CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206307Orig1s000

CHEMISTRY REVIEW(S)

NDA 206-307

Finafloxacin Otic Suspension, 0.3%

Alcon Research, Ltd.

Drug Substance Reviewer: Mariappan Chelliah, Ph.D.
Drug Product Reviewer: Chunchun Zhang, Ph.D.

ONDQA
Division of Pre-Marketing Assessment II
Branch V

Table of Contents

Chemistry Review Data Sheet

1. NDA 206-307

2. REVIEW #: 1

3. REVIEW DATE: 17-Sep, 2014

4. REVIEWER:

Drug Substance Reviewer: Mariappan Chelliah, Ph.D.
Drug Product Reviewer: Chunchun Zhang, Ph.D.

5. PREVIOUS DOCUMENTS:

None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	25-Apr-2014
Amendment	27-Jun-2014
Amendment	31-Jul-2014
Amendment	21-Aug-2014
Amendment	29-Aug-2014
Amendment	16-Sep-2014

7. NAME & ADDRESS OF APPLICANT:

Name: Alcon Research, Ltd.

Chemistry Review Data Sheet

Address: 6201 South Freeway, Fort Worth, TX 76134

Representative: Richard Reese

Telephone: 817-551-4345

8. DRUG PRODUCT NAME/CODE/TYPE:

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

- Chem. Type: 1
- Submission Priority: P

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

10. PHARMACOL. CATEGORY: Otitis Externa

11. DOSAGE FORM: Otic Suspension

12. STRENGTH/POTENCY: 0.3%

13. ROUTE OF ADMINISTRATION: Topical (Otic)

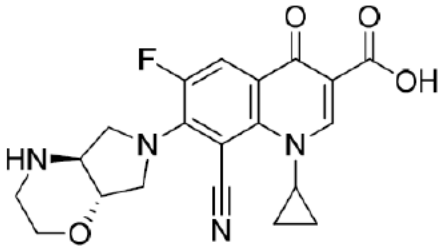
14. Rx/OTC DISPENSED: __X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

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

USAN: Finafloxacin
Chemical Name: (-)-8-cyano-1-cyclopropyl-6-fluoro-7-[(4a*S*,7a*S*)-hexahydropyrrolo[3,4-*b*]-1,4-oxazin-6(2*H*)-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



Molecular Formula: $C_{20}H_{19}FN_4O_4$
Molar Mass: 398.4 g/Mol
Chemical Abstract: 209342-40-5

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)	4			LoA: (b) (4)
	III			4			LoA (b) (4)
	III			4			LoA: (b) (4)
	III			4			LoA: (b) (4)
	I			2			LoA: (b) (4)
	I			2			LoA: (b) (4)

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

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

B. Other Documents: N/A

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		NA
EES	Acceptable	8/8/2014	
Pharm/Tox	Pending; Justification on the two genotoxic impurities were found acceptable by Dr. Andrew McDougal in the email communication on 9/10/2014.		Andrew McDougal
Biopharm	Pending; The Biopharmaceutics reviewer has indicated that the NDA is recommended for approval from the Biopharmaceutics perspective and a review will be filed in DARRTS by 9/25/2014.		Banu Zolnik
LNC	NA		NA
Methods Validation	Acceptable	8/20/2014	Michael Trehy
OPDRA	NA		NA
EA	NA		NA
Microbiology	Acceptable	9/15/2014	Vinayak Pawar

The Chemistry Review for NDA 206-307

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure the identity, strength, purity, and quality of the drug products. The Biopharmaceutics reviewer has indicated that the NDA is recommended for approval from Biopharmaceutics perspective and a review will be filed in DARRTS by 9/25/2014. An overall facilities recommendation of "Acceptable" has been made by the Office of Compliance (8/8/2014). Quality Micro also recommends approval of the NDA. Labeling is adequate from CMC perspective and will be finalized during team review . Therefore, from CMC perspective, this NDA is recommended for approval.

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

A PMC for developing a dissolution method is recommended by Biopharmaceutics. Please refer to ONDQA Biopharmaceutics review by Dr. Banu Zolnik.

II. Summary of Chemistry Assessments

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

Drug Substance

(S,S)-Finafloxacin, also known as AL-60371, is a fourth generation quinolone class of antibiotic indicated for acute otitis externa. AL-60371 is manufactured as an (b) (4) . The drug substance has low aqueous solubility and consequently is therefore formulated as a suspension in the drug product. The drug substance is manufactured by (b) (4)

The manufacturing process has been optimized by (b) (4) and four commercial batches of drug substance have been manufactured using this process. The impurity levels that could possibly affect the drug substance quality are controlled by a combination of operating

parameters and in-process controls. The levels of two potential mutagenic impurities, [redacted] are controlled by the drug product specification of NMT [redacted]% of any single unspecified impurity. This level is justified by the expected daily dose of <2.5µg/day which is less than the TTC of 20µg/day dose calculated on the basis of ICH M7 guideline. The adequacy of the level at which it is controlled was also verified to be acceptable with the Pharm Tox reviewer.

The drug substance is known to exist in [redacted]

Drug Product

Finafloxacin otic suspension, 0.3% is a sterile, multi-dose, preserved, aqueous, ototopical suspension. The maximum daily dose is 1.27 mg per day (four drops into the infected ear twice daily).

The suspension formulation contains 0.3% loading of finafloxacin and the following compendial excipients: sodium chloride, hydroxyethylcellulose, tyloxapol, magnesium chloride, benzalkonium chloride (0.005 %) as preservative, and purified water. Hydrochloric acid and/or sodium hydroxide may be added to adjust pH.

Commercial drug product with the commercial scale of [redacted] is manufactured at Fort Worth, TX. The commercial finafloxacin otic suspension 0.3% manufacturing process has the following steps: [redacted]

The drug product quality is tested for the following quality attributes in the release specification: appearance, identification, assay, impurity, BAC, osmolality, pH, viscosity, redispersibility, sterility and particle size. The applicant has agreed to develop a dissolution method and will be fulfilled via a PMC (See ONDQA Biopharmaceutics review). Quality microbiology has determined that the sterility process is assured and is therefore adequate. All analytical methods have been adequately validated and the specification acceptance criteria justified appropriately.

