging consists of boxes each containing two (2) fold-over peel/push-through blister cards for a total of 28 packaged capsules. The applicant stated that the boxes are intended to facilitate transport and storage and do not contribute to the drug product integrity. *Comment: The applicant should provide a sample of the proposed commercial container closure system* (b) (4) *and a sample without* (b) (4) *feature for comparison purposes.*

Stability data submitted in section 3.2.P.8.3 include data for several batches of the drug product (including 18-month long term and 6-month accelerated for three batches manufactured at the commercial facility). Stability data include: Based on these data, an expiration dating period of (b) (4) has been proposed for the proposed commercial drug product when stored at 15-30 deg C in the proposed commercial container closure system. Stability data provided in the application include the following:

- Batch 7G5416: 48 months at 25°C/60% RH, 6 months at 40°C/75% RH
- Batch 8J7717: 36 months at 25°C/60% RH
- Batch 0G0288: 18 months at 25°C/60% RH, 18 months at 30°C/75% RH, 6 months at 40°C/75% RH
- Batch 0G0289: 18 months at 25°C/60% RH, 18 months at 30°C/75% RH, 6 months at 40°C/75% RH
- Batch 0G0290: 18 months at 25°C/60% RH, 18 months at 30°C/75% RH, 6 months at 40°C/75% RH
- Batch 1F2639: 9 months at 25°C/60% RH, 6 months at 30°C/65% RH, 6 months at 30°C/75% RH, 6 months at 40°C/75% RH
- Batch 1M3150: 6 months at 25°C/60% RH, 6 months at 30°C/75% RH, 6 months at 40°C/75% RH
- Batch 2C3816: 3 months at 25°C/60% RH, 3 months at 40°C/75% RH

Batches 1F2639, 1M3150 and 2C3816 were manufactured by (b) (4) (b) (4) (b) (4) the previous batches were manufactured by (b) (4) As discussed at the January 13, 2012 pre-NDA meeting, one batch (2C3816) was packaged in the peel/push through (b) (4) blisters contained in the (b) (4) carton proposed for marketing; all other batches were packaged in the same way without the (b) (4) carton. *Comment: No photostability studies were performed on the drug product (however, the drug substance does not appear to be photosensitive). As several months have passed since the first NDA submission more stability data should be available for the above drug product batches. Therefore, a request for the stability update will be forwarded to the applicant.*

Description of Facility-Related Risks or Complexities (i.e. number of foreign sites, large number of sites involved, etc.)

Three (3) out of four (4) proposed commercial facilities involved in the manufacture of both drug substance and drug product are foreign. All manufacturing facilities are currently scheduled for inspection. See EES for complete list of facilities related to this application.

Biopharmaceutics Summary: Critical Issues, Complexities, and Consults

General Summary

As noted above, miltefosine is freely soluble in aqueous media throughout the physiological pH range (b) (4) The drug product is a relatively straightforward immediate release capsule. The proposed regulatory dissolution test for miltefosine capsules, 50 mg, is conducted with USP Apparatus Type II (paddle) at 50 rpm in a medium consisting of 750 mL of 0.1 N HCl at 37°C. An acceptance criterion of Not Less Than (b) (4) dissolved in (b) (4) is proposed.

The applicant notes that maximum dissolution is achieved (b) (4)

The applicant also notes that, "the same basic capsule formulation of miltefosine has been used throughout clinical development so that no bioequivalence studies were [conducted] to compare different formulations."

Dissolution testing was used to compare batches 1F2639 and 1C2130, which were "the first available postchange and last available prechange batches, respectively, (b) (4) The data demonstrate that the process change did not affect drug product performance. Similarity factors f2 could not be calculated because dissolution was essentially complete by (b) (4)

No claim is made with regard to BCS classification.

Biopharmaceutics Review Issues

Because the observed mean amount dissolved of release and stability samples at release at (b) (4) is typically at least (b) (4) the proposed acceptance criterion of NLT (b) (4) is not justified. Other than for the batches referred to above, dissolution data were only obtained at the (b) (4) time point. It would appear that testing at (b) (4) is accepted by the foreign regulatory authorities. The applicant was therefore asked to re-evaluate the sampling time and acceptance criteria (see 24-JAN-2013 Information Request):

> The proposed regulatory dissolution test for miltefosine capsules, 50 mg, is conducted with USP Apparatus Type II (paddle) at 50 rpm in a medium consisting of 750 mL of 0.1 N HCl at 37°C. An acceptance criterion of Not Less Than (b) (4) dissolved in (b) (4) is proposed. However, the observed mean amount dissolved at (b) (4) is typically at least (b) (4).
>
> For immediate release product the selection of the test sampling time point should be where Q= (b) (4) dissolution occurs. Therefore, please provide dissolution profiles (including 15, 20, 30, and 45 minutes sampling time points, n=12) for your drug product at release and on stability.

