

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202408Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA 202408/Addendum 1

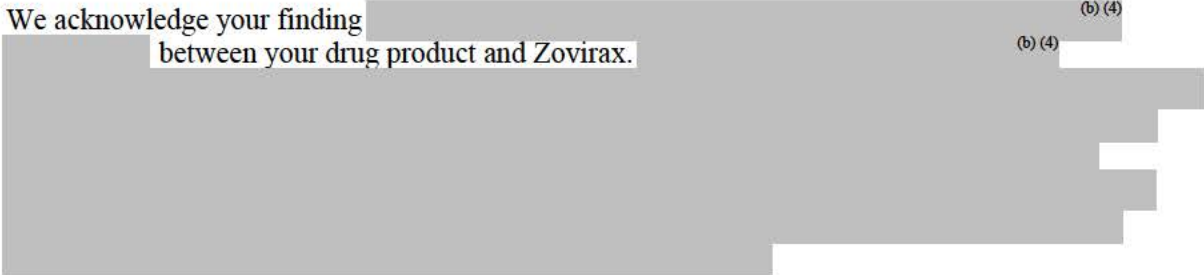
Drug Name/Dosage Form	Avaclyr (acyclovir ophthalmic ointment)
Strength	3.0%
Route of Administration	Topical
Applicant	Fera Pharmaceuticals

Product Quality Review Team

REVIEWERS	AFFILIATION
Manar Al- Ghabeish, Ph.D.	OTR
Xiaoming Xu, Ph.D.	OTR
Celia Cruz, Ph.D.	OTR
Bala Shanmugam, Ph.D. (ATL)	ONDP
Raney Sameersingh, Ph.D.	OGD
Richard Chang, Ph.D.	OLDP
Mohamed Ghorab, Ph.D.	OPPQ
Paul Seo, Ph.D.	ONDP

The following CR comments are provided by the review team for inclusion in the Action Letter.

1. We acknowledge that you have developed an in vitro release testing (IVRT) procedure (b) (4) as described in USP<1724>, in an attempt to demonstrate the suitability of the IVRT method and to establish the scientific bridge between your drug product and the comparator product (Zovirax) (*In-Vitro Release Testing Report to Support Acyclovir Release Rate Comparisons from Acyclovir Ophthalmic Ointment Formulations*). However, based on the data provided, the IVRT method is found to be inadequately validated for the following reasons:
 - a. The method failed (b) (4)

Provide the investigational report and description of the final method based on any improvements.
 - b. Provide a full validation report of the final IVRT method, after addressing (a). Close attention should be paid to the sensitivity of the method, which is the ability to detect changes in the release rate as a function of drug concentration in the formulation.
 - c. It is unclear if polymorphism of the drug substance has an influence on the IVRT results (refer to Comment #2). Provide solubility data as well as intrinsic dissolution rate (as per USP <1087> Apparent Intrinsic Dissolution) for acyclovir drug substance used in your product, in Zovirax and in the (b) (4) formulations. Compare this data to the literature reports, if available, for the various polymorphs of acyclovir.
2. We acknowledge your finding (b) (4) between your drug product and Zovirax. (b) (4)

3. We acknowledge your amendment dated June 22, 2016. However, as it was submitted at a very late stage in the review cycle we are unable to review the information provided.

There is no change in the overall recommendation of **Complete Response** from Product Quality perspective.



QUALITY ASSESSMENT



Recommendation: Complete Response

NDA 202408

Drug Name/Dosage Form	Avaclyr (acyclovir ophthalmic ointment)
Strength	3.0%
Route of Administration	Topical
Applicant	Fera Pharmaceuticals

Product Quality Review Team

REVIEWERS	AFFILIATION
Manar Al- Ghabeish, Ph.D.	OTR
Xiaoming Xu, Ph.D.	OTR
Celia Cruz, Ph.D.	OTR
Bala Shanmugam, Ph.D. (ATL)	ONDP
Raney Sameersingh, Ph.D.	OGD
Richard Chang, Ph.D.	OLDP
Mohamed Ghorab, Ph.D.	OPPQ
Paul Seo, Ph.D.	ONDP

Summary

I. Background

This 505 (b)(2) NDA providing for acyclovir ophthalmic ointment, 3% for use in the treatment of herpetic keratitis was first submitted on May 31, 2013 by Fera Pharmaceuticals. The CMC information submitted in the NDA for Fera's Avaclyr (acyclovir ophthalmic ointment) 3% was found acceptable by ONDQA, refer to CMC reviews (Dr. Suresh Pagay, dated 3/13/2014) and tertiary review (Dr. Sarah Pope Miksinski, dated 3/31/2014) for details. During the first review cycle, in response to a consult request from the Clinical Division on bridging, OGD Chemists reviewed submissions dated March 12 and 25, 2014 and determined the information provided in the NDA was not sufficient to establish a scientific bridge between Zovirax (acyclovir ophthalmic ointment), 3% approved in the UK and the applicant's product. Their memorandum (Dr. Sammersingh Raney, dated March 31, 2014) listed the additional product quality information needed to help establish a scientific bridge. The NDA was therefore issued a Complete Response on March 31, 2014. The current review evaluates the responses submitted by the applicant to address the CR issues.

Review Recommendations:

The resubmission addressing the deficiencies in the CR was submitted on December 24, 2015. In view of the substantial new CMC information and extensive In Vitro Release Test (IVRT) studies submitted, it was determined by OPQ that the submission would be reviewed by a team represented by OPQ offices (ONDP, OLDP, OPPQ and OTR) and OGD Chemists.

In response to addressing the recommendations provided in the Complete Response, the applicant submitted additional CMC information characterizing GSK's currently marketed Zovirax and comparing it to their own product. Several quality attributes such as viscosity, specific gravity, pH, melting temperature, particle size were tested by comparing three lots of Fera's product with three lots of U.K. marketed Zovirax. The review team concludes that the results of the characterization of the above mentioned attributes comparing the two products are acceptable (details in the review section below). Issues still surrounding IVRT and Polymorphism are discussed below.

As noted in the review below, the in-vitro release testing (IVRT) method has been determined to be inadequate and therefore a bridge between Fera's product and the nominal RLD Zovirax (acyclovir ophthalmic ointment), 3% has not been established given an inadequate method for in-vitro release testing. During the review cycle, the team generated several IR issues involving the study reports submitted, including IVRT method development. Since Fera has been unable to develop a IVRT method, we requested that they evaluate the impact of several factors (b) (4) in developing a validated IVRT method. As of the review date Fera has not submitted a response.

(b) (4)

Overall, based on the observed (b) (4) between the two products and the lack of a validated IVRT method, the Product Quality review team determines the NDA resubmission deficient and therefore recommends Complete Response.

¹Lutker, K.M. et al. (2011). Polymorphs and Hydrates of Acyclovir. J. Pharm.Sci. 100 (3); 949-963).

Balajee Shanmugam, Ph.D.

Manar Al- Ghabeish, Ph.D.

Xiaoming Xu, Ph.D.

Celia Cruz, Ph.D.

Paul Seo, Ph.D.

Raney Sameersingh, Ph.D.

Richard Chang, Ph.D.

Mohamed Ghorab, Ph.D.

Office of Testing and Research**Product Background:**

NDA: 202408

Drug Product Name / Strength: AVACLYR™ / Acyclovir Ophthalmic Ointment, 3%**Route of Administration:** ophthalmic**Applicant Name:** Fera Pharmaceuticals, LLC**Review Summary:**

Sequence	Submission(s) Reviewed	Date of Submission
0027	Resubmission/Class 2	12/24/2015
0029	Quality/Response to information request	2/29/2016
0031	Quality/Response to information request	04/11/2016
0032	Quality/Response to information request	04/15/2016
0033	Quality/Response to information request	04/20/2016
0034	Quality/Response to information request	04/25/2016
0035	Quality/Response to information request	05/13/2016

This application, dated May 31, 2013, is submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA). A Complete Response (CR) letter was issued on March 31, 2014 with recommendations to establish scientific bridge between the proposed drug product and the product used in the published clinical trials (referred to as the “nominal RLD”, Zovirax). The scientific bridge is to be supported by tests representing the physical qualities as well as the performance behavior of the ophthalmic ointment. These tests include: melting point, specific gravity, viscosity, thermal analysis, XRPD analysis, particle size analysis, and In Vitro Release Test (IVRT). A response was submitted by the Applicant on December 24, 2015 (Seq. 0027).