Overall, the controls in place for the manufacturing process and the drug product specification will ensure consistent drug product quality to provide safe and effective treatment of patients.

Stability data of the drug product packaged in 5 mL fill in 8 mL LDPE bottle (trade size) and 0.5 mL fill in 4 mL LDPE bottle (sample size) stored under long term (25 °C/40% RH) for 78 weeks

and accelerated conditions (40 °C/<25% RH) for 26 weeks show very little change in the drug product quality. Overall, the stability data supports 104 weeks for 5 mL fill and 78 weeks for 0.5 mL fill expiration dating when stored at 2°C to 25°C .

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

Finafloxacin otic suspension, 0.3% is intended for treating otic bacterial infections in patients with Acute Otic Externa. The recommendation dosage is four drops into the effected ear twice daily for 7 days .

Finafloxacin otic suspension, 0.3% will be packaged in 4 mL (sample size) and 8 mL (trade size) white low density polyethylene (LDPE) bottles, with (b) (4) white (b) (4) closures. The bottles label instruction recommends to "store at 2°C to 25°C" and is assigned an expiration date of 104 weeks for 5 mL fill trade size and 78 weeks for 0.5 fill mL sample size.

C. Basis for Approvability or Not-Approval Recommendation

The applicant has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specification to assure consistent product quality of the drug substance and drug product. The NDA has also provided sufficient stability information on the drug product to assure the drug product throughout the expiration dating period 104 weeks for 5 mL fill trade size and 78 weeks for 0.5 mL fill sample size. The Biopharmaceutics reviewer has indicated that the NDA is recommended for approval from the Biopharmaceutics perspective and a review will be filed in DARRTS by 9/25/2014. Quality Micro also recommended approval of this NDA.

All facilities have acceptable site recommendations (see attached EES report).

All labels have the required information.

Executive Summary Section

From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	Factors that can impact the CQA	Risk Ranking	Risk Mitigation approach	Risk Evaluation	Lifecycle Considerations/ Comments
Drug Substance (DS) starting material (SM)	Potential impurities and overall quality	Medium	Impurities are controlled in the intermediate and drug substance specification.	Low	(b) (4)
Drug Substance Quality	Potential impurities and overall quality	Medium	DS impurities are well controlled by the process and not detected in the drug product.	Low	NA
Sterile manufacturing	(b) (4)	High	Refer to product Quality Micro Vinayak Pawar's review.	Medium	Per Micro review the microbiological processes are adequately validated.
Sterilization of drug substance (b) (4)	Impurity profile	Medium	Impurities levels are controlled in the specification. No new impurities nor the levels of the impurities increased (b) (4)	Low	NA
(b) (4)					
Stability of the drug product	Assay, impurity, osmolality, pH, viscosity, redispersibility, BAC and sterility	Low	No significant changes were observed on the tests. A shelf life of 104 weeks for 5 fill trade size and 78 weeks for 0.5 fill sample size is acceptable based on the available 78 weeks long term stability data.	Low	NA

III. Administrative

A. Reviewer's Signature

Mariappan Chelliah, Chunchun Zhang, CMC Reviewers, Branch V, ONDQA

B. Endorsement Block

Balajee Shanmugam, CMC Lead, Branch V, ONDQA
Rapti Madurawe, Branch Chief, Branch V, ONDQA

C. CC Block

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/s/

CHUNCHUN N ZHANG
09/17/2014

MARIAPPAN V CHELLIAH
09/17/2014

BALAJEE SHANMUGAM
09/17/2014

RAPTI D MADURAWE
09/17/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION REPORT SUMMARY

TO: Chunchun Zhang, CMC Reviewer

Office of New Drug Quality Assessment (ONDQA)
E-mail Address: chunchun.zhang@fda.hhs.gov
Phone: (301)-796-5168
Fax: (301)-796-9877

FROM: FDA
Division of Pharmaceutical Analysis
Michael Trehy, MVP Coordinator
645 S Newstead Avenue
St. Louis, MO 63110
Phone: (314) 539-3815

Through: John Kauffman, Deputy Director
Phone: (b) (4)

SUBJECT: Methods Validation Report Summary

Application Number: 206307

Name of Product: Finafloxacin Otic Suspension, 0.3%

Applicant: Alcon Research Ltd.

Applicant's Contact Person: Paul Nitschmann

Address: 6201 South Freeway, Mail code TC-45, Fort Worth, Texas 76134-2099

Telephone: (817) 551-4345 Fax: (817) 551-4630

Date Methods Validation Consult Request Form Received by DPA: Jun-4-2014

Date Methods Validation Package Received by DPA: Jun-4-2014

Date Samples Received by DPA: Jun-10-2014

Date Analytical Completed by DPA: Aug-14-2014

Laboratory Classification: **1.** Methods are acceptable for control and regulatory purposes. ☒
2. Methods are acceptable with modifications (as stated in accompanying report). ☐
3. Methods are unacceptable for regulatory purposes. ☐

Comments: See attached review for analyst's comments and summary of results.

DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration

Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis
645 S. Newstead Ave.
St. Louis, Missouri 63110
Telephone (314) 539-2168
FAX (314) 539-2113

