

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203791Orig1s000**

**CHEMISTRY REVIEW(S)**

# **NDA 203791**

**Sitavig  
(acyclovir) Buccal Tablets, 50 mg**

**BioAlliance**

**Addendum 1 to  
Review 1**

**Shrikant Pagay  
Fuqiang Liu**

**Office of New Drug Quality Assessment**

**For the Division of Anti Viral Drug Product**

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# Chemistry Review Data Sheet

1. NDA 203791
2. REVIEW #: Addendum 1 to Review #1
3. REVIEW DATE: 05-Apr-2013 (application recd. 3/12/2012)
4. REVIEWER: Fuqiang Liu (drug substance)/Shrikant Pagay (drug product)
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Pre-NDA Meeting	5/26/2011

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
	3/12/2012
	6/15/2012
	8/1/2012
	8/29/2012
Original and Amendments	10/19/2012
	12/3/2012
	3/7/2013
	4/4/2013
	4/9/2013

7. NAME & ADDRESS OF APPLICANT:

Name: BioAlliance Pharma  
49 boulevard du Général Martial Valin  
Address: 75015 Paris  
France  
Representative: Jim Carter, Principal, Regulatory Compliance Initiatives  
US Agent for BioAlliance Pharma  
Telephone: 702-914-0798

## Chemistry Review Data Sheet

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Acyclovir Buccal Tablet(Sitavig)
- b) Non-Proprietary Name (USAN): Acyclovir Extended Release Tablet
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type:3
  - Submission Priority: S

## 9. LEGAL BASIS FOR SUBMISSION: 505 (b) (2)

## 10. PHARMACOL. CATEGORY: Antiviral

## 11. DOSAGE FORM: Tablet (inserted in buccal cavity)

## 12. STRENGTH/POTENCY: 50 mg

## 13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

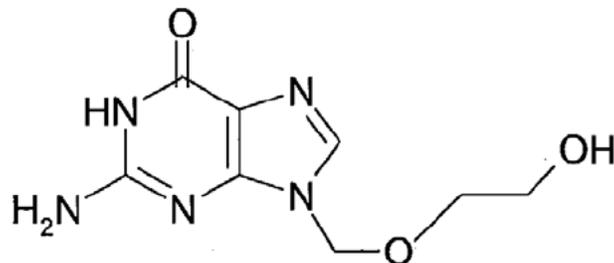
## 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

**Chemical Name:**

- 1) 9-(2-Hydroxyethoxymethyl) guanine
- 2) 2-amino-1, 9-dihydro-9-(2-hydroxyethoxymethyl)-6H-purin-6-one
- 3) Acycloguanosine

## Chemistry Review Data Sheet

## Chemical Structure:



**Molecular Formula:** C<sub>8</sub>H<sub>11</sub>N<sub>5</sub>O<sub>3</sub>      **Formula Weight:** 225.2

## 17. RELATED/SUPPORTING DOCUMENTS:

## A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	2	(b) (4)	Acyclovir DS	1	Adequate	27-Nov-2012 F. Liu	LOA date Nov. 22, 2011

<sup>1</sup> 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")

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

## B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	22404	Micranazole Buccal Tablet

## Chemistry Review Data Sheet

## 18. STATUS:

**ONDQA:**

<b>CONSULTS/ CMC RELATED REVIEWS</b>	<b>RECOMMENDATION</b>	<b>DATE</b>	<b>REVIEWER</b>
Biometrics	NA		
EES	Acceptable	4/9/2013	Report attached
Pharm/Tox	NA		
Biopharm	Adequate	12/6/2012	Dr. Ghosh
LNC	NA		
Methods Validation	NA		
OPDRA	NA		
EA	NA		
Microbiology	NA		

# The Chemistry Review for NDA 203791

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

This NDA has provided adequate information to assure the identity, strength, purity, and quality of the drug product. The drug master file for Acyclovir drug substance supporting this NDA is adequate. An "Acceptable" site recommendation from the Office of Compliance was made on 4/9/2013. Labeling for the blister, carton and the CMC related information in the package insert are adequate. From the CMC perspective the NDA is recommended for approval.

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

None

### II. Summary of Chemistry Assessments

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

##### Drug Substance

Acyclovir drug substance was referenced to Drug Master File (DMF) (b)(4) and a letter of authorization was provided in the NDA. The DMF holder is (b)(4). DMF (b)(4) was reviewed to support NDA 203791 and found adequate on Nov 29, 2012.