At the time of concluding this review, the method being proposed by the Applicant for IVRT is considered inadequately validated. In particular, the method is (b) (4)

But at the time of concluding this review, we have yet to receive the full investigation report to allow us to make further assessment.



Primary Reviewer Overall Assessment:

I concur with the overall assessment that the current submission contains insufficient information to establish a bridge between the proposed product and the referenced product, given an inadequate method for in-vitro release testing, therefore the response to the complete response letter dated 31-Mar-2014 is incomplete.

Manar Al-Ghabeish, Ph.D.
DPQR/OTR/OPQ

5/26/2016

Secondary Reviewer Overall Assessment:

I concur with the overall assessment that the current submission contains insufficient information to establish a bridge between the proposed product and the referenced product, given an inadequate method for in-vitro release testing, therefore the response to the complete response letter dated 31-Mar-2014 is incomplete.

Xiaoming Xu, Ph.D.
DQPR/OTR/OPQ
5/26/2016

Tertiary Reviewer Overall Assessment:

I concur with the overall assessment that the current submission contains insufficient information to establish a bridge between the proposed product and the referenced product, given an inadequate method for in-vitro release testing.

Neither an adequate IVRT method to perform comparability studies nor complete information [REDACTED] ^{(b) (4)} was provided at the time of this review; therefore the response to the complete response letter dated 31-Mar-2014 is incomplete.

Celia N. Cruz, Ph.D.
Acting Division Director, DQPR/OTR/OPQ
26-May-2016

Office of Generic Drugs

Submission Type: NDA submitted under 505(b)(2)
 NDA Number: 202408
 NDA Submission Date: 31-MAY-2013, most recently amended 13-JAN-2015
 Drug Product: Acyclovir ophthalmic ointment, 3%
 Applicant: Fera Pharmaceuticals, LLC
 Reviewer: Sameersingh G. Raney, Ph.D.

Summary

On 07-JAN-2015, the Division of Transplant and Ophthalmology Products (DTOP) in the Office of New Drugs (OND) sent an e-mail (shown in Appendix 1) to the Office of Generic Drugs (OGD) Office of Research and Standards (ORS) requesting feedback to an e-mail sent to DTOP from Fera Pharmaceuticals (Fera) on 05-JAN-2015, which inquired about the acceptability of an In Vitro Release Test (IVRT) apparatus. The inquiry from John G. D'Angelo of Fera was:

"I would like to ask if it will be acceptable to the chemist to use data (b) (4) to evaluate our Acyclovir 3% ophthalmic ointment when compared to the Zovirax[®] Eye Ointment requested in the 03-31-2014 Complete Response Letter?"

On 08-JAN-2015, the OGD ORS responded by e-mail (shown in Appendix 2):

"Our feedback to DTOP is: Yes, it is acceptable (b) (4) We suggest you confirm that others involved with the eventual chemistry/biopharm review for this NDA concur with our opinion prior to responding to Fera. We invite you to send us a consult request if you need a formal explanation or rationale for why we consider (b) (4) to be acceptable."

On 16-JAN-2015, DTOP submitted a consult request (shown in Appendix 3), stating:

"Fera Pharmaceuticals (Fera), NDA 202408/Avaclyr (acyclovir ophthalmic ointment) 3.0%, was issued a Complete Response (CR) letter on March 31, 2014, and the deficiencies listed in the CR letter were based on recommendations provided by OGD. Fera is working to address these deficiencies. Fera sent an email Monday, January 5, 2015, asking whether they could submit data (b) (4) to compare their Acyclovir 3% ophthalmic ointment to the Zovirax[®] Eye Ointment, as requested in the CR letter. Fera subsequently submitted this request to NDA 202408 on January 13, 2015. ... We request that you provide a formal explanation or rationale for why you consider (b) (4) to be acceptable."

It was not within the scope of the consult to evaluate whether the use (b) (4) would be acceptable to the chemistry or biopharmaceutics reviewers who might eventually review the IVRT method development and validation reports, as well as the results of the IVRT pivotal study that might be submitted by Fera.

The scope of the consult was to provide a formal explanation or rationale for why (b) (4) was considered acceptable by OGD ORS for an IVRT method. Also within the scope of the consult was a review of the documents submitted by Fera in their amendment of NDA 202408 on 13-JAN-2015, supporting their request (b) (4)

The Consult

General Comments

The controlling rationale supporting the acceptance (b) (4) for an IVRT method is (b) (4) that can be used for an IVRT method with semisolid drug products. It is not necessary for Fera to demonstrate that an IVRT method cannot be satisfactorily developed (b) (4) in order to support a justification (b) (4)

An important distinction is that (b) (4) it must be appropriately developed and validated to demonstrate the reproducibility and discrimination sensitivity of the method (b) (4)

(b) (4)

1 Page has been Withheld in Full as B4 (CCI/TS) immediately following this page



Conclusion

In conclusion, while the documents submitted by Fera do not provide compelling evidence (b) (4) for the Acyclovir ointment 3% IVRT method, it is not necessary for Fera to provide any evidence to justify (b) (4) for this test method (b) (4)

(b) (4) If Fera believes that the IVRT method can be successfully developed (b) (4)
 (b) (4) there is insufficient basis to deny it. Nonetheless, since the inquiry from Fera was whether it “*will be acceptable to the chemist to use data*” (b) (4)
 (b) (4) *o evaluate our Acyclovir 3% ophthalmic ointment when compared to the Zovirax Eye Ointment*” we suggest you confirm that others involved with the eventual chemistry/biopharmaceutics review for this NDA concur with our opinion prior to responding to Fera.

56 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

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

/s/

SAMEERSINGH G RANEY
01/27/2015

LARISSA LAPTEVA
01/27/2015

ROBERT A LIONBERGER
01/27/2015

Memorandum

To: NDA 202-408
From: Sarah Pope Miksinski, Ph.D.
Date: 3/31/2014
Re: Overall CMC Recommendation

The purpose of this memorandum is to confirm the findings and recommendation of the Chemistry, Manufacturing and Controls (CMC) team for NDA 202-408 (Acyclovir Ophthalmic Ointment), as submitted on 31-MAY-2013 by Fera Pharmaceuticals, Inc. Reference is made to Chemistry Review #1 (18-OCT-2013), Addendum to Chemistry Review #1 (13-MAR-2014), and memorandum to Chemistry Review #1 (27-MAR-2014). In the 13-MAR-2014 addendum, the primary reviewer (Dr. S. Pagay) recommends approval of this application from a CMC perspective. Reference is also made to the Deputy Division Director's Review (18-MAR-2014), with specific reference to Section 4 – "505(b)(2) Bridging". The confirmations contained in this section are consistent with determinations discussed with the CMC team throughout the review cycle.

This bridging issue was identified at the time of NDA filing, and discussions occurred in both the multidisciplinary team and ONDQA Precedence Committee arenas during the review cycle. From a multidisciplinary standpoint, the CMC team alerted the primary and secondary clinical reviewers regarding the issue, and a determination was conveyed that such a bridge was unnecessary. From an ONDQA precedence standpoint, it was determined that the lack of a bridge was not a CMC issue; additionally, the ONDQA Precedence Committee confirmed that, even with the submission of additional CMC data, establishment of a CMC "bridge" may or may not be possible. Based on these discussions, the ONDQA review team assessed the CMC information contained in NDA 202-408 in support of the proposed Fera product.

The 27-MAR-2014 Memorandum to Chemistry Review #1 provides updated review comments for amendments #18-20 and confirms that the previous approval recommendation remains unchanged. The memorandum also summarized scientific bridging information requested in a 14-MAR-2014 Information Request. The primary reviewer states that "Overall, from the product quality consideration, the test results of the Fera and Zovirax drug product attributes evaluated appear to be similar."

It is important to note that the provided CMC data are preliminary and do not sufficiently establish a bridge between the Fera and Zovirax products. Accordingly, there is no confirmation of CMC equivalence and/or comparability (or lack thereof) between the Fera and Zovirax products. It is also important to note that the reviewer's assessment of "similarity" is very specific to the test results only, and no inference of comparability and/or equivalence between the two products can be assumed based solely on the similarity of those test results.

I concur with the findings of the CMC review team. Based on the information provided, the overall CMC recommendation remains as an approval recommendation for this NDA.