Date: August 13, 2014

To: Rapti Madurawe PhD, ONDQA

From: Jeffrey T. Woodruff, Chemist, DPA

Through: John Kauffman PhD, Deputy Director, DPA

Subject: Method Evaluation of NDA 206307 Finafloxacin Otic Suspension, 0.3%

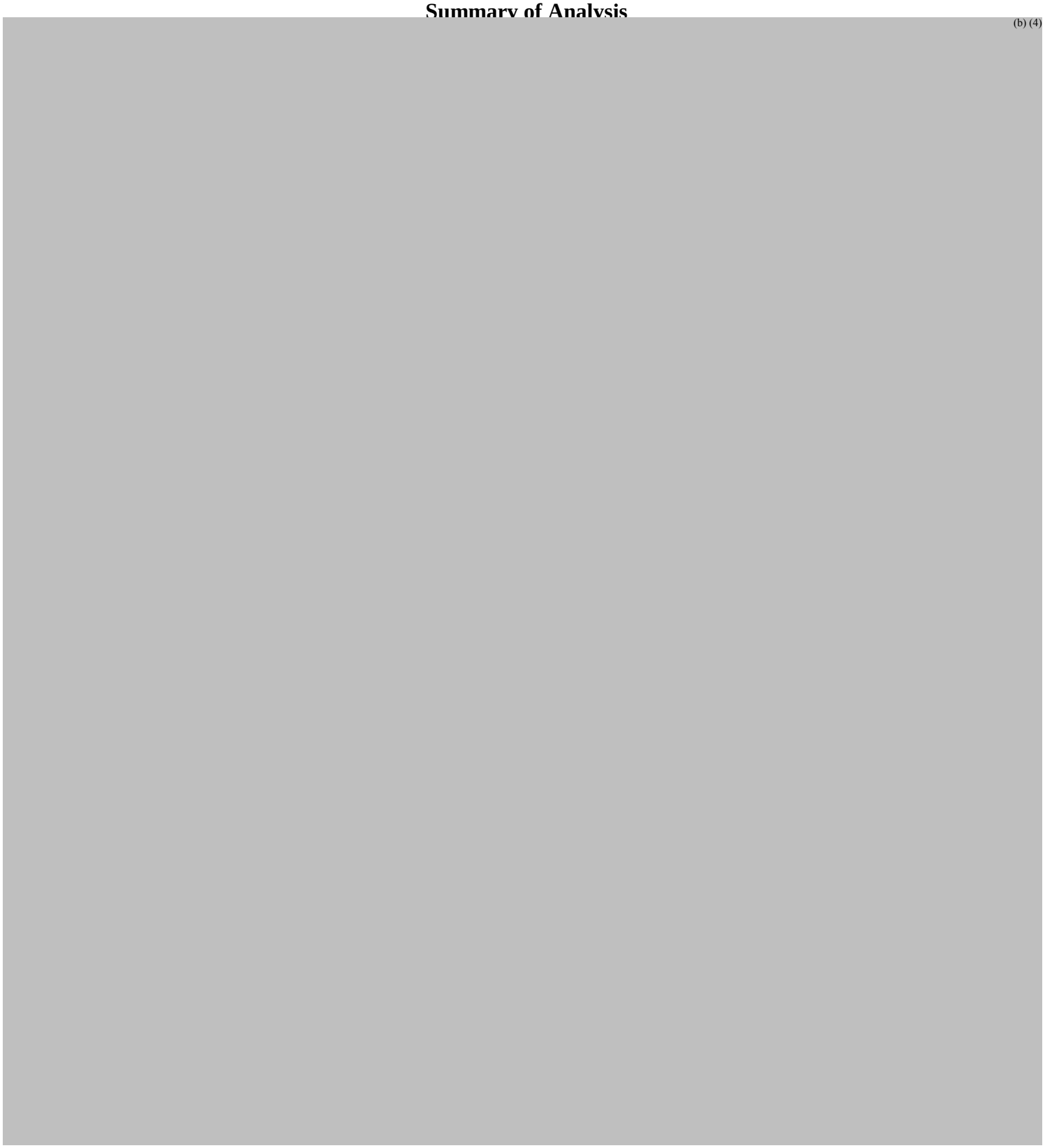
The following methods were evaluated and found acceptable for quality control and regulatory purposes:

HPLC Assay and Identification of Finafloxacin Drug Substance and Impurities in [redacted] (b) (4) Finafloxacin Free Base (AL-60371)

Analyst's work sheets and chromatograms are available at
http://ecmsweb.fda.gov:8080/webtop/drl/objectId/090026f88079040b

Summary of Analysis

(b) (4)



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/s/

MICHAEL L TREHY
08/20/2014

JOHN F KAUFFMAN
08/20/2014

Initial Manufacturing (CGMP/Facilities) Assessment (IMA) and Filing Review for Pre-Marketing Applications (Original)

I. Review Cover Sheet

1. OMPQ Reviewer: Linda Ng, Ph.D.

2. NDA Number: NDA 206-307
   Submission Date: April 25, 2014
   21st C. Review Goal Date: October 25, 2014
   PDUFA Goal Date: December 25, 2014

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	Xtoro™
Established or Non-Proprietary Name (USAN) and strength:	Finafloxacin Otic Suspension, 0.3%
Dosage Form:	Otic Suspension

4. SUBMISSION PROPERTIES:

Review Priority :	PRIORITY
Applicant Name:	Alcon Research
Responsible Organization (OND Division):	DTOP

II. Application Detail

1. INDICATION: Treatment of acute otitis externa
2. ROUTE OF ADMINISTRATION: ear drops
3. STRENGTH/POTENCY: 0.3%
4. Rx/OTC DISPENSED: x☐Rx ☐OTC
5. ELECTRONIC SUBMISSION (yes/no)? yes
6. PRIORITY CONSIDERATIONS:

	Parameter	Yes	No	Unk	Comment
1.	NME / PDUFA V	X			
2.	Breakthrough Therapy Designation		X		
3.	Orphan Drug Designation		X		
4.	Unapproved New Drug		X		
5.	Medically Necessary Determination		X		
6.	Potential Shortage Issues [either alleviating or non-approval may cause a shortage]		X		
7.	Rolling Submission		X		
8.	Drug/device combination product with consult		X		
9.	Complex manufacturing		X		
10.	Other (e.g., expedited for an unlisted reason)	X			Priority due to submission of Pediatric data

III. FILING CHECKLIST

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

A. COMPLETENESS OF FACILITY INFORMATION				
	Parameter	**Yes**	**No**	**Comment**
11.	Is all site information complete (e.g., contact information, responsibilities, address)?	X		
12.	Do all sites indicate they are ready to be inspected (on 356h)?	X		
13.	Is a single comprehensive list of all involved facilities available in one location in the application?	X		The container closure manufacturers and sterilizer of the cc are all submitted but not entered in EES
14.	For testing labs, is complete information provided regarding which specific test is performed at each facility and what stage of manufacturing?		X	Not indicated; assume that the testing is performed by the respective DS & DP manufacturers. The ONDQA PM should follow up & confirm.
15.	Additional notes (non-filing issue) 1. Are all sites registered or have FEI #?	X		
	2. Do comments in EES indicate a request to participate on inspection(s)?		X	
	3. Is this first application by the applicant?		X	

*If any information regarding the facilities is missing/omitted, communicate to OPS/ONDQA regarding missing information and copy EESQuestions. Notify OMPQ management if problems are not resolved within 3 days and it can be a *potential* filing issue.