A potential genotoxic impurity identified during DMF review was later concluded to be of low risk due to its extreme reactivity (hence low carryover) and downstream purification capability considering its safety threshold (i.e. 0 (b)(4) % based on a 50 mg single dose). This Acyclovir DS is (b)(4) as referenced in literature. Therefore, during NDA review, (b)(4) specification. The revised (b)(4) specification of (u)(4) % (instead of NMT (u)(4) %) is consistent with the DMF (u)(4) drug substance specification. Acyclovir drug substance manufactured by the DMF holder has the (b)(4).

Based on data from long term stability studies, no evidence of degradation is noted. The recommended retest period is 60 months from the manufacturing date when stored at room temperature.

A CMC information request (IR) letter conveyed to the DMF holder on August 15, 2012 is pending response. Questions in this IR are not holding issues thus the DMF is still

## Executive Summary Section

considered to be adequate to support the use of the Acyclovir drug substance in NDA 203791. Refer to the review of DMF (b) (4) for more details.

Drug product

The drug product is acyclovir 50 mg buccal tablet; it is placed in the buccal cavity for drug delivery. The tablet surface is flat on one side and convex surface on the other side. The flat surface is debossed with AL21. The tablet is formulated with USP grade microcrystalline cellulose used as a (b) (4), povidone as a (b) (4), sodium laurel sulfate as a (b) (4), magnesium stearate as a (b) (4) and silicon dioxide for (b) (4). Hypromellose is used for (b) (4). Milk protein concentrate is used for (b) (4). The tablets are manufactured by (b) (4). (b) (4). The tablets are packaged in blister with one tablet contained in each blister and 2 blister packs are placed in each carton. All three primary stability batches were manufactured at the commercial production facility with at least one batch manufactured at the commercial scale ((b) (4) tablets). The two other batches were manufactured at (b) (4)% of the commercial scale and manufactured on the equipments of the same design and principle as that of the commercial scale. The quality parameters monitored for the tablet performance are dissolution for drug release and adhesivity for the tablet to attach to the upper gum. The remaining tests - assay, impurities etc., are performed to insure that the tablet quality is maintained through the shelf life. Most of the testing is performed by compendial test methods except for assay, impurities and adhesivity. These 3 tests were developed in-house and validated. The drug release is controlled by in-vitro dissolution test. The dissolution specification include 3 time points with not more than (b) (4)% of the drug dissolved in one hour, not more than (b) (4)% in 5 hours and more than (b) (4)% in 12 hours. The drug product is assigned 3 years shelf life when stored under controlled room temperature.

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

The drug product is indicated for the treatment of herpes. The entire treatment requires only one tablet. However, 2 tablets are dispensed in the event the first tablet falls off from buccal cavity within 6 hours after administration. The NDA review team has found the inclusion of an extra tablet acceptable. The tablet is administered by adhering the convex surface of the tablet to the upper gum above the incisor tooth. Package insert includes detailed information on how the drug is administered and when to use the extra tablet. The drug is slowly released through saliva.

## Executive Summary Section

**C. Basis for Approvability or Not-Approval Recommendation**

The DMF for Acyclovir DS is adequate. The controlled strategy of the drug product is material controls, manufacturing process controls, and adequate specifications to assure reproducible quality. Microbiological quality of the tablets is well controlled specially considering that the tablet contains milk protein concentrate. Tablet dissolution performance was found acceptable by the biopharmaceutics reviewer. Sufficient stability data was provided including the stability data of the targeted production scale batch. Sufficient manufacturing experience was demonstrated in manufacturing batch at the commercial facility. The quality of the primary stability batches assures strength, quality and purity of the drug product through the proposed shelf life. The approved shelf life is 36 months. All facilities have acceptable site recommendations as of 4/9/2013. The labeling information for the blister pack, carton, the description section and how supplied and storage statement in the package insert is adequate. The NDA is recommended for approval from a CMC perspective.

**III. Administrative****A. Reviewer's Signatures**

Shrikant Pagay, Fuqiang Liu  
*on file*

**B. Endorsement Block**

Rapti Madurawe  
*On file*

**C. CC Block**

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/s/  
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SHRIKANT N PAGAY  
04/09/2013

FUQIANG P LIU  
04/09/2013

RAPTI D MADURawe  
04/10/2013



# CHEMISTRY REVIEW



## Executive Summary Section

### Compliance Report

### FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

<b>Application:</b>	NDA 203791/000	<b>Sponsor:</b>	BIOALLIANCE PHARMA
<b>Org. Code:</b>	530		95651
<b>Priority:</b>	3		LAS VEGAS, NV 89193
<b>Stamp Date:</b>	12-MAR-2012	<b>Brand Name:</b>	Acyclovir Buccal Tablet (Topical)
<b>PDUFA Date:</b>	12-APR-2013	<b>Estab. Name:</b>	Acyclovir Buccal Tablet (Topical)
<b>Action Goal:</b>		<b>Generic Name:</b>	
<b>District Goal:</b>	14-JUL-2012	<b>Product Number; Dosage Form; Ingredient; Strengths</b>	001; TABLET, EXTENDED RELEASE; ACYCLOVIR; 50MG