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

/s/

SARAH P MIKSINSKI
03/31/2014

DATE: March 27, 2014
FROM: Shrikant Pagay, ONDQA
THROUGH: Rapti Madurawe, ONDQA
TO: NDA 202-408
SUBJECT: Amendments Sequence Number 18, 19 and 20

Summary and Overall Conclusion

Please refer to CMC review dated February 24, 2014 and the review addendum dated March 13, 2014 for an assessment of the CMC information provided in the NDA. The review addendum dated March 13, 2014 recommended approval of NDA 202408 from a CMC perspective. All facilities had been found "Overall Acceptable" in EES, product quality microbiology had recommended approval and the NDA had provided sufficient CMC information to assure the identity, strength, purity and quality of the drug product. Three new amendments, Sequence #18, 19 and 20, were submitted March 19-25, 2014. The new amendments are reviewed below. The risk of leachables from the container closure system is found to be minimal. The overall conclusion recommending approval of NDA 202408 from a CMC perspective remains unchanged.

The DTOP Division Director requested to provide certain test attributes of Fera and Zovirax drug products. Overall, from the product quality consideration, these test results appear to be similar

Review for Amendment Sequence #18 and 20

During the NDA review, the following information was requested on 12/31/2013 by this reviewer.

"Clarify if the leachable/extractable studies were performed for the drug formulation in contact with the container closure system. If not, provide the above data".

Since this information was not available from the supplier for the container closure, the sponsor conducted these studies through [REDACTED] (b) (4) contract laboratory. The sponsor provided the results of this study through Amendment 3/19/2014, Sequence # 18 and Amendment 3/25/2014 Sequence #20.

Extractable Study for Caps

The caps were extracted with [REDACTED] (b) (4). The extracts were analyzed for volatile extractables, semi-volatile extractable and non-volatile extractable using various gas and liquid chromatographic methods coupled with mass spectrometry. The caps were also extracted for metal [REDACTED] (b) (4).

(b) (4)

The actual leachable material is expected to be extremely small based on these results.

Extractable (migration) Study for Tin Tubes

(b) (4)

(b) (4) The actual leachable material is expected to be extremely small based on these results.

Conclusion:

In CMC review dated February 24, 2014 this reviewer concluded that from a risk-perspective, the probability that leachable material from (b) (4) tin tube (b) (4) is minimal. Previously, 9 ANDAs were approved without this data, and

leachable, extractable studies are usually required for LDPE containers only. This reviewer concluded it is possible to complete reviewing leachable/extractable study results submitted late before the NDA due date and due to the low risk, recommended approval of the NDA. The extractable data provided confirm the risk of leachables from the container closure system is minimal.

Review for Amendment Sequence #19

Data for Zovirax Eye Ointment and NDA Acyclovir 3% Ophthalmic Ointment:

The following information was provided as a response to the information request dated March 14, 2014 originated by DTOP Division Director. The information request was to provide data for Zovirax Eye Ointment and for the drug product for this NDA for assay, related substances, particle size distribution and viscosity.

The information provided is as follows:

Test	Acceptance Criteria	Zovirax® Lot No. OL909	Fera's acyclovir ophthalmic ointment, 3%		
			11443	11470	11471
Assay – acyclovir (%)	label claim				
Related Substances and Impurities (%)					
	NMT %				
	NMT %				
	NMT %				
	NMT %				
Total known and unknown	NMT %				
Particle Size (cumulative % retained)					
	NLT %				
	NLT %				

b(4)

Kinematic Viscosity (cSt)				
Acceptance Criteria	Zovirax® Lot No. 8N931	11443/KJA	11470/KJL	1147/KJM

b(4)

Conclusion and Assessment:

Overall, from the product quality consideration, the test results of the Fera and Zovirax drug product attributes evaluated appear to be similar.

The drug product specifications for Fera's product were found acceptable in review dated February 24, 2014. The specifications for the Fera drug product are established from the

information and the data submitted in the NDA 202-408 and Fera's samples comply with the specifications.

Regarding the related substances and impurities, the qualification threshold for specified identified impurity for a maximum daily dose of the drug (1.935 mg of acyclovir) is (b) (4)%. For Fera's product, no individual impurity exceeds this limit. The limit for (b) (4) (b) (4) was revised to NMT (b) (4)% by the pharmacology/toxicology reviewer during the review cycle. The limit of NMT (b) (4)% for (b) (4) was also found to be acceptable. Please see the PharmTox review dated February 24, 2014. The viscosity and particle size acceptance criteria for the Fera drug product, were based on the available data for the drug product under review. Both particle size and viscosity measurements were performed using standard instrumental methods. Both tests required sample preparation and test conditions appropriate for reproducible measurements.

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

/s/

SHRIKANT N PAGAY
03/27/2014

RAPTI D MADURawe
03/27/2014

NDA 202-408

Acyclovir Ophthalmic Ointment

Fera Pharmaceuticals, LLC

Shrikant Pagay, Ph.D.
Chemistry Review for DTOP

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	7
I. Recommendations.....	7
A. Recommendation and Conclusion on Approvability.....	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	7
II. Summary of Chemistry Assessments.....	7
A. Description of the Drug Product(s) and Drug Substance(s).....	7
B. Description of How the Drug Product is Intended to be Used.....	8
C. Basis for Approvability or Not-Approval Recommendation.....	8
III. Administrative.....	9
A. Reviewer's Signature.....	9
B. Endorsement Block.....	9
C. CC Block	9
Chemistry Assessment	10

Chemistry Review Data Sheet

1. NDA 202-408
2. REVIEW #: Addendum 1 to Review #1
3. REVIEW DATE: 3/11/2014
4. REVIEWER: Shrikant Pagay

5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original Submission

5/31/2013

Amendment

7/24/2013

Amendment

11/27/2013

Amendment

12/31/2013

Amendment

2/14/2014

Amendment

2/20/2014

Amendment

2/26/2014

7. NAME & ADDRESS OF APPLICANT:

Name:

Fera Pharmaceuticals

Address:

134 Birch Hill Road,
Locust Vlle, NY 11560

Chemistry Review Data Sheet

Representative: John D'Angelo
Telephone: 516-277-1449

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name:
- b) Non-Proprietary Name (USAN): Acyclovir Ophthalmic Ointment, 3.0%
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type:
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Antiviral against HCV

11. DOSAGE FORM: Ointment

12. STRENGTH/POTENCY: 3%

13. ROUTE OF ADMINISTRATION: Ophthalmic

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

___ SPOTS product – Form Completed

 Not a SPOTS product

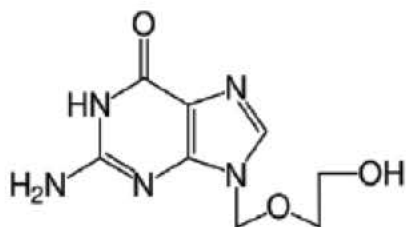
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemistry Review Data Sheet

9-[(2-hydroxyethoxy) methyl] guanine

Molecular Formula: C₈H₁₁N₅O₃

Molecular Weight: 225.21



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	4-24-2013	

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

Chemistry Review Data Sheet

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable	1/27/2014	
Pharm/Tox			
Biopharm			
LNC			
Methods Validation			
OPDRA			
EA			
Microbiology	Approval	1/23/2014	Neal Sweeney

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ___ Yes ___ No If no, explain reason(s) below:

The Chemistry Review for NDA 202-408

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The office of compliance has made an "Overall Acceptable" recommendation for the manufacturing sites. The CMC information provided in the DMF is adequate. The quality microbiology reviewer has recommended approval. The post approval studies protocol is now acceptable. The NDA has provided sufficient CMC information to assure the identity, strength, purity and quality of the drug product. The labeling is finalized by the team. Therefore, from CMC perspective, the application is recommended for approval.

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

There are no Phase IV commitments from CMC perspective.

II. Summary of Chemistry Assessments

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

Drug Substance

The drug substance information for Acyclovir is referenced through Drug Master File (DMF) (b)(4) and a letter of authorization was provided in the NDA on January 25, 2012. The DMF holder is (b)(4). Based on the data from long term stability studies, no evidence of degradation is noted. The recommended retest period is (b)(4) months (b)(4).

Drug Product

The drug product is Acyclovir 3% sterile ointment for topical use in eye and is indicated for anti-viral treatment. At the pre-NDA meeting on December 6, 2010, the Division agreed to accept this NDA as a 505(b)(2) submission with GalxoSmithKline's Zovirax ophthalmic ointment as the Reference Listed Drug (RLD). The applicant's drug product is of the same strength as the RLD.

The drug product is packaged in a tin tube and contains 3.5 grams of the ointment. Each tube is packaged in an individual carton. The closure is a black LDPE screw cap. The formulation is composed of acyclovir in white petrolatum base.