Based on the results, propose a sampling time point at which a mean of Not Less Than (b) (4) (Q) is dissolved (see USP <711> Acceptance Table 1).

The NDA resubmission does not appear to address this issue, although in pre-NDA correspondence (see 3.2.R.4), Palidin claimed that testing at an earlier time point such as 15 minutes "would require very short sample withdrawal times, which would be random in nature and would not be a diagnostic control to differentiate batches based on quality criteria." This rationale is not justified by the available data. It is not clear if the applicant understands the USP requirements for dissolution testing since there is no mention of "Q"; the acceptance criterion is present only as NLT (b) (4) dissolved in (b) (4) The following request is provided for the applicant:

Based on the available dissolution data, a mean of (b) (4) miltefosine dissolved occurs at (b) (4) 15 minutes. The proposed acceptance criterion of NLT (b) (4) at (b) (4) is not justified. Accordingly, revise the acceptance criterion for miltefosine capsules to NLT (b) (4) (Q) at 15 minutes (see USP <711> Dissolution, Acceptance Table 1).

FILING REVIEW CHECKLIST

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

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

B. FACILITIES*				
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	☒	☐	Form 356h dated April 19, 2013.

6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**	☐	☒	N/A
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	☒	☐	
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	☒	☐	

9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	☒	☐	
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	☒	☐	

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

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	☒	☐	

D. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
12.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	☐	☐	N/A (all drug substance information is submitted in NDA)

E. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
13.	Does the section contain a description of the DS manufacturing process?	☒	☐	
14.	Does the section contain identification and controls of critical steps and intermediates of the DS in process parameters?	☒	☐	*There are no* (b) (4) *in the proposed route of synthesis.*
15.	Does the section contain information on impurities?	☒	☐	
16.	Does the section contain information regarding the characterization of the DS?	☒	☐	
17.	Does the section contain controls for the DS?	☒	☐	
18.	Has stability data and analysis been provided for the drug substance?	☒	☐	
19.	Does the application contain Quality by Design (QbD) information regarding the DS?	☐	☒	
20.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?	☐	☒	?
21.	Does the section contain container and closure information?	☒	☐	

F. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
22.	Does the section contain quality controls of excipients?	☒	☐	
23.	Does the section contain information on composition?	☒	☐	
24.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	☒	☐	
25.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	☒	☐	
26.	Is there a batch production record and a proposed master batch record?	☒	☐	Provided in section 3.2.R. Regional Information
27.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	☒	☐	N/A
28.	Have any Comparability Protocols been requested	☐	☒	
29.	Does the section contain description of to-be-marketed container/closure system and presentations?	☒	☐	Two (b) (4) blister cards in a box (28 capsule in total per box)
30.	Does the section contain controls of the final drug product?	☒	☐	
31.	Has stability data and analysis been provided to support the requested expiration date?	☒	☐	Stability data submitted in section 3.2.P.8.3 include data for 8 batches
32.	Does the application contain Quality by Design (QbD) information regarding the DP?	☐	☒	
33.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?	☐	☒	*Not obvious*

G. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
34.	Is there a methods validation package?	☒	☐	

H. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
35.	If appropriate, is a separate microbiological section included discussing sterility of the drug product?	☐	☒	N/A (not a sterile product)

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
36.	Has the draft package insert been provided?	☒	☐	
37.	Have the immediate container and carton labels been provided?	☒	☐	Blister and carton labels
38.	Does section contain trade name and established name?	☒	☐	IMPAVIDO (miltefosine) Capsules.

J. BIOPHARMACEUTICS				
	Parameter	**Yes**	**No**	**Comment**
39.	Does the application contain dissolution data?	x		
40.	Is the dissolution test part of the DP specifications?	x		
41.	Does the application contain the dissolution method development report?	x		Consists only of profiles in different pH media. Given the (b) (4) soluble drug substance, additional method development is not warranted.
42.	Is there a validation package for the analytical method and dissolution methodology?	x		
43.	Does the application include a biowaiver request?		x	Not Applicable: the drug product is an NME (in the U.S.); there is no approved RLD.
44.	Does the application include an IVIVC model?		x	
45.	Is information such as BCS classification mentioned, and supportive data provided?		x	No claim made with regard to BCS classification.