<b>FDA Contacts:</b>	S. PAGAY	Prod Qual Reviewer		3017961429
	A. CUFF	Product Quality PM	(HF-01)	3017964061
	S. MOSADDEGH	Regulatory Project Mgr	(HFD-530)	3017964876
	S. MILLER	Team Leader		3017961418

<b>Overall Recommendation:</b>	ACCEPTABLE	on 08-APR-2013	by M. HEAYN	(HFD-320)	3017964753
	PENDING	on 27-MAR-2012	by EES_PROD		

<b>Establishment:</b>	<b>CFN:</b>	<b>FEI:</b>	(b) (4)
	(b) (4)		
<b>DMF No:</b>		<b>AADA:</b>	
<b>Responsibilities:</b>	(b) (4)	<b>OAI Status:</b>	NONE
<b>Profile:</b>			
<b>Last Milestone:</b>	OC RECOMMENDATION		
<b>Milestone Date:</b>	30-MAR-2012		
<b>Decision:</b>	ACCEPTABLE		
<b>Reason:</b>	DISTRICT RECOMMENDATION		

Executive Summary Section

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT**

CFN: 9615801 FEI: 3003583056

FARMEA ANGERS  
10 RUE BOUCHE THOMAS  
ANGERS, , FRANCE

AADA:

FINISHED DOSAGE MANUFACTURER  
FINISHED DOSAGE PACKAGER  
FINISHED DOSAGE RELEASE TESTER  
FINISHED DOSAGE STABILITY TESTER  
TABLETS, EXTENDED RELEASE

OAI Status: NONE

OC RECOMMENDATION

04-APR-2013

ACCEPTABLE

DISTRICT RECOMMENDATION

---

CFN: (b) (4) FEI: (b) (4)

(b) (4)

AADA:

OAI Status: NONE

OC RECOMMENDATION

27-MAR-2012

ACCEPTABLE

BASED ON PROFILE

---

CFN: FEI: (b) (4)

(b) (4)

AADA:

OAI Status: NONE

OC RECOMMENDATION

27-NOV-2012

ACCEPTABLE

DISTRICT RECOMMENDATION

# **NDA 203791**

**Sitavig  
Acyclovir 50 mg Buccal Tablet**

**BioAlliance**

**Shrikant Pagay  
Fuqiang Liu  
Division of Anti Viral Drug Product**

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# Chemistry Review Data Sheet

1. NDA 203791
2. REVIEW #: 01
3. REVIEW DATE: 05-Dec-2012 (application recd. 3/12/2012)
4. REVIEWER: Fuqiang Liu (drug substance)/Shrikant Pagay (drug product)
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Pre-NDA Meeting	5/26/2011

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
	3/12/2012
	6/15/2012
	8/1/2012
Original and Amendments	8/29/2012
	10/19/2012
	12/3/2012

7. NAME & ADDRESS OF APPLICANT:

Name: BioAlliance Pharma  
49 boulevard du Général Martial Valin  
Address: 75015 Paris  
France  
Representative: Jim Carter, Principal, Regulatory Compliance Initiatives  
US Agent for BioAlliance Pharma  
Telephone: 702-914-0798

8. DRUG PRODUCT NAME/CODE/TYPE:

## Chemistry Review Data Sheet

- a) Proprietary Name: Acyclovir Buccal Tablet(Sitavig)  
b) Non-Proprietary Name (USAN): Acyclovir Extended Release Tablet  
c) Code Name/# (ONDC only):  
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type:3
  - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (2)

10. PHARMACOL. CATEGORY: Antiviral

11. DOSAGE FORM: Tablet (inserted in buccal cavity)

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

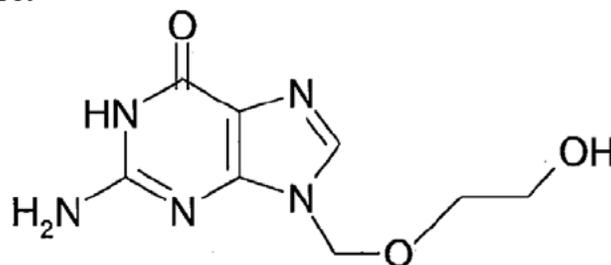
Not a SPOTS product

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

**Chemical Name:**

- 1) 9-(2-Hydroxyethoxymethyl) guanine
- 2) 2-amino-1, 9-dihydro-9-(2-hydroxyethoxymethyl)-6H-purin-6-one
- 3) acycloguanosine