Executive Summary Section

All three primary stability batches were manufactured at the commercial production facility at the commercial scale ((b) (4) Kg ointment). The drug product is (b) (4)

The drug product release testing quality attributes include leak test, metal particles, particle size of the dispersed drug in the ointment base and ointment homogeneity; these are also important from patient consideration for an ophthalmic drug delivery system.. The assay, impurities etc., are performed to insure that the ointment quality is maintained through the shelf life. Most of the testing is performed by compendial test methods except for assay, impurities, particle size and viscosity. The viscosity of the applicant's drug is similar to that of the RLD. These 4 tests were developed in-house and validated. The drug product shelf life is 2 years when stored at 20-25°C.

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

The drug product is an anti viral agent indicated for the treatment of herpetic keratitis in patients with herpes simplex virus. The drug product is a sterile ointment applied as a 1 cm long ribbon in the cul-de-sac of the affected eye. The dosage regimen is 5 times a day (every 3 hours during the day) until the corneal ulcer heals and then 3 times a day for 7 days.

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 ointment is well controlled. Sufficient stability data was provided. Sufficient manufacturing experience was demonstrated in manufacturing all 3 batches at the commercial scale. All facilities have acceptable site recommendations as of 1/27/2014. The microbiology reviewer has recommended approval on 1/23/2014 from a quality microbiology perspective. The two pending items noted in CMC Review #1, the post approval stability study protocol and the label, are now acceptable. Therefore, NDA 202-408 is now recommended for approval from a CMC-perspective.

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

ChemistName/Date: Shrikant N.Pagay,Ph.D.,
ChemistryBranch Chief Name/Date: Rapti Madurawe, Ph.D.
ProjectManagerName/Date

C. CC Block

Chemistry Assessment Section

Chemistry Assessment

Please refer to CMC Review #1 dated 2/21/2014 for a complete review of the CMC sections of NDA 202-408. Although the NDA had provided sufficient information to assure the identity, strength, purity and quality of the drug product, a recommendation for approval was not made in Review #1 as the post-approval stability protocol and the labeling had not been finalized. The applicant has provided the revised post-approval stability protocol, updated stability data and labeling, which are reviewed in this addendum. Also, shelf life is assigned.

DRUG PRODUCT**Stability**Update on Stability Studies for the Registration Batches

Stability data for the 3 process validation batches are updated through 24 months storage at 25°C/40% RH and through 12 months at 30°C/65% RH. The new data are submitted for the long term storage at 18 and 24 months test points. Twelve months test results are provided for the intermediate storage condition at 30°C/65% RH. The data included for the assay, related substances, (b) (4) sterility, and weight loss. The test results for these later time intervals generally show assay about (b) (4) % and total related substances (b) (4) % range. (b) (4)

When the data is assessed for all time intervals under long term, the values for the different test attributes show (b) (4)

Expiration Date:

Based on the stability data, the proposed expiration date for the drug product is (b) (4) months when stored at 20- 25°C.(USP controlled room temperature)

Post Approval Stability Commitments.

The post approval stability protocol revised (b) (4)

The revised post-approval protocol is shown below.

Additional details provided for the post approval studies for annual batches are as follow:

Chemistry Assessment Section

(b) (4)

Criteria for Acceptance:

(b) (4)

Chemistry Assessment Section

Table 1: Annual Batch Testing Schedule

(b) (4)



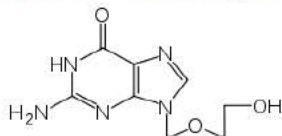
The acceptance criteria for the post approval stability studies comply with the regulatory specifications that are agreeable to the sponsor.

Labeling & Package Insert**11 DESCRIPTION**

(b) (4)



The chemical name of acyclovir is 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]6H-purin-6-one, it has the following chemical structure:



AVACL^{YR} is a sterile ointment for topical administration in eyes (b) (4) Each gram of ointment contains 30 mg of acyclovir in a white petrolatum base.

16 HOW SUPPLIED/STORAGE AND HANDLING

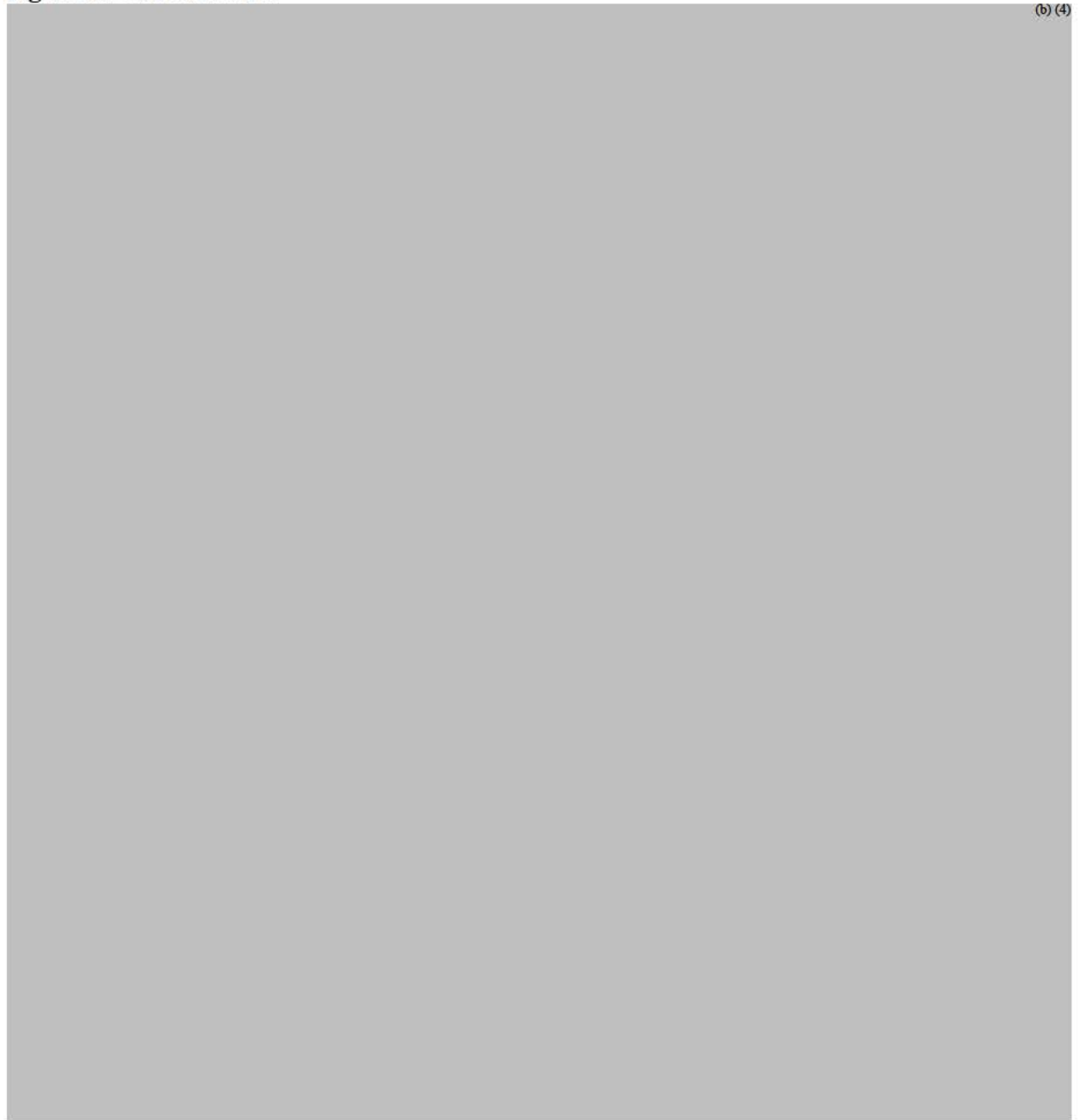
AVACL^{YR} is available as a 3.5 g tin tube as a clear, colorless, sterile ophthalmic ointment for topical use containing 3% acyclovir active drug. Each tube is packaged in an individual carton.

Chemistry Assessment Section

3.5 g tube (NDC 48102-026-35)

Store at 20°C to 25°C (68°F to 77°F)  (b) (4)

Manufactured for Fera Pharmaceuticals LLC, 134 Birch Hill Road, Locust Valley, NY 11560

Figure 1: Carton Label

Chemistry Assessment Section

Figure 2: Container Label

Based on the dimensions of the ointment tube orifice, a single dose of the ointment administered as a 1 cm ribbon is approximately 13 mg.