B. DRUG SUBSTANCE (DS) / DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
16.	Have any Comparability Protocols been requested?		X	None claimed

IMA CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
17.	Does this application fit one of the EES Product Specific Categories?	X		This is an NME
18.	Have EERs been cross referenced against the 356h and product specific profile for accuracy and completion? Have all EERs been updated with final PAI recommendation?	X		
19.	**From a CGMP/facilities perspective, is the application fileable?** If the NDA is not fileable from a product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	X		

IV. Manufacturing Summary: Critical Issues and Complexities

Does the submission contain any of the following elements?			No
Nanotechnology	RTRT Proposal	PAT	Drug/Device Combo
☐	☐	☐	☐
PET	Design Space	Continuous Mfg	Naturally derived API
☐	☐	☐	☐
Other (explain):			

Manufacturing Highlights

1. Drug Substance

	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		X	This is an NME

Include process flow chart/diagram (see eCTD Section 2.3.S.1)

Figure 3.2.S.2.2–1 Flow Diagram of the Manufacturing Process

2. Drug Product

	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		X	Alcon has been manufacturing suspension and solution products for decades.

Include process flow chart/diagram (see eCTD Section 2.3.P.1)

Figure 3.2.P.3.3–1 Title Manufacturing Process Flowchart for Finafloxacin Otic Suspension

(b) (4)

3. **Facility-Related Risks (e.g., expected in-process testing not being performed, questionable development, unexplained stability failures, data integrity issues, etc.). Describe any potential 21CFR 211 compliance issues.** Nothing obvious

4. **Drug Product Facility Inspectional History that could impact the manufacturing of this product** None

Additional information not covered above

None

Manufacturing Facilities Chart (generated from 602A DARRTS report and OMPQ macro):

NDA:	**206307 Finafloxacin (AL-60371)**
Sponsor:	**ALCON RESEARCH LTD**
Indication:	**Treatment of acute otitis externa**
PDUFA:	**12/25/2014 under PRIORITY Review**
Responsible Orga	**CDER/OAP/DTOP**
EERS Submitted By:	
Chart Generated C	**6/12/2014**
	Overall OC Recomendation: **PENDING entered into EES on 5/12/2014 10:09:00 AM**
	Reevaluation date:

Establishment Name	EER Creation Date	FEI Num	District Short	Country Code	Responsibilities	Profile Code	Firm Profiles - Current Status	Inspection History, Dates, Classifications	Most Recent Milestone	Most Recent EER
										(b) (4)
ALCON RESEARCH, LTD.	5/1/2014	1610287	DAL	USA	Drug Product Manufacturer	SES	http://intranetapps.fda.gov/scripts/mpga/profile.cfm?FEI=1610287	Found AC from inspection of (b) (4)	SUBMITTED TO DO	PN

For each EER, indicate PAI recommendation on the Manufacturing Facilities Chart above (e.g., PS, GMP, 10 Day, AC based on file review). This is the recommendation that will be entered into EES. **For PAI, include the reason for the PAI (i.e. PAI Trigger) in the comment section of the facilities chart.**

V. Overall Conclusions and Recommendations

Is the application fileable? (yes/no, Yes to questions 11-12) Yes
Based on Section IV, is a (b) (4) warranted for any PAI? (yes/no). If yes, please identify the sites in the above chart. Does not appear to need any (b) (4)
Are there comments/issues to be included in the 74 day letter, including appropriate identification of facilities? (yes/no) Not likely. ONDQA PM will follow up with applicant for testing facilities.
Comments for 74 Day Letter
1.
2.
3.

REVIEW AND APPROVAL
(DARRTS)

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

/s/

LINDA L NG
06/27/2014

VIPULCHANDRA N DHOLAKIA
06/27/2014

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Trade or Proprietary Name:	Xtoro™
Established or Non-Proprietary Name (USAN) and strength:	Finafloxacin Otic Suspension, 0.3%
Dosage Form:	Otic Suspension

4. SUBMISSION PROPERTIES:

Review Priority :	PRIORITY
Applicant Name:	Alcon Research
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II. Application Detail

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3. STRENGTH/POTENCY: 0.3%
4. Rx/OTC DISPENSED: x☐Rx ☐OTC
5. ELECTRONIC SUBMISSION (yes/no)? yes
6. PRIORITY CONSIDERATIONS:

	Parameter	Yes	No	Unk	Comment
1.	NME / PDUFA V	X			
2.	Breakthrough Therapy Designation		X		
3.	Orphan Drug Designation		X		
4.	Unapproved New Drug		X		
5.	Medically Necessary Determination		X		
6.	Potential Shortage Issues [either alleviating or non-approval may cause a shortage]		X		
7.	Rolling Submission		X		
8.	Drug/device combination product with consult		X		
9.	Complex manufacturing		X		
10.	Other (e.g., expedited for an unlisted reason)	X			Priority due to submission of Pediatric data

III. FILING CHECKLIST

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

A. COMPLETENESS OF FACILITY INFORMATION				
	Parameter	**Yes**	**No**	**Comment**
11.	Is all site information complete (e.g., contact information, responsibilities, address)?	X		
12.	Do all sites indicate they are ready to be inspected (on 356h)?	X		
13.	Is a single comprehensive list of all involved facilities available in one location in the application?	X		The container closure manufacturers and sterilizer of the cc are all submitted but not entered in EES
14.	For testing labs, is complete information provided regarding which specific test is performed at each facility and what stage of manufacturing?		X	Not indicated; assume that the testing is performed by the respective DS & DP manufacturers. The ONDQA PM should follow up & confirm.
15.	Additional notes (non-filing issue) 1. Are all sites registered or have FEI #?	X		
	2. Do comments in EES indicate a request to participate on inspection(s)?		X	
	3. Is this first application by the applicant?		X	

*If any information regarding the facilities is missing/omitted, communicate to OPS/ONDQA regarding missing information and copy EESQuestions. Notify OMPQ management if problems are not resolved within 3 days and it can be a *potential* filing issue.