**Chemical Structure:**



**Molecular Formula:** C<sub>8</sub>H<sub>11</sub>N<sub>5</sub>O<sub>3</sub>

**Formula Weight:** 225.2

Chemistry Review Data Sheet

**17. RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	2	(b) (4)	Acyclovir DS	1	Adequate	27-Nov-2012 F. Liu	LOA date Nov. 22, 2011

<sup>1</sup> 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")

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

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	22404	Miconazole Buccal Tablet

**18. STATUS:**

**ONDQA:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Pending		
Pharm/Tox	NA		
Biopharm			
LNC	NA		
Methods Validation	NA		
OPDRA	NA		
EA	NA		
Microbiology	NA		

# The Chemistry Review for NDA 203791

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

This NDA has provided adequate information to assure the identity, strength, purity, and quality of the drug product. The drug master file for Acyclovir drug substance supporting this NDA is adequate. However, a recommendation from the Office of Compliance on the site acceptability has not been made as of the date of this review. Therefore, from the CMC perspective, this NDA is not recommended for approval until the site acceptability is established.

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

None

### II. Summary of Chemistry Assessments

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

##### Drug Substance

Acyclovir drug substance was referenced to Drug Master File (DMF) (b)(4) and a letter of authorization was provided in the NDA. The DMF holder is (b)(4). DMF (b)(4) was reviewed to support NDA 203791 and found adequate on Nov 29, 2012.

A potential genotoxic impurity identified during DMF review was later concluded to be of low risk due to its extreme reactivity (hence low carryover) and downstream purification capability considering its safety threshold (i.e. (b)(4)% based on a 50 mg single dose). This Acyclovir DS is a (b)(4) as referenced in literature. Therefore, during NDA review, a (b)(4) specification. The revised (b)(4) specification of (b)(4)% (instead of NMT (b)(4)% ) is consistent with the DMF (b)(4) drug substance specification. Acyclovir drug substance manufactured by the DMF holder has the (b)(4).

Based on data from long term stability studies, no evidence of degradation is noted. The recommended retest period is 60 months from the manufacturing date when stored at room temperature.

A CMC information request (IR) letter conveyed to the DMF holder on August 15, 2012 is pending response. Questions in this IR are not holding issues thus the DMF is still

## Executive Summary Section

considered to be adequate to support the use of the Acyclovir drug substance in NDA 203791. Refer to the review of DMF (b) (4) for more details.

Drug product

The drug product is acyclovir 50 mg extended release tablet; it is placed in the buccal cavity for drug delivery. The tablet is formulated with USP grade microcrystalline cellulose used as a (b) (4), povidone as a (b) (4), sodium laurel sulfate as a (b) (4), magnesium stearate as a (b) (4) and silicon dioxide for (b) (4). Hypromellose is used for (b) (4); milk protein concentrate is used to (b) (4). The tablets are manufactured by (b) (4). The tablet surface is flat on one side and convex surface on the other side. The flat surface is debossed with AL21. The tablets are packaged in blister with 2 tablets per blister. All three primary stability batches were manufactured at the commercial production facility with at least one batch manufactured at the commercial scale ((b) (4) tablets). The two other batches were manufactured at (b) (4) % of the commercial scale and manufactured on the equipments of the same design and principle as that of the commercial scale. The quality parameters monitored for the tablet performance are dissolution for drug release and adhesivity for the tablet to attach to the upper gum. The remaining tests - assay, impurities etc., are performed to insure that the tablet quality is maintained through the shelf life. Most of the testing is performed by compendial test methods except for assay, impurities and adhesivity. These 3 tests were developed in-house and validated. The drug product is assigned 3 years shelf life when stored under controlled room temperature.

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

The drug product is indicated for the treatment of herpes. The tablet is designed to stick to the upper gum just above the incisor tooth at the site of infection. The drug is slowly released through saliva. Acyclovir acts as a pro-drug; it undergoes phosphorylation in response to HSV (Herpes Simplex Virus) thymidine kinase, and it is then further phosphorylated by infected host cell enzymes into triphosphate, which selectively inhibits HSV viral DNA replication.