Chemistry Assessment Section

List Of Deficiencies Communicated During the NDA Review Cycle

Responses were submitted for all IRs. There are no pending issues.

Information Request #1 NDA (Response received on 11/27/2013)

1. To ensure consistent quality of the in-coming raw material, include a test for viscosity in the specification for white petrolatum and propose acceptance criteria.
2. The manufacturing flow diagram lists QC testing, but provides no further details. Identify the QC tests performed and the proposed in-process specifications for the QC tests.
3. With regards to acyclovir particle size in the bulk ointment:

We acknowledge the proposed specification for particle size distribution (b) (4)

(b) (4)

They are:

(b) (4)

(b) (4)

Clarify this discrepancy and explain

(b) (4)

4. Update the manufacturing process description in the NDA with the process parameters (b) (4) and identify the critical process parameters.
5. We recommend the finished drug product specification be revised as follows:
 - a. Include a second identification test, identification solely by a single chromatographic retention time; for example, is not regarded as being specific. The use of two chromatographic procedures, where the separation is based on different principles is acceptable or simply use infrared spectroscopy as a second identification test.
 - b. Include a test for viscosity and propose an acceptance criterion. (b) (4)
6. According to the Certificate of Analysis, the tin tubes (b) (4)

Chemistry Assessment Section

Information Request #2 NDA (Response received on 12/31/2013)

(1). The development report states, (b) (4)
 (b) (4) However, no information is provided
 (b) (4) Clarify if the drug substance is
 (b) (4) and describe the process, equipment used and process controls used. Provide an
 updated establishment list including the name, address and contact information for the
 (b) (4) facility.

2). You have proposed an acceptance criteria (b) (4)
 (b) (4) Provide additional justification for the proposed
 viscosity acceptance criteria. The justification provided should include a discussion (b) (4)
 (b) (4)

(3). The development report lists viscosity data for the development batches of the drug product and for the reference listed drug (RLD). Clarify if this data was obtained by the same experimental method as the batch 11443? Provide viscosity in cSt for the development batches. Briefly describe the experimental method used in the viscosity measurement for the development batches and batch 11443.

(4). Clarify if the leachable/extractable studies were performed for the drug formulation in contact with the container closure system. If not, provide the above data.

(5). Please describe the orientation of the container during storage for stability studies. If the containers are placed during storage without consideration for orientation of the container (vertical upside, vertical upside-down or sideways), provide justification why the container orientation is not critical for this study, particularly with respect to leakage, phase separation and/or ointment integrity.

6). We recommend the drug product specification be revised as follows. Note that the regulatory specification applies over product shelf-life.

- (a) Description for the drug product specification revised (b) (4)
 (b) (4)
 (b) Shelf life acceptance criteria (b) (4) revised (b) (4)
 (c) Shelf life acceptance criteria (b) (4) revised (b) (4)

Chemistry Assessment Section

NDA 202408

Information Request #3 NDA (Response received 2/14/2014)

The following comments were conveyed to the sponsor via telephone on 2/10/2014.

We Recommend the drug product specification [REDACTED]^{(b) (4)} be further revised [REDACTED]^{(b) (4)} based on ICH Q3 qualification level and the stability data. Please note that no safety data is provided to support a [REDACTED]^{(b) (4)} specification.

Also, provide the pending information for the comments 2 and 4 from the previous submission (12/18/2013).

Information Request #4 (Response received on 2/26/2014)

1). The long-term storage condition in the NDA is 25 °C/40% RH. Although this long term storage condition is appropriate for semi permeable containers, for tin containers such as yours, the ICH Q1A(R2) General case (2.1.7.1) is more appropriate. Revise the long term storage condition in the post approval stability study protocol to 25°C/60% RH; the intermediate and accelerated conditions may remain the same as in Table 3.2.P.8.1-2 in the NDA (i.e., 30°C/65% RH and 40°C/75% RH, respectively). Provide the updated post-approval stability protocol in a tabular format with the storage conditions, testing intervals, and the tests performed at each interval.

2). Based on the date of manufacture [REDACTED]^{(b) (4)} the 18 month and 24 month data at 25°C/40% RH, and the 9 and 12 month data at 30°C/65% RH should be available for the primary stability batches. Please submit the updated stability data for the primary stability batches.



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application:	NDA 202408/000	Sponsor:	FERA PHARMS
Org. Code:	590		134 BIRCH HILL RD
Priority:	3		LOCUST VALLEY, NY 11560
Stamp Date:	31-MAY-2013	Brand Name:	ACYCLOVIR OPHTHALMIC OINTMENT, 3.0%
PDUFA Date:	31-MAR-2014	Estab. Name:	
Action Goal:		Generic Name:	ACYCLOVIR OPHTHALMIC OINTMENT, 3.0%
District Goal:	01-OCT-2013	Product Number; Dosage Form; Ingredient; Strengths	001; OINTMENT; ACYCLOVIR; 3%

FDA Contacts:	S. PAGAY	Prod Qual Reviewer		3017961429
	N. SWEENEY	Micro Reviewer	(HFD-805)	2404023793
	N. BHANDARI	Product Quality PM		2404023815
	L. ALMOZA	Regulatory Project Mgr		2404025146
	B. SHANMUGAM	Team Leader		3017961457

Overall Recommendation:	ACCEPTABLE	on 27-JAN-2014	by J. WILLIAMS	()	3017964196
	PENDING	on 10-OCT-2013	by EES_PROD		
	PENDING	on 22-AUG-2013	by EES_PROD		
	PENDING	on 10-JUL-2013	by EES_PROD		
	PENDING	on 10-JUL-2013	by EES_PROD		
	PENDING	on 10-JUL-2013	by EES_PROD		

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

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE OTHER TESTER
FINISHED DOSAGE PACKAGER

Profile: STERILE OINTMENT **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 20-NOV-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

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

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE (b) (4)

Profile: (b) (4) **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 21-OCT-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE PACKAGER

Profile: (b) (4) **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 27-JAN-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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

/s/

SHRIKANT N PAGAY
03/12/2014

RAPTI D MADURawe
03/13/2014

NDA 202-408

Acyclovir Ophthalmic Ointment

Fera Pharmaceuticals, LLC

Shrikant Pagay, Ph.D.
Chemistry Review for DTOP

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	7
I. Recommendations.....	7
A. Recommendation and Conclusion on Approvability.....	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	7
II. Summary of Chemistry Assessments.....	7
A. Description of the Drug Product(s) and Drug Substance(s).....	7
B. Description of How the Drug Product is Intended to be Used.....	8
C. Basis for Approvability or Not-Approval Recommendation.....	8
III. Administrative.....	9
A. Reviewer's Signature.....	9
B. Endorsement Block.....	9
C. CC Block	9
Chemistry Assessment	10
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	10
S DRUG SUBSTANCE [Name, Manufacturer].....	10
P DRUG PRODUCT [Name, Dosage form].....	17
A APPENDICES	49
R REGIONAL INFORMATION	49
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	49
A. Labeling & Package Insert	49
B. Environmental Assessment Or Claim Of Categorical Exclusion	52
III. List Of Deficiencies To Be Communicated.....	53

Chemistry Review Data Sheet

1. NDA 202-408
2. REVIEW #:1
3. REVIEW DATE: 10/18/2013
4. REVIEWER: Shrikant Pagay

5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original Submission

5/31/2013

Amendment

7/24/2013

Amendment

11/27/2013

Amendment

12/31/2013

Amendment

2/14/2014

Amendment

2/20/2014

7. NAME & ADDRESS OF APPLICANT:

Name:	Fera Pharmaceuticals
Address:	134 Birch Hill Road, Locust Vllely, NY 11560



Chemistry Review Data Sheet

Representative: John D'Angelo
Telephone: 516-277-1449

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name:
- b) Non-Proprietary Name (USAN): Acyclovir Ophthalmic Ointment, 3.0%
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type:
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Antiviral against HCV

11. DOSAGE FORM: Ointment

12. STRENGTH/POTENCY: 3%

13. ROUTE OF ADMINISTRATION: Ophthalmic

14. Rx/OTC DISPENSED: ___ Rx ___ OTC

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

___ SPOTS product – Form Completed

Not a SPOTS product

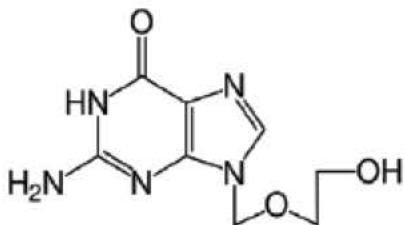
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemistry Review Data Sheet

9-[(2-hydroxyethoxy) methyl] guanine

Molecular Formula: C₈H₁₁N₅O₃

Molecular Weight: 225.21



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	4-24-2013	

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

Chemistry Review Data Sheet

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable	1/27/2014	
Pharm/Tox			
Biopharm			
LNC			
Methods Validation			
OPDRA			
EA			
Microbiology	Approval	1/23/2014	Neal Sweeney

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ___ Yes ___ No If no, explain reason(s) below:

The Chemistry Review for NDA 202-408

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The office of compliance has made an "Overall Acceptable" recommendation for the manufacturing sites. The CMC information provided in the DMF is adequate. The quality microbiology reviewer has recommended approval. The NDA has provided sufficient CMC information to assure the identity, strength, purity and quality of the drug product. However, the post approval stability protocol has not been finalized as of the date of this review. The labeling has adequate CMC information and minor revisions marked up in the review will be finalized at the time of labeling team review. Therefore, from CMC perspective, the application is not recommended for approval at this time until finalization of the post approval stability protocol and completion of the label by the project team.