B. DRUG SUBSTANCE (DS) / DRUG PRODUCT (DP)				
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IMA CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
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18.	Have EERs been cross referenced against the 356h and product specific profile for accuracy and completion? Have all EERs been updated with final PAI recommendation?	X		
19.	**From a CGMP/facilities perspective, is the application fileable?** If the NDA is not fileable from a product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	X		

IV. Manufacturing Summary: Critical Issues and Complexities

Does the submission contain any of the following elements?			No
Nanotechnology	RTRT Proposal	PAT	Drug/Device Combo
☐	☐	☐	☐
PET	Design Space	Continuous Mfg	Naturally derived API
☐	☐	☐	☐
Other (explain):			

Manufacturing Highlights

1. Drug Substance

	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		X	This is an NME

Include process flow chart/diagram (see eCTD Section 2.3.S.1)

(b) (4)

2. Drug Product

	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		X	Alcon has been manufacturing suspension and solution products for decades.

Include process flow chart/diagram (see eCTD Section 2.3.P.1)

Figure 3.2.P.3.3–1 Title Manufacturing Process Flowchart for Finafloxacin Otic Suspension

3. **Facility-Related Risks (e.g., expected in-process testing not being performed, questionable development, unexplained stability failures, data integrity issues, etc.). Describe any potential 21CFR 211 compliance issues.** Nothing obvious

4. **Drug Product Facility Inspectional History that could impact the manufacturing of this product** None

Additional information not covered above

None

Manufacturing Facilities Chart (generated from 602A DARRTS report and OMPQ macro):

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EERS Submitted By:	
Chart Generated C	**6/12/2014**
	Overall OC Recomendation: **PENDING entered into EES on 5/12/2014 10:09:00 AM**
	Reevaluation date:

Establishment Name	EER Creation Date	FEI Num	District Short	Country Code	Responsibilities	Profile Code	Firm Profiles - Current Status	Inspection History, Dates, Classifications	Most Recent Milestone	Most Recent EER
										(b) (4)
ALCON RESEARCH, LTD.	5/1/2014	1610287	DAL	USA	Drug Product Manufacturer	SES	http://intranetapps.fda.gov/scripts/mpga/profile.cfm?FEI=1610287	Found AC from inspection of (b) (4)	SUBMITTED TO DO	PN

For each EER, indicate PAI recommendation on the Manufacturing Facilities Chart above (e.g., PS, GMP, 10 Day, AC based on file review). This is the recommendation that will be entered into EES. **For PAI, include the reason for the PAI (i.e. PAI Trigger) in the comment section of the facilities chart.**

V. Overall Conclusions and Recommendations

Is the application fileable? (yes/no, Yes to questions 11-12) Yes
Based on Section IV, is a (b) (4) warranted for any PAI? (yes/no). If yes, please identify the sites in the above chart. Does not appear to need any (b) (4)
Are there comments/issues to be included in the 74 day letter, including appropriate identification of facilities? (yes/no) Not likely. ONDQA PM will follow up with applicant for testing facilities.
Comments for 74 Day Letter
1.
2.
3.

REVIEW AND APPROVAL
(DARRTS)

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

/s/

LINDA L NG
06/27/2014

VIPULCHANDRA N DHOLAKIA
06/27/2014

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

Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: 206307

2. SUBMISSION TYPE : Original

3. SUBMISSION NUMBER: 0

4. PRODUCT PROPERTIES: Sterile otic suspension

Trade or Proprietary Name:	Xtoro (*under review)*
Established or Non-Proprietary Name (USAN):	Finafloxacin
Dosage Form:	Otic suspension

5. NAME & ADDRESS OF APPLICANT:

Name:	Alcon Research, Ltd.
Address:	6201 South Freeway, Fort Worth, TX
Representative:	NA

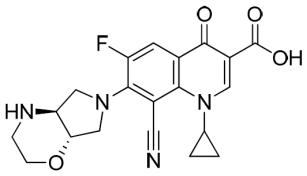
6. SUBMISSION PROPERTIES:

Review Priority :	Standard
Classification (Chem. Code and Type):	1
Property (Legal Basis):	505 (b) (1)
Responsible Organization:	CDER

Review Information

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

(-)-8-cyano-1-cyclopropyl-6-fluoro-7-[(4a*S*, 7a*S*)-hexahydropyrrolo[3,4-*b*]-1,4-oxazin-6(2H)-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid.



$C_{20}H_{19}FN_4O_4$
398.4

2. INDICATION: Treatment of acute otitis externa in pediatric (ages (b) (4) (b) (4) and older), adult and elderly patients.

3. PHARMACOLOGICAL CATEGORY: Antibiotic

4. ROUTE OF ADMINISTRATION: Otic

5. STRENGTH/POTENCY: 0.3%

6. Rx/OTC DISPENSED: ☒Rx ☐OTC

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

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

RELATED REVIEW DOCUMENTS:

a. Drug Master Files listed on 356h form:

DMF	TYPE		ITEM	LOA DATE	COMMENTS
(b) (4)	II			(b) (4)	
	II				
	II				
	II				
	V				
	V				

b. Consults Recommended by CMC and Biopharmaceutics

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics	☐	☒	
Clin Pharm	☐	☐	
EES	☒	☐	
Pharm/Tox	☒	☐	
Methods Validation	☐	☐	
EA	☐	☐	
New Drug Micro	☒	☐	
CDRH	☐	☐	
Other	☐	☐	

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

DOCUMENT NAME	DATE	APPLICATION NUMBER	DESCRIPTION
IND		110576	

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

DOCUMENT NAME	DATE	APPLICATION NUMBER	DESCRIPTION
EOP1 meeting	Nov-03-2011	IND 110576	CMC, non-clinical & clinical
Pre-NDA meeting	Sep-27-2013	IND 110576	Clinical

Overall Conclusions and Recommendations

Is the Product Quality Section of the application fileable from a CMC perspective?		
Yes	No	CMC Filing Issues
☒	☐	1.