**C. Basis for Approvability or Not-Approval Recommendation**

The DMF for Acyclovir DS is adequate. The controlled strategy of the drug product is material controls, manufacturing process controls, and adequate specifications to assure reproducible quality. Microbiological quality of the tablets is well controlled specially considering that the tablet contains milk protein concentrate. Sufficient stability data was provided including the stability of the targeted production size batch. Sufficient experience was developed in manufacturing batch at the commercial facility. The quality of the primary stability batches assures strength, quality and purity of the drug

**Executive Summary Section**

product through the proposed shelf life. However, the following deficiency for non-approval will need to be resolved:

Recommendation from the Office of Compliance on the site acceptability has not been made as of the date of this review.

**III. Administrative****A. Reviewer's Signatures**

Shrikant Pagay, Fuqiang Liu  
*on file*

**B. Endorsement Block**

Rapti Madurawe  
*On file*

**C. CC Block**

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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.**  
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/s/  
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SHRIKANT N PAGAY

12/06/2012

I have checked and rechecked the document.

FUQIANG P LIU

12/06/2012

RAPTI D MADURawe

12/07/2012

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

## Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER:203-791
2. SUBMISSION TYPE :Original
3. SUBMISSION NUMBER:000
4. PRODUCT PROPERTIES:

Trade or Proprietary Name:	Sitavig
Established or Non-Proprietary Name (USAN):	acyclovir
Dosage Form:	buccal tablet

5. NAME & ADDRESS OF APPLICANT:

Name:	BioAlliance Pharma
Address:	Paris, France
Representative:	Regulatory Compliance Initiatives

6. SUBMISSION PROPERTIES:

Review Priority :	Standard
Classification (Code):	New Dosage Form

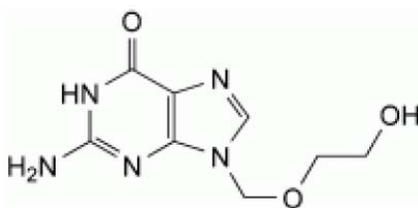
ONDQA Initial Quality Assessment (IQA) and Filing Review  
For Pre-Marking Applications

NDA #: 203-791

Property (Legal Basis):	505 (b) 2
Responsible Organization:	OND

## Review Information

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



Acyclovir

2. INDICATION Treatment of recurrent oral Herpes lesions and

(b) (4)

3. PHARMACOLOGICAL CATEGORY: Antiviral

4. ROUTE OF ADMINISTRATION: Oral

5. STRENGTH/POTENCY: 50 mg

6. Rx/OTC DISPENSED:  Rx  OTC

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
For Pre-Marking Applications**

NDA #: 203-791

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

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

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
For Pre-Marking Applications**

NDA #: 203-791

**8. RELATED REVIEW DOCUMENTS:**

**a. Drug Master Files listed on 356h form:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	2	(b) (4)	Acyclovir DS	Nov 22, 2011	(b) (4) ; updated in Aug 2011

**b. Consults Recommended by CMC and Biopharmaceutics**

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Generate a Statistics consult to evaluate the mathematical modeling submitted in the NDA in support of biowaiver request to waive BE study requirements to bridge products manufactured at two different sites.
Clin Pharm	<input type="checkbox"/>	<input checked="" type="checkbox"/>	No formal consult, but collaboration by reviewers will be needed
EES	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Submitted
Pharm/Tox	<input type="checkbox"/>	<input checked="" type="checkbox"/>	No formal consult, but collaboration by reviewers will be needed
Methods Validation	<input type="checkbox"/>	<input type="checkbox"/>	Per Reviewers' recommendations
EA	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
New Drug Micro	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Microbial controls and specifications for Milk Protein Concentrate (MPC) were found acceptable by New Drug Micro under NDA 22-404. Consult would only be needed if supplier, controls or specification for MPC have been changed.
CDRH	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Other	<input type="checkbox"/>	<input type="checkbox"/>	

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

DOCUMENT NAME	DATE	APPLICATION NUMBER	DESCRIPTION



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<input checked="" type="checkbox"/>	<input type="checkbox"/>	1.
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**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
<input checked="" type="checkbox"/>	<input type="checkbox"/>	1. Request individual data from all 10 batches in an electronic format in support of the proposed dissolution specifications; only summary data are found in the submission.

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## CMC Summary: Critical Issues and Complexities

<b>CMC Critical Issues or Complexities</b>			
Issues noted are listed in Summary below, but are not considered critical.			
<b>Does the submission contain any of the following elements?</b>			
Nanotechnology	QbD Elements	PET	Other, please explain
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

<b>Is a team review recommended?</b>		
Yes	No	Suggested expertise for team
<input checked="" type="checkbox"/>	<input type="checkbox"/>	DS, DP and BP expertise
<b>Review Team Assignments (if known)</b>		
Fuqiang Liu	Drug Substance	
Suresh Pagay	Drug Product	
Tapash Ghosh	BioPharmaceutics	
Althea Cuff	ONDQA PM	

**Summary or Highlights of the Application** *(not already mentioned in other sections)*  
 Mucoadhesive tablet designed to stick to the “upper gum just above the incisor tooth (canine fossa).” Slowly releases acyclovir over approx 12-18 hrs. Safety and efficacy are supported with: pharmacokinetic trial (BA2004/21/01), and one Phase 3 clinical trial (BA2005/21/02).