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

There are no Phase IV commitments from CMC perspective.

II. Summary of Chemistry Assessments

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

Drug Substance

The drug substance information for Acyclovir is referenced through Drug Master File (DMF) (b)(4) and a letter of authorization was provided in the NDA on January 25, 2012. The DMF holder is (b)(4). Based on the data from long term stability studies, no evidence of degradation is noted. The recommended retest period is (b)(4) months (b)(4).

Drug Product

The drug product is Acyclovir 3% sterile ointment for topical use in eye and is indicated for anti-viral treatment. At the pre-NDA meeting on December 6, 2010, the Division agreed to accept this NDA as a 505(b)(2) submission with GalxoSmithKline's Zovirax ophthalmic ointment as the Reference Listed Drug (RLD). The applicant's drug product is of the same strength as the RLD.

Executive Summary Section

The drug product is packaged in a tin tube and contains 3.5 grams of the ointment. Each tube is packaged in an individual carton. The closure is a black LDPE screw cap. The formulation is composed of acyclovir in white petrolatum base.

All three primary stability batches were manufactured at the commercial production facility at the commercial scale ((b) (4) Kg ointment). The drug product is (b) (4)

The drug product release testing quality attributes include leak test, metal particles, particle size of the dispersed drug in the ointment base and ointment homogeneity; these are also important from patient consideration for an ophthalmic drug delivery system. The assay, impurities etc., are performed to insure that the ointment quality is maintained through the shelf life. Most of the testing is performed by compendial test methods except for assay, impurities, particle size and viscosity. The viscosity of the applicant's drug is similar to that of the RLD. These 4 tests were developed in-house and validated. The drug product shelf life will be assigned pending completion of post approval stability protocol and additional stability data.

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

The drug product is an anti viral agent indicated for the treatment of herpetic keratitis in patients with herpes simplex virus. The drug product is a sterile ointment applied as a 1 cm long ribbon in the cul-de-sac of the affected eye. The dosage regimen is 5 times a day (every 3 hours during the day) until the corneal ulcer heals and then 3 times a day for 7 days.

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 ointment is well controlled. Sufficient stability data was provided. Sufficient manufacturing experience was demonstrated in manufacturing all 3 batches at the commercial scale. All facilities have acceptable site recommendations as of 1/27/2014. The microbiology reviewer has recommended approval on 1/23/2014 from a quality microbiology perspective. The labeling review for CMC is complete with minor revisions. Although the stability data provided appears acceptable, the shelf life will be assigned upon finalization of the post approval protocol and additional stability data. The application is not recommended for approval at this time. Approval of this NDA is contingent upon finalization of the post approval stability protocol and completion of the label by the project team.

Executive Summary Section

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

ChemistName/Date: Shrikant N.Pagay,Ph.D., 7/21/2014
ChemistryBranch Chief Name/Date: Rapti Madurawe, Ph.D.
ProjectManagerName/Date

C. CC Block

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

The following information for the drug substance is provided from the open portion of the reference DMF (b) (4) for information only. DMF was last reviewed on 4/24/2013 and found to be adequate. DMF is separately being reviewed for a recent amendment. However, there are no DMF issues that will hold the NDA from approval.

(b) (4)

38 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

Chemistry Assessment Section

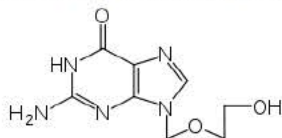
(b) (4)

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1**A. Labeling & Package Insert**

11 DESCRIPTION

(b) (4)

The chemical name of acyclovir is 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]6H-purin-6-one, it has the following chemical structure:



AVACL_{YR} is a sterile ointment for topical administration in *eyes* (b) (4) Each gram of ointment contains 30 mg of acyclovir in a white petrolatum base.

Chemistry Assessment Section

16 HOW SUPPLIED/STORAGE AND HANDLING

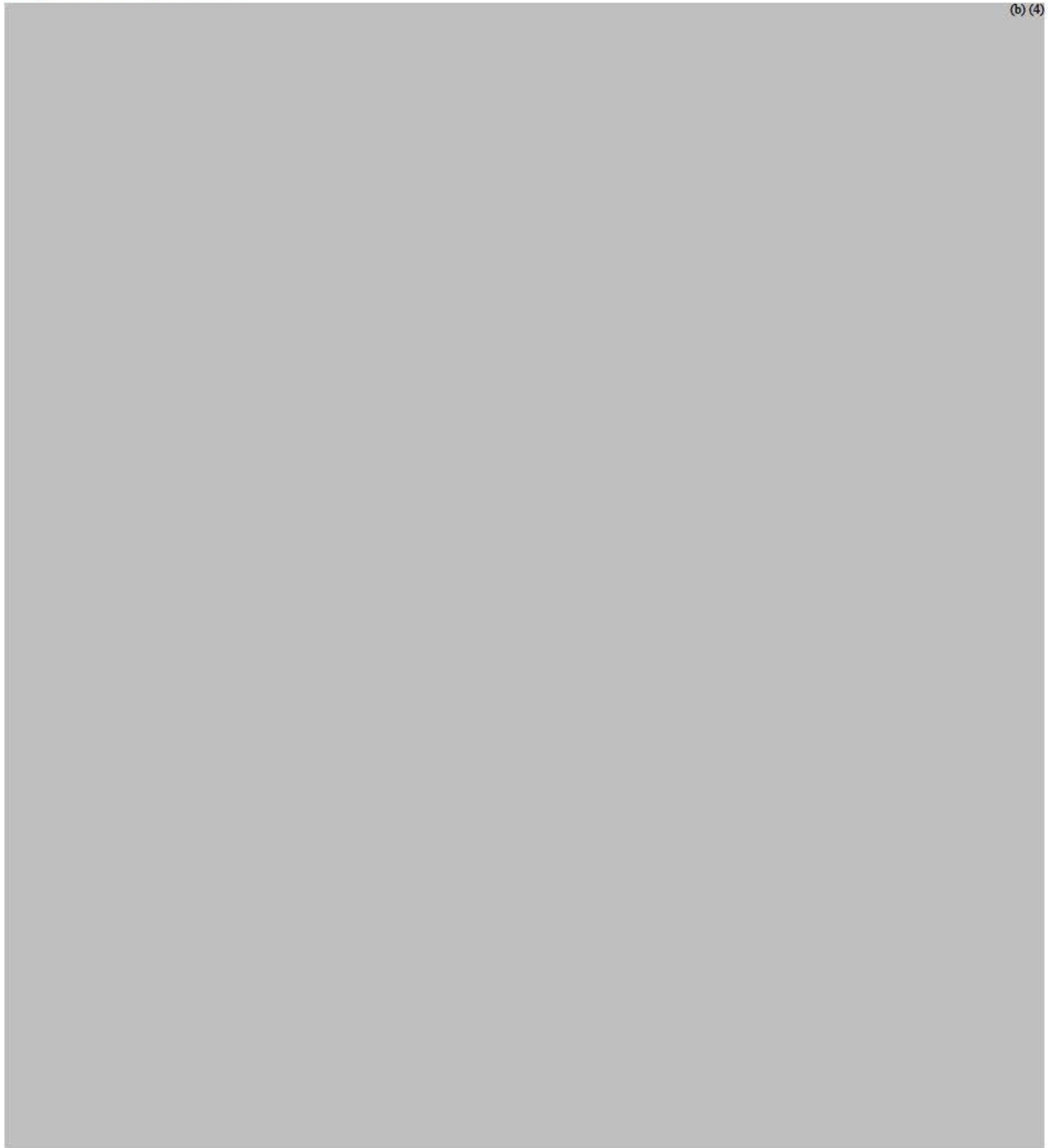
AVACLYR is available as a 3.5 g tin tube as a clear, colorless, sterile ophthalmic ointment for topical use containing 3% acyclovir active drug. Each tube is packaged in an individual carton.