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

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

Are there potential biopharmaceutics review issues to be forward to the Applicant with the IR letter?		
Yes	No	Biopharmaceutics Comments for IR Letter dated 6/10/2014 sent to the Applicant
☒	☐	*1) Since your proposed drug product is a suspension, the dissolution test should be added to the specifications of the drug product. Therefore, develop an in vitro dissolution test that is optimal for your proposed otic suspension product.* *2) Provide the dissolution method development report with the following information/data:* *a) Detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters (i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.) used to select the proposed dissolution method as the optimal test for your product. It is noted that in general, lower rotation speeds are used for the dissolution of suspensions (25 rpm). If a surfactant is used, include the data supporting the selection of the type and amount of surfactant. The testing conditions used for each test should be clearly specified.*

b) Provide the complete dissolution profile data (individual, mean, SD, profiles) generated during the method development. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (the percentage is based on the product's label claim);

c) A list of all relevant manufacturing variables and material attributes affecting the dissolution of your proposed product;

d) Data supporting the discriminating capability of the proposed dissolution method for meaningful manufacturing changes implemented to your proposed product. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the drug product manufactured under target conditions vs. the drug products that are intentionally manufactured with meaningful variations (i.e., ± 10-20% change to the specification-ranges of these variables) for the most relevant manufacturing variables (e.g. drug substance particle size etc.).

3) *Note that the discriminating ability is not only determined by the dissolution method settings but also by the selected specification-sampling time point and specification value. For the selection of the dissolution acceptance criterion of your product, the following points should be considered:*
   - *The complete dissolution profile data (e.g., 15, 20, 30, 45, 60, etc. minutes) from the pivotal clinical and PK batches and primary (registration) stability batches should be used for the setting of the dissolution acceptance criteria of your product.*
   - *Specifications should be based on average in vitro dissolution data (n=12).*
   - *The specification-time point should be selected when Q = (b) (4) % dissolution occurs.*

ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications – CMC and Biopharmaceutics
NDA #: 206307

CMC Summary:
Critical Issues and Complexities

CMC Critical Issues or Complexities
This NDA presents finafloxacin otic suspension, 0.3% for treating otic bacterial infections in patients with Acute Otitis Externa. Finafloxacin is a NME which belongs to fluoroquinolone class of broad spectrum antibacterials. The critical issue identified relates to the designation of (b) (4) [redacted] The non-critical quality issues are mentioned below for further evaluation.

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

Is a team review recommended?		
Yes	No	Suggested expertise for team
☒	☐	Product Quality – Chunchun Zhang, Ph.D. Biopharmaceutics Reviewer – Banu Zolnik, Ph.D.

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

Biopharmaceutics Initial Assessment

Biopharmaceutics Synopsis, Critical Issues or Complexities

Submission:
This 505 (b)(1) NDA submission for Finafloxacin Otic Suspension, 0.3% for the treatment of acute otitis externa in pediatric (age (b) (4) and older), adult and elderly patients.

Introduction:
Finafloxacin (aka AL-60371) otic suspension is formulated sterile, preserved multi-dose aqueous suspension. The Applicant conducted the following clinical studies in support of the approval of the proposed product: 1) **C-10-007 Phase 1 Study**-Randomized, multiple dose, fixed sequence pharmacokinetic study in healthy subjects (period 1 otic suspension and in period 2 200 mg oral tablet is administered), 2) **C-10-022 Phase 1 Study**-Open-label, single visit study, 3) **C-10-018 Phase 3 Study**- Multicenter, randomized, double-masked, parallel-group, vehicle-controlled, 4) **C-10-019 Phase 3 Study**- Multicenter, randomized, double-masked, parallel-group, vehicle –controlled.

Product Description:
The Applicant stated that formulation (FID 119420 as shown below) used in clinical studies (C-10-007, C-10-018, C-10-019, and C-10-022) is the to-be marketed formulation.

Table 2.3.P.1–1 Composition of Finafloxacin Otic Suspension (FID 119420)

Component	Concentration % w/v	Function	Compendial Status
Finafloxacin (AL-60371)	0.3[a]	Active	NOC[b]
Tyloxapol	(b) (4)	(b) (4)	USP
Hydroxyethyl Cellulose (b) (4)			NF
Sodium Chloride			USP
Magnesium Chloride (b) (4)			USP
Benzalkonium Chloride		Preservative	NF
Sodium Hydroxide And / or Hydrochloric Acid		Adjust pH	NF NF
Purified Water		(b) (4)	USP

Note: FID = Formulation Identification Number
[a] Adjust for purity
[b] NOC = non-compendial
[c] Added as a (b) (4) % solution, based on assay.

The Applicant used different formulations- solution (FID 116616) and suspension formulation (FID 118325 and FID 117374) below for the toxicology batches. The need for any bridging studies will be evaluated during the NDA review.

Table 2.3.P.5–8 Toxicology Batch Composition for the Solution Formulation (FID 116616)

Component	Concentration % w/v	Function
Finafloxacin Hydrochloride (AL-60371A)	0.33[a]	Active
Magnesium Chloride (b) (4)	(b) (4)	(b) (4)
(b) (4)		
Benzalkonium Chloride		Preservative
(b) (4)		(b) (4)
Sodium Hydroxide And / or Hydrochloric Acid		Adjust pH
Purified Water		(b) (4)
(b) (4)		

Table 2.3.P.5–10 Toxicology Batch Composition for Suspension Formulations

Component	Concentration % w/v		Function
	FID 118325	FID 117374	
Finafloxacin (AL-60371)	0.3	None	Active
Finafloxacin Hydrochloride (AL-60371A)	None	0.33[a]	Active
Tyloxapol		(b) (4)	(b) (4)
Hydroxyethyl Cellulose (b) (4)			
Sodium Chloride			
Benzalkonium Chloride			Preservative
Sodium Hydroxide and / or Hydrochloric Acid			(b) (4)
Purified Water			
(b) (4)			

(b) (4)

Review Objectives:
The Biopharmaceutics review will be focused on *1)* the evaluation and acceptability of dissolution data and acceptance criterion, 2) the evaluation of the biowaiver request.