Clinical Tablets	Commercial Tablets
DP made at (b) (4) facility	DP made at Farmea facility
Magnesium Stearate (b) (4) % of formulation	Magnesium Stearate (b) (4) % of formulation
(b) (4) kg pilot scale	(b) (4) kg production scale
Packaged in HDPE bottles with desiccant	Packaged in (b) (4) child-resistant blisters
(b) (4)	(b) (4) used
Un-debossed tablet	Tablet debossed: “AL21”

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50 and 100 mg tablets	50 mg tablet only
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**Drug Substance**

[REDACTED] (b) (4)

[REDACTED]

Should Farmea's acceptance spec list the range rather than only upper limit? [REDACTED] (b) (4).

Particle size for the Standard Grade is given as [REDACTED] (b) (4) um in the Specification in the DMF. This is a bit [REDACTED] (b) (4) than the range specified for tablet and capsule drug products in NDA 18-603 (see edr). However, the particle size grading is said to be "for information only", and the one-sided limits essentially allow any [REDACTED] (b) (4) grade to pass. The NDA applicant states that given the high solubility of acyclovir no particle size control is needed. Two CoA (one from DS manufacturer; one from DP manufacturer) for one batch of Standard Grade acyclovir ([REDACTED] (b) (4); used to make DP stability batches) is presented in the NDA (3.2.S.4.4). The particle size results fit with the specification in the DMF: [REDACTED] (b) (4) um

Information on the individually-specified impurities are presented in the second document (68 pages) within the Characterization Section 3.2.S.3.

Microbiological Control within DS: listed in the DMF, but not performed routinely

Other acyclovir applications for reference purposes:

- NDA 21-478 Acyclovir Cream (references NDA 18-603 for drug substance information)
- NDA 18-604 Acyclovir Ointment (refs NDA 18-603 for drug substance information)
- NDA 18-603 Acyclovir Injection (edr has DS specification)
- ANDA 77-309 Acyclovir Tablets (AP 2005)
- ANDA 75-382 Acyclovir Tablets (AP 1999)
- Multiple earlier ANDAs for Acyclovir Tablets

**Drug Product**

If additional release data are needed, there are two batches that were used in clinical trials

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but are not included in the Batch Analyses: (b) (4) (50 mg; (b) (4) %MgSt) and (b) (4) (100 mg; (b) (4) %MgSt).

Blister Packaging: A number of references to compliance with 21CFR and European regulations are given in the 3.2.P.7 including:

- PVC Blister Forming Laminate - "According to U.S. regulations, the laminates provided meet the requirements of FDA 21CFR 178.3910, 175.300, 175.1500 and 177.105."
- Foil and Sealing Lacquer - "According to U.S. regulations, the laminates provided meet the requirements of FDA 21CFR 178.3910 and 175.300."

These compliance statements may be sufficient since this is a solid oral dosage form. If not, a LOA could be requested for access to (b) (4) DMF(s). A mention of DMF (b) (4) appears on one of the documents from (b) (4) that is included in 3.2.P.7. (Technical Data Sheet – (b) (4) Backing).

A placebo version of BioAlliance's miconazole buccal tablet was discussed during that review as a possible way for physicians to demonstrate how to use the tablet.

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

*See EES for complete list of facilities related to this application.*

- No special concerns regarding facilities
- A (b) (4) site ((b) (4)) was added to the drug substance DMF in June 2011. In Mod 3 section P2 of the NDA it is stated that the Standard grade of acyclovir was selected for development of the buccal tablet. This is described in the DMF with the internal code (b) (4), and has a (b) (4) value of  $\leq$  (b) (4) um. Therefore, the (b) (4) site is not relevant to this NDA and does not need to be added to EES.

## **Biopharmaceutics Summary: Critical Issues, Complexities, and Consults**

**Critical Issues or Complexities**

Biopharm will be looking into Clinical Pharmacology review of accepting the applicant's rationale for not conducting a human BE study to qualify an alternative manufacturing site. Also, Biopharm will be looking into the validity of the supportive mathematical modeling approach in lieu of the human BE study to be reviewed by the

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Biometrics group.