3.5 g tube (NDC 48102-026-35)

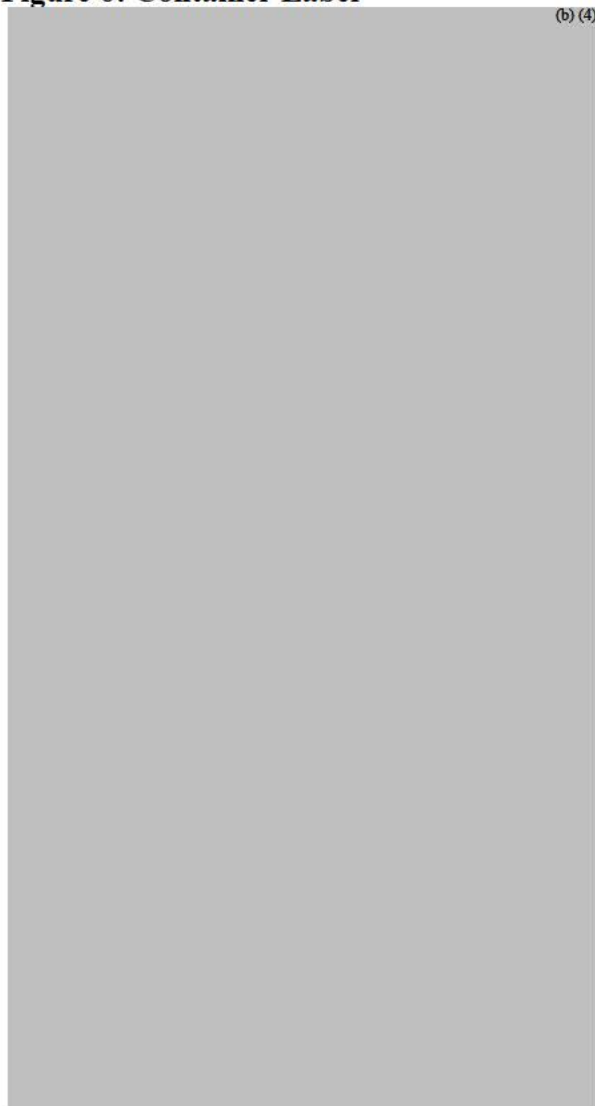
Store at ^{(b) (4)} 20°C to 25°C (^{(b) (4)} 68°F to 77°F) ^{(b) (4)}

Manufactured for Fera Pharmaceuticals LLC, 134 Birch Hill Road, Locust Valley, NY 11560

Chemistry Assessment Section

Figure 5: Carton Label

Chemistry Assessment Section

Figure 6: Container Label

Based on the dimensions of the ointment tube orifice, a single dose of the ointment administered as a 1 cm ribbon is approximately 13 mg.

B. Environmental Assessment Or Claim Of Categorical Exclusion

The firm has requested categorical exclusion for the preparation of environmental assessment report as per 21CFR 25.31(a). The application is a 505(b)(2). Therefore, this product will not increase the use of active moiety. It is acceptable.

Chemistry Assessment Section

III. List Of Deficiencies To Be Communicated**Information Request #1 NDA Response on 11/27/2013**

1. To ensure consistent quality of the in-coming raw material, include a test for viscosity in the specification for white petrolatum and propose acceptance criteria.
2. The manufacturing flow diagram lists QC testing, but provides no further details. Identify the QC tests performed and the proposed in-process specifications for the QC tests.
3. With regards to acyclovir particle size in the bulk ointment:

We acknowledge the proposed specification for particle size distribution [REDACTED] (b) (4)

[REDACTED] (b) (4)

They are:

[REDACTED] (b) (4)

[REDACTED] (b) (4)

4. Update the manufacturing process description in the NDA with the process parameters [REDACTED] (b) (4) and identify the critical process parameters.
5. We recommend the finished drug product specification be revised as follows:
 - a. Include a second identification test, identification solely by a single chromatographic retention time; for example, is not regarded as being specific. The use of two chromatographic procedures, where the separation is based on different principles is acceptable or simply use infrared spectroscopy as a second identification test.
 - b. Include a test for viscosity and propose an acceptance criterion. [REDACTED] (b) (4)
6. According to the Certificate of Analysis, the tin tubes [REDACTED] (b) (4)

Chemistry Assessment Section

Information Request #2 NDA Response 12/31/2013

(1). The development report states, (b) (4)
(b) (4) However, no information is provided
(b) (4) Clarify if the drug substance is
(u) (4) and describe the process, equipment used and process controls used. Provide an
updated establishment list including the name, address and contact information for the
(b) (4) facility.

2). You have proposed an acceptance criteria (b) (4)
(b) (4) Provide additional justification for the proposed
viscosity acceptance criteria. The justification provided should include a discussion (b) (4)
(b) (4)

(3). The development report lists viscosity data for the development batches of the drug product and for the reference listed drug (RLD). Clarify if this data was obtained by the same experimental method as the batch 11443? Provide viscosity in cSt for the development batches . Briefly describe the experimental method used in the viscosity measurement for the development batches and batch 11443.

(4). Clarify if the leachable/extractable studies were performed for the drug formulation in contact with the container closure system. If not, provide the above data.

(5). Please describe the orientation of the container during storage for stability studies. If the containers are placed during storage without consideration for orientation of the container (vertical upside, vertical upside-down or sideways), provide justification why the container orientation is not critical for this study, particularly with respect to leakage, phase separation and/or ointment integrity.

6). We recommend the drug product specification be revised as follows. Note that the regulatory specification applies over product shelf-life.

(a) Description for the drug product specification revised (b) (4)

(b). Shelf life acceptance criteria (b) (4) revised (b) (4)

(c) Shelf life acceptance criteria (b) (4) revised (b) (4)

Chemistry Assessment Section

NDA 202408

Information Request #3 NDA Response 2/14/2014

The following comments were conveyed to the sponsor via telephone on 2/10/2014.

We Recommend the drug product specification [REDACTED] (b) (4) be further revised [REDACTED] (b) (4) based on ICH Q3 qualification level and the stability data. Please note that no safety data is provided to support a [REDACTED] (b) (4) specification.

Also, provide the pending information for the comments 2 and 4 from the previous submission (12/18/2013).

Information Request #4 (Response pending)

1). The long-term storage condition in the NDA is 25 °C/40% RH. Although this long term storage condition is appropriate for semi permeable containers, for tin containers such as yours, the ICH Q1A(R2) General case (2.1.7.1) is more appropriate. Revise the long term storage condition in the post approval stability study protocol to 25°C/60% RH; the intermediate and accelerated conditions may remain the same as in Table 3.2.P.8.1-2 in the NDA (i.e., 30°C/65% RH and 40°C/75% RH, respectively). Provide the updated post-approval stability protocol in a tabular format with the storage conditions, testing intervals, and the tests performed at each interval.

2). Based on the date of manufacture [REDACTED] (b) (4) the 18 month and 24 month data at 25°C/40% RH, and the 9 and 12 month data at 30°C/65% RH should be available for the primary stability batches. Please submit the updated stability data for the primary stability batches.