46.	Is there a modified-release claim? If yes, address the following: (a) Is there information submitted to support the claim in accordance with 320.25(f)? (b) Does the application include information/data on in vitro alcohol dose-dumping potential?		x	
47.	Is information on mixing the product with foods or liquids included?		x	
48.	Is there any in *vivo* BA or BE information in the submission?	x		
49.	Is there any Biopharmaceutics requests/comments for the Applicant ?	x		See above.
FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
50.	**ARE THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	x		
51.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Not applicable.
52.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Not applicable.
53.	Are there any potential review issues identified?			*See comments above.*

REVIEW AND APPROVAL

See appended electronic signature page}
Dorota Matecka, Ph.D.
CMC Lead
Division of Pre-Marketing Assessment II, Branch V
Office of New Drug Quality Assessment

{See appended electronic signature page}
Mark Seggel, Ph.D.
Biopharmaceutics Reviewer
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Tapash Ghosh, Ph.D.
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Office of New Drug Quality Assessment

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Rapti Madurawe, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment II, Branch V
Office of New Drug Quality Assessment

Appendix 1. DS synthesis (b) (4)

Figure 3.2.S.2.2-1. Overview of Miltefosine Synthesis

Appendix 2. DS Specification

Table 3.2.S.4.1-1. Drug Substance Specifications

Test	Acceptance Criteria	Method
Description	White (b) (4) essentially free of visible foreign matter	Visual inspection
Identification (IR)	IR spectrum corresponds to that of standard similarly measured	USP <197>
Identification (HPLC)	HPLC retention time corresponds to that of standard similarly measured	*Section 3.2.S.4.2.1*
(b) (4)	NMT (b) (4)	USP (b) (4) Method (b) (4)
Assay (HPLC)	(b) (4)	*Section 3.2.S.4.2.1*
Impurities: (b) (4) Total (HPLC + HPTLC)	NMT (b) (4) NMT NMT NMT NMT NMT (b) (4) each NMT (b) (4)	*Section 3.2.S.4.2.1* (HPLC); *Section 3.2.S.4.2.2* (HPTLC)
(b) (4)	NMT (b) (4)	*Section 3.2.S.4.2.3*
	NMT	*Section 3.2.S.4.2.3*
Heavy Metals	NMT (b) (4)	USP <231>, Method II
Residual Solvents (GC):* (b) (4)	NMT (b) (4) NMT NMT	*Section 3.2.S.4.2.4*

* The above acceptance criteria correspond to the ICH Q3C(R5) limits for Class (b) solvents. Alert limits of NMT (b) (4) NMT (b) (4) and NMT (b) (4) have been established.

Appendix 3. DP Composition

Table 3.2.P.1-1. Drug Product Components/Composition

Component	Composition		Function
	mg/capsule	wt %	
Miltefosine	50.0	(b) (4)	Active ingredient
Colloidal Silicon Dioxide NF		(b) (4)	(b) (4)
Microcrystalline Cellulose NF (b) (4)			
Lactose Monohydrate NF			
Talc NF			
Magnesium Stearate NF			
Opaque red hard gelatin capsule size 2*			
(b) (4) white ink**			
Total***	190.0	(b) (4)	

* The capsule shells nominally consist of Gelatin NF (b) (4) Titanium Dioxide USP (b) (4) Ferric Oxide NF Red (b) (4) and Purified Water USP (b) (4) with a typical empty capsule shell weight of about (b) (4) Additional information for the capsule shell is incorporated by reference to (b) (4) Type IV DMF (b) (4) with an authorization letter provided in *Section 1.4.2* of this submission.