Issues Identified:
The Applicant did not provide any dissolution data. Therefore, dissolution data is requested in the IR letter dated 6/10/2014.

Filing Recommendation:
From Biopharmaceutics perspective, NDA 206-307 for finafloxacin otic suspension is fileable. However, Biopharmaceutics filing comments in page 4 and 5 under "Overall Conclusion and Recommendation" Section was sent to the Applicant in the information request (IR) letter.

FILING REVIEW CHECKLIST

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

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

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

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

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

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

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

D. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
12.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	☒	☐	*See table on cover page.*

E. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
13.	Does the section contain a description of the DS manufacturing process?	☒	☐	
14.	Does the section contain identification and controls of critical steps and intermediates of the DS (in process parameters?	☒	☐	
15.	Does the section contain information on impurities?	☒	☐	
16.	Does the section contain information regarding the characterization of the DS?	☒	☐	
17.	Does the section contain controls for the DS?	☒	☐	
18.	Has stability data and analysis been provided for the drug substance?	☒	☐	
19.	Does the application contain Quality by Design (QbD) information regarding the DS?	☐	☒	
20.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?	☐	☒	
21.	Does the section contain container and closure information?	☒	☐	Several DMF's have been referenced for container closures. Please see IQA for details.

F. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
22.	Does the section contain quality controls of excipients?	☒	☐	
23.	Does the section contain information on composition?	☒	☐	
24.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	☒	☐	
25.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	☒	☐	
26.	Is there a batch production record and a proposed master batch record?	☒	☐	
27.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	☒	☐	
28.	Have any biowaivers been requested?	☒	☐	
29.	Does the section contain description of to-be-marketed container/closure system and presentations?	☒	☐	
30.	Does the section contain controls of the final drug product?	☒	☐	
31.	Has stability data and analysis been provided to support the requested expiration date?	☒	☐	
32.	Does the application contain Quality by Design (QbD) information regarding the DP?	☐	☒	
33.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?	☐	☒	

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

H. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
35.	If appropriate, is a separate microbiological section included discussing sterility of the drug product?	☒	☐	

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

J. BIOPHARMACEUTICS FILING PARAMETERS				
	Parameter	**Yes**	**No**	**Comment**
39.	Does the application contain dissolution data?		X	The Applicant did not provide dissolution data for this suspension formulation. Dissolution data was requested in the IR letter dated 6/10/2014.
40.	Is the dissolution test part of the drug product specifications?		X	The Applicant did not provide specifications for the dissolution test. This information was requested in the IR letter dated 6/10/2014.
41.	Does the application contain the dissolution method development report including data supporting the discriminating ability?		X	
42.	Is there a validation package for the analytical method and dissolution methodology?		X	

43.	Does the application include a biowaiver request?	X		The Applicant requests a waiver from the requirements for submission of in vivo bioavailability or BE data. The Applicant conducted C-10-007 and C10-022 PK studies in healthy subjects and in patients with acute otitis externa, respectively. The Applicant concluded that in both PK studies systemic exposure to AL-6031 was low; as a result there were insufficient data to determine PK parameters.
44.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development?	X		The Applicant stated that the formulation used in clinical studies (C-10-007, C-10-018, C-10-019, and C-10-022) is the to-be marketed formulation.
45.	Are there any formulation and/or manufacturing changes implemented to the clinical formulation? If yes. Are data supporting the bridging between the clinical and commercial drug products and/or manufacturing sites?		X	The Applicant used different formulations-solution (FID 116616) and suspension formulation (FID 118325 and FID 117374) for the **toxicology batches**. The need for any bridging studies will be evaluated during the NDA review.
46.	Is the proposed drug product a modified release dosage form (e.g., controlled release, delayed release)?	--	--	Not Applicable
47.	Does the application include an IVIVC model?		X	
48.	Does the application include information/data on the in vitro alcohol dose-dumping potential of the proposed drug product?	--	--	NA
49.	Is there enough information to assess the extended release designation claim?	--	--	NA
50.	Is there any in vivo BA or BE study in the submission?	X		
51.	Is the Biopharmaceutics team responsible of reviewing the in vivo BA or BE studies? If yes. • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies)?		X	

52.	Is there any design space proposed using in vitro release as a response variable?	--	--	NA
53.	Is the control strategy related to in vitro drug release?	--	--	NA

K. BIOPHARMACEUTICS FILING CONCLUSION AND COMMENTS

	Parameter	Yes	No	Comment
54.	**IS THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	X		
55.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.	--	--	NA
56.	Are there any potential review issues identified?	X		
57.	Are there any comments to be sent to the Applicant as part of the 74-Day letter?	X		The Biopharmaceutics comments in pages 4 and 5, under filing recommendation were requested in the IR letter dated 6/10/2014.
58.	Are there any internal comments for the other disciplines?		X	

REVIEW AND APPROVAL

See appended electronic signature page}
Balajee Shanmugam, Ph.D.
CMC-Lead
Division II
Office of New Drug Quality Assessment

{See appended electronic signature page}
Banu Sizanli Zolnik, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

{See appended electronic signature page}
Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

{See appended electronic signature page}
Rapti Madurawe, Ph.D.
Branch Chief
Office of New Drug Quality Assessment

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/s/

BALAJEE SHANMUGAM
06/12/2014

BANU S ZOLNIK
06/12/2014

ANGELICA DORANTES
06/12/2014

RAPTI D MADURAWE
06/13/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION CONSULT REQUEST FORM

TO: **FDA**
Division of Pharmaceutical Analysis
Attn: Michael Trehy
Suite 1002
1114 Market Street
St. Louis, MO 63101

FROM: Chunchun Zhang, Method Validation Requestor, CMC Reviewer
Balajee Shanmugam, Method Validation Requestor, CMC Lead
Office of New Drug Quality Assessment (ONDQA)
E-mail Address: chunchun.zhang@fda.hhs.gov
Phone: (301)-796-5168
Fax.: (301)-796-9877

Through: Rapti Madurawe, Branch Chief, Division V
Phone: (301)-796-1408

And Youbang Liu
ONDQA Methods Validation Project Manager
Phone: (301)-796-1926

SUBJECT: Methods Validation Request

Application Number: NDA 206-307

Name of Product: Finafloxacin Otic Suspension, 0.3%

Applicant: Alcon Research Ltd.