Also, the Biopharm review will focus on the development and validation of the dissolution method, multi-media dissolution profiles comparison and acceptance of dissolution criterion in the review process.

## 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?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
3.	Are all the pages in the CMC section legible?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	See section 30 below for one difference relative to PreNDA recommendations (microbiological control)  The reports in Sec 1.12.15 which were submitted to the IND in Nov 2011 has information relevant to the biowaiver request from July 2011..

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

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6.	<p>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? <b>This question is not applicable for synthesized API.</b></p>	<input type="checkbox"/>	<input type="checkbox"/>	NA
7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Some discrepancies resolved prior to submission of EES

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8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
9.	<p>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:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
10.	<p>Is a statement provided that all facilities are ready for GMP inspection at the time of submission?</p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	This should not prevent filing

\* 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**

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	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Categorical exclusion claims are presented for both 21 CFR 25.31(a) and 21 CFR 25.31(b). BioAlliance's estimated use of acyclovir will be less than 1/100 of the amount that would trigger the need for environmental assessment information.

<b>D. MASTER FILES (DMF/MAF)</b>				
	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?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<i>See table on cover page.</i>

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<b>E. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
13.	Does the section contain a description of the DS manufacturing process?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	This is included in DMF (b) (4)
14.	Does the section contain identification and controls of critical steps and intermediates of the DS(in process parameters)?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	This is included in DMF (b) (4)
15.	Does the section contain information on impurities?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Information on degradants relevant to the drug product is included in 3.2.P. Process-related impurities are described in DMF (b) (4)
16.	Does the section contain information regarding the characterization of the DS?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	This is included in DMF (b) (4)
17.	Does the section contain controls for the DS?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	DS specification and method description for Assay/Impurity method only.
18.	Has stability data and analysis been provided for the drug substance?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	This is included in DMF (b) (4)
19.	Does the application contain Quality by Design (QbD) information regarding the DS?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
20.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
21.	Does the section contain container and closure information?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	(b) (4) in drum

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<b>F. DRUG PRODUCT (DP)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
22.	Does the section contain quality controls of excipients?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Milk Protein Concentrate is the only unusual excipient although preceded by NDA 22-404; (b) (4) is the (b) (4) supplier; specification in 3.2.P.4.1
23.	Does the section contain information on composition?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Drug load is (b) (4); acyclovir is (b) (4)% of tablet
24.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	(b) (4)
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?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	(b) (4) (mostly for tableting) in 3.2.P.3.3 and 3.2.P.3.4
26.	Is there a batch production record and a proposed master batch record?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Master batch record (as apparently required for b2 applications) is provided in 3.2.R along with executed batch record for a commercial-scale lot (batch 101).  Commercial scale = (b) (4) tablets (b) (4) kg)
27.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
28.	Have any Comparability Protocols been requested	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
29.	Does the section contain description of to-be-marketed container/closure system and presentations?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Carton of two blister cards ( (b) (4) each containing a single tablet.  Packaging for bulk tablets is also described: (b) (4) bags with desiccant.

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30.	Does the section contain controls of the final drug product?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<p>Microbial testing is part of the DP specification but will not be performed on all batches as was recommended in the PreNDA CMC mtg. Also not consistent with BioAlliance's response in the PreNDA minutes. Is the type of justification discussed in the PreNDA minutes included in the NDA?</p> <p>Adhesion test is unusual, but probably relevant for a buccal tablet.</p> <p>Dissolution has three timepoints (1, 5, and 12 hrs) and middle timepoint has a wide proposed range ( (b) (4) %). There was significant discussion on this point during the PreNDA CMC/BP meeting.</p> <p>The end of life specification has identical acceptance criteria to the release specification.</p>
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31.	Has stability data and analysis been provided to support the requested expiration date?	<input checked="" type="checkbox"/>	<p>Primary stability data: 2 pilot-scale batches (12 mo) and 1 commercial batch (18 mo); all made at the intended commercial facility (Farnea) with commercial formulation (b)(4)% MgSt) and packaged in (b)(4) blisters. Debossed with "A" instead of "AL21."</p> <p>The proposed expiration dating period is (b)(4) months.</p> <p>Supportive stability data: 30 mo at 25/60% and 12 mo at 30/65% on pilot-scale development batch 08.81.008-1 (b)(4)0% MgSt; (b)(4) (b)(4) blister); two clinical batches in HDPE bottles with desiccant (24 mo and 36 mo, respectively).</p> <p>Formal photostability studies not performed because little decomposition occurred in photo stress studies, and the (b)(4) blister is opaque.</p> <p>No trends apparent in 25/60% and 30/65% data on primary and supportive batches packaged in (b)(4) blisters. At 40/75% there is a possible minor drop in assay, and the development lot goes out of spec for color by 6 months. Applicant reports that some yellowing is observed at 40/75% after 6 mo in all packaging.</p> <p>Moisture control is important, because slowing of dissolution seen in (b)(4) blisters after 6 mo at 40/75% but not in (b)(4) blisters. No significant change in water content for either blister at 40/75% or at 25/60% for 24 mo. In studies at 40/75% for 6 mo in bottles without desiccant, water content increased substantially, hardness dropped, and tablets swelled.</p> <p>It does not appear that a commitment has been provided to put the first three commercial batches on stability. Since batch 001 is commercial-scale (although with a slight difference in debossing), the commitment could be for an additional 2 commercial batches.</p> <p>The 18-mo data for two of the primary stability batches will likely be available in June 2012.</p>
32.	Does the application contain Quality by Design (QbD) information regarding the DP?	<input type="checkbox"/>	<input checked="" type="checkbox"/>