(b) (4)

*** The total weight includes the (b) (4)

Appendix 4. DP Specification

Table 3.2.P.5.1-1. Proposed Drug Product Specifications

Test	Acceptance Criteria	Method
Description	White powder, essentially free of foreign matter, encapsulated in a size 2 red opaque hard capsule with "PLB" imprinted on the capsule body and "MILT 50" imprinted on the cap in white.	Visual inspection
Identification (HPTLC)	R_f corresponds to that of standard similarly measured	*Section 3.2.P.5.2.1*
(b) (4)	NMT (b) (4)	USP (b) (4) Method (b) (4)
Assay (HPTLC)	(b) (4)	*Section 3.2.P.5.2.1*
Degradants (HPTLC)	(b) (4) NMT NMT Total: NMT (b) (4)	*Section 3.2.P.5.2.2, Section 3.2.P.5.2.3*
Weight Variation	Conforms to USP <905>	Gravimetric
Dissolution (USP <711>, HPTLC)	NLT (b) (4) dissolved in (b) (4)	*Section 3.2.P.5.2.4*
Microbial Limits:	Total Aerobic Count: NMT Total Yeasts and Molds: NMT (b) (4) (b) (4)	USP <61>/<62>

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

/s/

DOROTA M MATECKA
06/17/2013

MARK R SEGGEL
06/17/2013

TAPASH K GHOSH
06/17/2013

RAPTI D MADURAWE
06/17/2013

Initial Quality Assessment (IQA) and Filing Review

Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: 204-684
   Submission Date: September 26, 2012
   GRMP Goal Date: February 27, 2013
   PDUFA Goal Date: March 27, 2013

2. PRODUCT PROPERTIES:

Trade or Proprietary Name:	IMPAVIDO®*
Established or Non-Proprietary Name (USAN) and strength:	Miltefosine capsules, 50 mg
Dosage Form:	Capsule

** Proposed in the NDA (under review - previously granted on 02/08/20122)*

3. APPLICANT:

Name:	Paladin Therapeutics Inc.

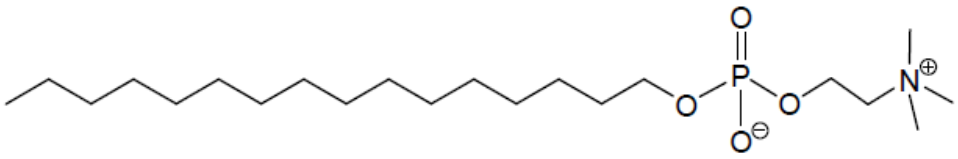
4. SUBMISSION PROPERTIES:

Review Priority :	PRIORITY
Property (Legal Basis):	505 (b)(2)
Responsible Organization:	DAIP

Review Information

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

Miltefosine: choline hydroxide, hexadecyl hydrogen phosphate, inner salt (USAN)
2-(Hexadecoxy-oxido-phosphoryl)oxyethyl-trimethyl-azanium



$C_{21}H_{46}NO_4P$
MW = 407.6

2. INDICATION: Treatment of visceral, cutaneous, and mucosal leishmaniasis

3. ROUTE OF ADMINISTRATION: Oral

4. STRENGTH/POTENCY: 50 mg

5. Rx/OTC DISPENSED: ☒Rx ☐OTC

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

Is this a SPOTS product? ☐Yes ☒No ☐ Not evaluated at time of IQA.

7. RELATED REVIEW DOCUMENTS:

a. Drug Master Files listed on 356h form:

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	IV		(b) (4)	August 31, 2012	
	III			August 24, 2012	
	III			September 10, 2012	
	IV			Included in DMF (b) (4)	

b. Consults Recommended by CMC and Biopharmaceutics

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics	☐	☒	
Clin Pharm	☐	☐	
EES	☒	☐	Submitted (October 12, 2012)
Pharm/Tox	☒	☐	To be submitted
Methods Validation	☒	☐	To be submitted
EA	☐	☒	Categorical exclusion claim
New Drug Micro	☐	☐	TBD (*if needed*)
CDRH	☐	☐	
Other ( )	☐	☐	

c. Other Applications or Submissions to note (if any):

DOCUMENT NAME	DATE	APPLICATION NUMBER	DESCRIPTION
IND		105430	Submitted March 8, 2010

d. Previous Communications with the Applicant to note (if any):

DOCUMENT NAME	Document DATE	APPLICATION NUMBER	DESCRIPTION
STP letter	04/09/2010	105430	CMC comments included
Advice letter	6/28/201o	105430	Comments sent (meeting denied)
Pre-NDA meeting	01/11/2012	105430	Preliminary responses
Pre-NDA meeting	02/09/2012	105430	Meeting minutes

Overall Conclusions and Recommendations

Is the Product Quality Section of the application fileable from a CMC perspective?		
Yes	No	CMC Filing Issues
☒	☐	

Are there potential CMC review issues to be forward to the applicant with the 74 day letter?		
Yes	No	CMC Comments for 74 Day Letter
☒	☐	1. Please provide a description and a validation report for the HPLC analytical procedure used for the detection of [redacted] (b) (4) in miltefosine drug substance described in section 3.2.S.3.2. Impurities. 2. Add tests for [redacted] (b) (4) residual solvents in the drug substance specifications or provide justification for exclusion of these tests from the specification. 3. For the drug substance, include the Postapproval Stability Protocol (with the testing intervals, storage conditions and tests) in section 3.2.S.7.2. Postapproval Stability Protocol and Stability Commitment.