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application:	NDA 202408/000	Sponsor:	FERA PHARMS
Org. Code:	590		134 BIRCH HILL RD
Priority:	3		LOCUST VALLEY, NY 11560
Stamp Date:	31-MAY-2013	Brand Name:	ACYCLOVIR OPHTHALMIC OINTMENT, 3.0%
PDUFA Date:	31-MAR-2014	Estab. Name:	
Action Goal:		Generic Name:	ACYCLOVIR OPHTHALMIC OINTMENT, 3.0%
District Goal:	01-OCT-2013	Product Number; Dosage Form; Ingredient; Strengths	001; OINTMENT; ACYCLOVIR; 3%

FDA Contacts:	S. PAGAY	Prod Qual Reviewer		3017961429
	N. SWEENEY	Micro Reviewer	(HFD-805)	2404023793
	N. BHANDARI	Product Quality PM		2404023815
	L. ALMOZA	Regulatory Project Mgr		2404025146
	B. SHANMUGAM	Team Leader		3017961457

Overall Recommendation:	ACCEPTABLE	on 27-JAN-2014	by J. WILLIAMS	()	3017964196
	PENDING	on 10-OCT-2013	by EES_PROD		
	PENDING	on 22-AUG-2013	by EES_PROD		
	PENDING	on 10-JUL-2013	by EES_PROD		
	PENDING	on 10-JUL-2013	by EES_PROD		
	PENDING	on 10-JUL-2013	by EES_PROD		

Establishment:	CFN: (b) (4)	FEI: (b) (4)	
	[REDACTED]		
DMF No:		AADA:	
Responsibilities:	FINISHED DOSAGE MANUFACTURER		
	FINISHED DOSAGE OTHER TESTER		
	FINISHED DOSAGE PACKAGER		
Profile:	STERILE OINTMENT	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	20-NOV-2013		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

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

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE (b) (4)

Profile: (b) (4) **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 21-OCT-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE PACKAGER

Profile: (b) (4) **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 27-JAN-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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

/s/

SHRIKANT N PAGAY
02/21/2014

RAPTI D MADURawe
02/24/2014

2

Initial Quality Assessment Branch V Pre-Marketing Assessment Division II

OND Division: Division of Transplant and Ophthalmology Products
NDA: 202-408

Applicant: Fera Pharmaceuticals

Stamp Date : 31 May, 2013

Proposed Trademark: Avaclyr*

Established Name: Acyclovir

Dosage Form: Ophthalmic ointment

Route of Administration: Topical

Strength: 3.0%

Indication: Treatment of herpetic keratitis (dendritic ulcers)

Reviewer : Suresh (Shrikant) Pagay

Biopharm Reviewer: Tapash Ghosh

Prdt. Qual. Micro Reviewer: Neal Sweeney

CMC Lead : Bala Shanmugam

	YES	NO
Acceptable for filing:	☒	☐
Comments for 74-Day Letter:	☐	☒

Summary and Critical Issues

Summary

Acyclovir is a synthetic nucleoside analog with antiviral properties and several different formulations (injection, topical ointment, capsules, suspension, tablets and topical cream) have been approved by the Agency. However, no ophthalmic ointment formulation of acyclovir has been approved in the US. The NDA is filed as a 505 (b) (2) and was granted Orphan Drug Designation. The submission, including methods validation is all electronic and located in the EDR. The drug product is formulated as a sterile ophthalmic ointment for topical administration and the proposed commercial package is 3.5 g tin tube. The company is requesting a shelf-life of (b) (4)-months when stored at (b) (4)-25°C.

All manufacturing and testing facilities have been entered in EES. Please note that a pre-NDA meeting was held on December 6, 2010. The minutes of the Pre-NDA meeting is provided in the NDA. The CMC question was about how much stability data is required to file the NDA. While there were a few communications on this topic (documented in the NDA), the sponsor has submitted adequate stability data as per ICH Q1A (R2) recommendations.

This NDA will be reviewed on a Standard time line. The PDUFA goal date is March 31, 2014.

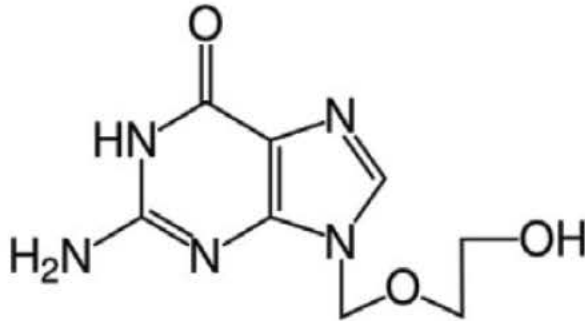
* Under review

Other Submissions to Note:

FDA Approved Acyclovir NDAs (Zovirax®)

Application No. (Applicant)	Active Ingredient	Dosage Form	Route of Administration	Strength
N018604	acyclovir	ointment	topical	5%
N021478	acyclovir	cream	topical	5%
N018828	acyclovir	capsule	oral	200 mg
N019909	acyclovir	suspension	oral	200 mg/mL
N020089	acyclovir	tablet	oral	400 mg and 800 mg
N018603	acyclovir	injectable	intravenous	500 mg and 1000 mg base

Drug Substance



All drug substance information related to manufacturing (manufactured by (b) (4)) and controls is referenced to DMF (b) (4) (see table for status of this DMF at the time of this IQA). A letter of authorization from the DMF holder has been provided.

Drug Substance	DMF #	LOA provided (Yes/No)	Status	Comments
Acyclovir	(b) (4)	Y	The last review is by R. Chang, dated April 25, 2013.	The last review found the DMF adequate. There are no new Quality submissions since this review.

- Particle size is considered to be critical attribute for product quality. *However, there is no details/discussion of how the desired particle size is achieved* (b) (4), *unless this process is part of the DMF.* (b) (4)

The reviewer should

verify this and if needed follow-up with Fera. An additional question to consider is what in-coming (acceptance) quality tests are conducted on receiving the drug substance (b)(4) by the drug product manufacturer.

- The (b)(4) drug substance (b)(4) will have to be evaluated by the Product Quality Microbiology Reviewer.
- A comparison of (b)(4) DS specifications provided in the NDA (b)(4) does not impact the quality of the DS.

Drug Product

The product is formulated as a sterile ophthalmic ointment.

- The drug product is manufactured by (b)(4)
- White Petrolatum is the only excipient used in the formulation and is USP quality
- The drug product composition is attached to this review.
- Manufacturing process is straight forward (b)(4)
(b)(4)
- The theoretical yield for each (b)(4) kg batch (commercial scale) is (b)(4) tubes. Executed batch record for batch 11443 has been provided.
- Section 3.2.P.5.4 provides the COA for three batches. While the batches appear to comply with the proposed specification, the acceptance criteria for impurities are listed as “TBD”. *The reviewer should clarify this and perhaps have Fera update and resubmit.*
- The DP specification is attached to serve as a quick reference for the reviewer. The company has proposed separate release and regulatory specification with differences in acceptance criteria for impurities (b)(4) proposed (b)(4) *The acceptance criteria proposed for the impurities should be evaluated and tightened if needed as based on batch and stability data. Only one test (HPLC) has been proposed for identity. ICH Q6A recommends one specific or two non-specific tests for identification. The reviewer should also determine the value of including a test for viscosity in the drug product specification. Additionally, (b)(4) and no justification has been provided (b)(4)*
- The container closure is (b)(4) *Reviewer should check if (b)(4) controlled.*
- The storage statement provided in the label and PI differ in the recommended temperature range. *This should be corrected by Fera.*

Early action needed:

- 1) Reviewer should evaluate items identified (*in italics*) in this IQA.

Comments for 74-day letter

None at this time.

Comments and Recommendation:

Based on the perusal of this NDA, it is determined to be complete and therefore filable from CMC perspective. Dr. Suresh (Shrikant) Pagay is assigned to review this NDA.

Balajee Shanmugam
CMC Lead

See DARRTS
Date

Dorota Matecka, Ph.D.
Branch Chief (Acting)

See DARRTS
Date

Drug Product Composition

Ingredient	Amount/gm	Amount w/w (%)	Function
acyclovir, USP	30 mg	(b) (4)	active
white petrolatum, USP	(b) (4)	(b) (4)	base
Total			(b) (4)

Drug Product Specification

Test	Analytical Method	Acceptance Criteria
Description	TMQC-203	Soft white ointment
ID	TMQC-203	Retention time of major peak is same for std and sample
Assay (30 mg/g)	TMQC-203	(b) (4) % label claim
Related Substances and Impurities (b) (4)	TMQC-203	NMT (b) (4) % NMT % NMT % NMT % NMT % NMT %
Individual unknown Total known and unknown (b) (4)	TMQC-203	NMT (b) (4) %
Minimum Fill USP <755>	TMQC-203	Meets USP <755> requirements
Metal Particles USP <751>	TMQC-203	NMT (b) (4) (b) (4)
Leak Test USP <771>	TMQC-203	No leakage (b) (4)
Sterility USP <71>	TMQC-203	Complies with USP <71>
Particle Size (b) (4)	TMQC-203	NLT (b) (4) % NLT % NLT %
Residual Solvents USP <467>	TMQC-203	Complies with USP <467>
Homogeneity: Assay (30 mg/g) Near tip Center Near crimp	TMQC-203	(b) (4) % label claim