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33.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
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<b>G. METHODS VALIDATION (MV)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
34.	Is there a methods validation package?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Via hyperlinks in 3.2.R

<b>H. MICROBIOLOGY</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
35.	If appropriate, is a separate microbiological section included discussing sterility of the drug product?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not a sterile product

<b>I. LABELING</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
36.	Has the draft package insert been provided?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
37.	Have the immediate container and carton labels been provided?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	A storage statement should be added to the carton label, such as "store at or below 25degC" or similar, since the long-term stability condition studied was 25degC/60%RH.
38.	Does section contain tradename and established name?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

<b>J. BIOPHARMACEUTICS</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>N o</b>	<b>Comment</b>
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		
42.	Is there a validation package for the analytical method and dissolution methodology?	X		

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43.	Does the application include a biowaiver request?	X		
44.	Does the application include an IVIVC model?		X	A mathematical model to correlate saliva concentration and dissolution data is included.
45.	Does the application include information/data on in vitro alcohol dose-dumping potential?		X	Not required
46.	Is there any in vivo BA or BE information in the submission?	X		OCP will review
<b>FILING CONCLUSION</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>N o</b>	<b>Comment</b>
47.	<b>IS THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?</b>	X		<ul style="list-style-type: none"> <li>➤ The NDA is filable from the Biopharmaceutics Perspective</li> <li>➤ The acceptability of the proposed dissolution method and acceptance criteria will be a review issue.</li> </ul>
48.	If the NDA is not fileable from the product quality perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.			Not applicable.
49.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.			Not applicable.
50.	Are there any potential review issues identified?			See comments above

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# **REVIEW AND APPROVAL**

This document will be signed in DARRTS by the following:

Biopharmaceutics Reviewer  
Biopharmaceutics Lead  
CMC Lead or CMC Reviewer  
Branch Chief

*{See appended electronic signature page}*

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**Appendix**

<b>Table 1      Composition of Acyclovir Lauriad™ 50 mg ABT</b>				
<b>Component</b>	<b>Reference to Quality Standard</b>	<b>Function</b>	<b>Quantity per Tablet</b>	
			<b>mg</b>	<b>% w/w</b>
Active Ingredient:				
Acyclovir	Current USP	Drug Substance	50.00	(b) (4)
Excipients:				
Microcrystalline cellulose	Current NF	(b) (4)	(b) (4)	(b) (4)
Povidone	Current USP			
Sodium Lauryl sulfate <sup>a</sup>	Current NF			
Hypromellose (b) (4)	Current USP			
Milk Protein Concentrate <sup>b</sup>	In-house standard			
Magnesium stearate	Current NF			
Colloidal Silicon Dioxide	Current NF			
Total				100.00
a = Sodium laurylsulfate is synonymous with sodium lauryl sulfate (SLS) and sodium monododecyl sulfate (SDS).				
b = Milk Protein Concentrate is a non-compendial non-novel excipient that has been approved by FDA for use in Oravig® tablets				
(b) (4)				



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**DS Specification from NDA 3.2.S.4**

Table 1: Proposed Acyclovir Specifications for		
Test	Acceptance Criteria	Analytical Method (Reference)
(b) (4)		

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DS Specification from DMF (b) (4)

Specification	Limit	Reference
(b) (4)		

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**Tests for information only**

(b) (4)

**Additional Tests**

(b) (4)

(b) (4)

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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.**  
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/s/  
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STEPHEN MILLER

05/03/2012

This NDA is recommended for filing from the CMC and BioPharm perspectives.

TAPASH K GHOSH

05/03/2012

ANGELICA DORANTES

05/03/2012

RAPTI D MADURAWAWE

05/04/2012