CMC Summary:
Critical Issues and Complexities

CMC Critical Issues or Complexities
Miltefosine is an antileishmanial drug, a new molecular entity, a relatively small synthetic molecule that [redacted] (b) (4). The proposed drug product consists of an encapsulated formulation of miltefosine drug substance containing 50 mg drug substance per capsule, [redacted] (b) (4) with the formulation excipients and filled into a size 2 opaque red hard gelatin capsule with "PLB" imprinted on the capsule body and "MILT 50" imprinted on the cap using a white ink. One of the most critical review issues will be to determine if the proposed method of analysis for impurities (HPTLC) for both drug substance and drug product is adequate. Other important issues for this NDA are discussed below in the Summary section.

Does the submission contain any of the following elements?			
Nanotechnology	QbD Elements	PET	Other, please explain
☐	☐	☐	

Is a team review recommended?		
Yes	No	Suggested expertise for team
☒	☐	

Review Team Assignments (if known)	
Drug Substance	Anamitro Banerjee
Drug Product	Mark Seggel
Biopharmaceutics	Mark Seggel
QbD	N/A
Product Quality Microbiology	TBD (*if needed*)
ONDQA PM	Althea Cuff

Summary or Highlights of the Application ***(not already mentioned in other sections)***

Changes between Clinical DP and Proposed Commercial DP

Clinical Tablets	Commercial Tablets
Changes in the manufacturing site and process are described below (in the Drug Product section).	

Miltefosine is an antileishmanial drug. The specific mode of action is unknown, but is likely to involve interaction with lipids (phospholipids and sterols) including membrane lipids. Miltefosine has been approved in the EU since 2002.

Miltefosine is to be taken daily for 28 days, with food. The number of 50 mg capsules per day is determined by bodyweight (two or three capsules daily).

Drug Substance

The miltefosine drug substance is a new molecular entity, a relatively small synthetic molecule (b) (4). It is freely soluble in water, 0.1N hydrochloric acid, 0.1N sodium hydroxide, methanol, ethanol and (b) (4) and insoluble in (b) (4) and it is quite hygroscopic. The scheme of the proposed manufacturing process described as route (b) (4) is attached below miltefosine (Appendix 1). The applicant reports that only (b) (4) form has been observed by (b) (4) for miltefosine (b) (4) according to the proposed commercial synthesis. *Comment: It is not clear if any formal* (b) (4) *studies were performed.*

The applicant states that prior to manufacture at the proposed commercial site (b) (4) the drug substance was manufactured at various development sites (b) (4) The first few batches were manufactured using earlier versions of the synthesis, (b) (4) There are no (b) (4) in the miltefosine synthesis. (b) (4) The proposed commercial synthesis route (b) (4) was introduced at (b) (4) in 1989, and all subsequent batches were manufactured by this route, with drug substance manufacture transferred to the proposed commercial (b) (4) site in 2001. *Comments: The applicant states that the impurity profile is similar for all batches manufactured at different facilities using previous and current routes of synthesis. This needs to be verified. As stated above, the proposed route of synthesis does not include any* (b) (4) *– the conditions and parameters of the proposed synthetic process will need to be evaluated in detail.*

Batch analysis includes data for several initial batches (b) (4) followed by three production at about (b) (4) and three validation batches at (b) (4) (proposed commercial scale about (b) (4)

The impurities include organic impurities related to miltefosine and relevant to the proposed

commercial synthesis and the applicant states the levels are very low - below the qualification level of ICH Q3A (R2). (b) (4) (starting material) and (b) (4) (potential degradant) are controlled using HPTLC method. *Comment: Is the proposed method sensitive enough? Some discussion regarding the method of analysis took place at the pre-IND and pre-NDA (meeting minutes are available in DARRTS).* Also, a discussion on drug substance impurities includes data on (b) (4) – the applicant states that they were below (b) (4) *Comment: Validation data of this analytical procedure do not seem to be provided in the NDA and will be requested. Also, the impurities levels and the adequacy of the proposed limits should be discussed with the pharm/tox reviewer of this application.*