Applicant's Contact Person: Richard Reese

Address: 6201 South Freeway, Mail code TC-45, Fort Worth, Texas 76134-2099

Telephone: 817-551-4345 Fax: 817-551-4630

Date NDA Received by CDER: **4/25/2014**

Submission Classification/Chemical Class: NME

Date of Amendment(s) containing the MVP: **4/25/2014**

Special Handling Required: No

DATE of Request: **6/2/2014**

DEA Class: N/A

Requested Completion Date: **8/2/2014**

Format of Methods Validation Package (MVP)

PDUFA User Fee Goal Date: **12/25/2014**

☐ Paper ☒ Electronic ☐ Mixed

We request suitability evaluation of the proposed manufacturing controls/analytical methods as described in the subject application. Please submit a letter to the applicant requesting the samples identified in the attached *Methods Validation Request*. Upon receipt of the samples, perform the tests indicated in Item 3 of the attached *Methods Validation Request* as described in the NDA. We request your report to be submitted in DARRTS promptly upon completion, but no later than 45 days from date of receipt of the required samples, laboratory safety information, equipment, components, etc. We request that you notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager of the date that the validation process begins. If the requested completion date cannot be met, please promptly notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager.

Upon completion of the requested evaluation, please assemble the necessary documentation (i.e., original work sheets, spectra, graphs, curves, calculations, conclusions, and accompanying *Methods Validation Report Summary*). The *Methods Validation Report Summary* should include a statement of your conclusions as to the suitability of the proposed methodology for control and regulatory purposes and be electronically signed by the laboratory director or by someone designated by the director via DARRTS. The ONDQA CMC Reviewer, ONDQA Methods Validation Project Manager, and ONDQA CMC Lead/Branch Chief should be included as cc: recipients for this document.

ATTACHMENT(S): *Methods Validation Request Sheet*, NDA Methods Validation Package (if not available in the EDR).

MVP Reference #	**METHODS VALIDATION REQUEST**	NDA # 206-307

⇒ ITEM 1: SAMPLES AND ANY SPECIAL EQUIPMENT/REAGENTS BEING FORWARDED BY APPLICANT

ITEM	QUANTITY	CONTROL NO. OR OTHER IDENTIFICATION
Finafloxacin AL-60317 Drug Substance Finafloxacin AL-60317 Reference Standard (b) (4)	(b) (4) (b) (4) for Std solutions 1	

⇒ ITEM 2: **Contents of Attached Methods Validation Package**	Volume/Page Number(s)
Statement of Composition of Finished Dosage Form(s)	3.2.P.1 Table 3.2.P 1-1
Specifications/Methods for New Drug Substance(s)	3.2.S.4..1 and 3.2.S.4.2
Specifications/Methods for Finished Dosage Form(s)	3.2.P.5.1 and 3.2.P.5.2
Supporting Data for Accuracy, Specificity, etc.	3.2.S.4.3/PROC-0004890
Applicant's Test Results on NME and Dosage Forms	3.2.P.5.4 Tables 3.2.P.5.4-5-3.2.P.5.4-8
Other: Reference standard information	3.2.S.5 AL-60317

⇒ ITEM 3: **REQUESTED DETERMINATIONS**
Perform following tests as directed in applicant's methods. Conduct ASSAY in duplicate.

Method ID	Method Title	Volume/Page	MV Request Category (see attached)	Comments
PROC-0004890	HPLC test method for Finofloxacin drug substance identification, assay and impurity.	3.2.S.4.3 Validation of Analytical procedures (Alcon technical report TDOC-0013713);	**0**	Please note very low (maximum (b) (4) %) or no impurities observed in several drug substance batches.

Additional Comments: Also need:
Purified water
Acetonitrile: HPLC grade
Methanol: HPLC grade
Trifluoroacetic Acid: HPLC grade
Sodium hydroxide, 50% solution, reagent grade
Hydrochloric acid, concentrated, reagent grade

Methods Validation Request Criteria

MV Request Category	Description
0	New Molecular Entity (NME) application, New Dosage Form or New Delivery System
1	Methods using new analytical technologies for pharmaceuticals which are not fully developed and/or accepted or in which the FDA laboratories lack adequate validation experience (e.g., NIR, Raman, imaging methods)
2	Critical analytical methods for certain drug delivery systems (e.g., liposomal and microemulsion parenteral drug products, transdermal and implanted drug products, aerosol, nasal, and dry powder inhalation systems, modified release oral dosage formulations with novel release mechanisms)
3	Methods for biological and biochemical attributes (e.g., peptide mapping, enzyme-based assay, bioassay)
4	Certain methods for physical attributes critical to the performance of a drug (e.g., particle size distribution for drug substance and/or drug product)

5	Novel or complex chromatographic methods (e.g., specialized columns/stationary phases, new detectors/instrument set-up, fingerprinting method(s) for a complex drug substance, uncommon chromatographic method
6	Methods for which there are concerns with their adequacy (e.g., capability of resolving closely eluting peaks, limits of detection and/or quantitation)
7	Methods that are subject to a “for cause” reason

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

/s/

CHUNCHUN N ZHANG
06/04/2014

RAPTI D MADURAWE
06/04/2014

YOUBANG LIU
06/04/2014