Drug substance specification is attached as Appendix 2 (below), and includes description, identity, chromatographic purity, assay, heavy metals, (b) (4), and residual solvents. There are several tests, which are not proposed to be included in the drug substance specification (b) (4) – justified by the applicant by the (b) (4) solubility of the drug substance across the physiological pH range (b) (4) and the (b) (4) step during drug product manufacture. *Comment: No microbial limits are proposed for drug substance (however, some water uptake observed during drug substance stability testing?).*

The container closure system used to package bulk drug substance at the manufacturing site consists of (b) (4)

The drug substance stability data generated in accordance with ICH Q1A(R2) guidelines are provided in Section 3.2.S.7.3 for batches manufactured by (b) (4) (the proposed commercial manufacturer) according to synthesis route (b) (4) (the proposed commercial process) in (b) (4) (the proposed commercial packaging contact surface):

- 1 batch (1079609) stored for 60 months at 25°C/60%RH
- 3 batches (813015, 813016, 813017) stored for 36 months at 25°C/60%RH
- 3 batches (5198309, 5198310, 5198311) stored for 12 months at 25°C/60% RH (ongoing) and 6 months at 40°C/75% RH

Based on these data, a retest period of (b) (4) is proposed for drug substance manufactured by (b) (4) using the proposed commercial route and stored at the proposed commercial drug product manufacturing facility in the proposed commercial bulk container closure system at warehouse conditions. *Comment: As noted by the drug substance reviewer, Dr. Banerjee, a formal stability protocol for commercial batches of the drug substance has not been included in section 3.2.S.7.2 (however, it will be requested via a 74-day letter).*

Comments: Almost no change in chromatographic impurity profile is observed during storage under accelerated and long term conditions up to 36 months (or 60 months for one small (b) (4) *batch 1079609).* (b) (4)

(b) (4) *Some results of stress studies on the proposed drug substance are provided in section P.5.5.*

Drug Product

The proposed drug product consists of an encapsulated formulation of miltefosine drug substance containing 50 mg drug substance per capsule, (b) (4) with the formulation excipients and filled into a size 2 opaque red hard gelatin capsule with "PLB" imprinted on the capsule body and "MILT 50" imprinted on the cap using a white ink.

Miltefosine capsules, 50 mg, contain standard compendial excipients (qualitative and quantitative composition provided in the table in Appendix 3, below). The capsule imprinting ink consists of (b) (4). The finished capsules will be packaged in (b) (4) blisters each containing seven (7) blisters per strip with two blister strips in a (b) (4) peel/push-through carton. *Comment: The applicant states that "other configurations may be possible." This statement is not clear and should be explained by the applicant.*

The drug product manufacturing process consists of (b) (4)
(b) (4)
(b) (4) *Comment: Comparative dissolution study was conducted* (b) (4) *between batch 1F2639 and the last prechange batch (1C2130) and data provided. These data will need to be reviewed from the biopharmaceutics perspective.*

Pharmaceutical Development section describes the drug product formulation and process development issues. *Comment: No "QbD elements" were identified upon this initial assessment.*

Drug product specification is attached as Appendix 4 (below), and includes description, identification (*only by HPTLC*), assay, degradants, uniformity of dosage forms (*weight variation*), water content, and microbiological limits. *Comment: HPTLC method is used for ID, assay and impurities. This method will need to be sent to the FDA laboratories for validation.*

The drug product specification also includes a test (a proposed analytical procedure and acceptance criteria) for dissolution, which will be reviewed as part of the evaluation of the proposed drug product from the biopharmaceutics perspective.

The proposed commercial container closure system consists of (b) (4) blisters, made of an (b) (4) with two (2) blister

cards enclosed in a (b) (4) configuration containing two (2) peel/push-through (b) (4) blister cards (b) (4) The secondary packaging consists of boxes each containing two (2) fold-over peel/push-through blister cards for a total of 28 packaged capsules. The boxes are intended to facilitate transport and storage and do not contribute to the drug product integrity

Stability data submitted in section 3.2.P.8.3 include data for several batches of the drug product (including 18-month long term and 6-month accelerated for three batches manufactured at the commercial facility at the proposed production scale). Based on these data, an expiration dating period of (b) (4) has been proposed for the proposed commercial drug product when stored at 15-30 deg C in the proposed commercial container closure system. *Comment: It is no clear which of the stability batches are considered primary. In addition, no photostability studies were performed on the drug product (however, the drug substance does not appear to be photosensitive).*

Description of Facility-Related Risks or Complexities (i.e. number of foreign sites, large number of sites involved, etc.)

Three (3) out of four (4) proposed commercial facilities involved in the manufacture of both drug substance and drug product are foreign. See EES for complete list of facilities related to this application.

FILING REVIEW CHECKLIST

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

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

B. FACILITIES*				
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	☒	☐	Attachment to FDA Form 356h dated September 26, 2012.
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**	☐	☒	N/A

7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	☒	☐	
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	☒	☐	
9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	☒	☐	

10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	☒	☐	

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

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	☒	☐	

D. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
12.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	☐	☐	N/A (all drug substance information is submitted in NDA)

E. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
13.	Does the section contain a description of the DS manufacturing process?	☒	☐	
14.	Does the section contain identification and controls of critical steps and intermediates of the DS in process parameters?	☒	☐	*There are no* (b) (4) *in the proposed route of synthesis.*
15.	Does the section contain information on impurities?	☒	☐	
16.	Does the section contain information regarding the characterization of the DS?	☒	☐	
17.	Does the section contain controls for the DS?	☒	☐	
18.	Has stability data and analysis been provided for the drug substance?	☒	☐	
19.	Does the application contain Quality by Design (QbD) information regarding the DS?	☐	☒	
20.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?	☐	☒	
21.	Does the section contain container and closure information?	☒	☐	

F. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
22.	Does the section contain quality controls of excipients?	☒	☐	
23.	Does the section contain information on composition?	☒	☐	
24.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	☒	☐	
25.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	☒	☐	
26.	Is there a batch production record and a proposed master batch record?	☒	☐	Provided in section 3.2.R. Regional Information
27.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	☒	☐	?
28.	Have any Comparability Protocols been requested	☐	☒	
29.	Does the section contain description of to-be-marketed container/closure system and presentations?	☒	☐	Two (b) (4) blister cards in a box (28 capsule in total per box)
30.	Does the section contain controls of the final drug product?	☒	☐	
31.	Has stability data and analysis been provided to support the requested expiration date?	☒	☐	Stability data submitted in section 3.2.P.8.3 include data for 8 batches (*not clear which ones are considered primary)*
32.	Does the application contain Quality by Design (QbD) information regarding the DP?	☐	☒	
33.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?	☐	☒	*Not obvious*

G. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
34.	Is there a methods validation package?	☒	☐	

H. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
35.	If appropriate, is a separate microbiological section included discussing sterility of the drug product?	☐	☒	N/A (not a sterile product)

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
36.	Has the draft package insert been provided?	☒	☐	
37.	Have the immediate container and carton labels been provided?	☒	☐	Blister and carton labels
38.	Does section contain trade name and established name?	☒	☐	IMPAVIDO (miltefosine) Capsules.

FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
39.	**ARE THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**	☒		
40.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			N/A
41.	Are there any potential review issues identified?	☒		*See comments above.*

REVIEW AND APPROVAL

See appended electronic signature page}
Dorota Matecka, Ph.D.
CMC Lead
Division of Pre-Marketing Assessment II, Branch V
Office of New Drug Quality Assessment

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Office of New Drug Quality Assessment

Appendix 1. DS synthesis (b) (4)

Figure 3.2.S.2.2-1. Overview of Miltefosine Synthesis

Appendix 2. DS Specification

Table 3.2.S.4.1-1. Drug Substance Specifications

Test	Acceptance Criteria	Method
Description	White (b) (4) essentially free of visible foreign matter	Visual inspection
Identification (IR)	IR spectrum corresponds to that of standard similarly measured	USP <197>
Identification (HPLC)	HPLC retention time corresponds to that of standard similarly measured	*Section 3.2.S.4.2.1*
(b) (4)	NMT (b) (4)	USP (b) (4) Method (b) (4)
Assay (HPLC)	(b) (4)	*Section 3.2.S.4.2.1*
Impurities: (b) (4) Total (HPLC + HPTLC)	 NMT (b) (4) NMT NMT NMT NMT NMT (b) (4) NMT (b) (4)	*Section 3.2.S.4.2.1* (HPLC); *Section 3.2.S.4.2.2* (HPTLC)
Phosphate (HPLC)	NMT	*Section 3.2.S.4.2.3*
Chloride (HPLC)	NMT	*Section 3.2.S.4.2.3*
Heavy Metals	NMT (b) (4)	USP <231>, Method II
Residual Solvents (GC):* (b) (4)	 NMT (b) (4) NMT NMT	*Section 3.2.S.4.2.4*

* The above acceptance criteria correspond to the ICH Q3C(R5) limits for Class (b) (4) solvents. Alert limits of NMT (b) (4) NMT (b) (4) and NMT (b) (4) have been established.

Appendix 3. DP Composition

Table 3.2.P.1-1. Drug Product Components/Composition

Component	Composition		Function
	mg/capsule	wt %	
Miltefosine	50.0	(b) (4)	Active ingredient
Colloidal Silicon Dioxide NF	(b) (4)	(b) (4)	(b) (4)
Microcrystalline Cellulose NF (b) (4)			
Lactose Monohydrate NF			
Talc NF			
Magnesium Stearate NF			
Opaque red hard gelatin capsule size 2*			
(b) (4) white ink**			
Total***	190.0		

* The capsule shells nominally consist of Gelatin NF (b) (4) Titanium Dioxide USP (b) (4) Ferric Oxide NF Red (b) (4) and Purified Water USP (b) (4) with a typical empty capsule shell weight of about (b) (4) Additional information for the capsule shell is incorporated by reference to (b) (4) Type IV DMF (b) (4) with an authorization letter provided in *Section 1.4.2* of this submission.

(b) (4)

*** The total weight includes the (b) (4)

Appendix 4. DP Specification

Table 3.2.P.5.1-1. Proposed Drug Product Specifications

Test	Acceptance Criteria	Method
Description	White powder, essentially free of foreign matter, encapsulated in a size 2 red opaque hard capsule with "PLB" imprinted on the capsule body and "MILT 50" imprinted on the cap in white.	Visual inspection
Identification (HPTLC)	R_f corresponds to that of standard similarly measured	*Section 3.2.P.5.2.1*
(b) (4)	NMT (b) (4)	USP (b) (4) Method (b) (4)
Assay (HPTLC)	(b) (4)	*Section 3.2.P.5.2.1*
Degradants (HPTLC)	1-Hexadecanol: NMT (b) (4) Unknowns: NMT Total: NMT	*Section 3.2.P.5.2.2, Section 3.2.P.5.2.3*
Weight Variation	Conforms to USP <905>	Gravimetric
Dissolution (USP <711>, HPTLC)	NLT (b) (4) dissolved in (b) (4)	*Section 3.2.P.5.2.4*
Microbial Limits:	Total Aerobic Count: NMT (b) (4) Total Yeasts and Molds: NMT (b) (4)	USP <61>/<62>

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/s/

DOROTA M MATECKA
11/26/2012

RAPTI D MADURAWE
11/26/2012

CMC Comments Section

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:		**CFN:**		**FEI:**	(b) (4)
	(b) (4)				
DMF No:				**AADA:**	
Responsibilities:	FINISHED DOSAGE RELEASE TESTER				
	FINISHED DOSAGE STABILITY TESTER				
Profile:	CONTROL TESTING LABORATORY			**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION				
Milestone Date:	17-JAN-2014				
Decision:	ACCEPTABLE				
Reason:	DISTRICT RECOMMENDATION				

Establishment:		**CFN:**	(b) (4)	**FEI:**	(b) (4)
	(b) (4)				
DMF No:				**AADA:**	
Responsibilities:	FINISHED DOSAGE PACKAGER				
Profile:	CAPSULES, PROMPT RELEASE			**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION				
Milestone Date:	18-NOV-2013				
Decision:	ACCEPTABLE				
Reason:	DISTRICT RECOMMENDATION				

Establishment:		**CFN:**		**FEI:**	(b) (4)
	(b) (4)				
DMF No:				**AADA:**	
Responsibilities:	FINISHED DOSAGE MANUFACTURER				
	FINISHED DOSAGE PACKAGER				
	FINISHED DOSAGE STABILITY TESTER				
Profile:	CAPSULES, PROMPT RELEASE			**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION				
Milestone Date:	17-JAN-2014				
Decision:	ACCEPTABLE				
Reason:	DISTRICT RECOMMENDATION				
