CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-186

CHEMISTRY REVIEW(S)

Chemistry Review Data Sheet

NDA 22-186

AK-Fluor
(fluorescein sodium) Injection
25% (2 mL Vial) and 10% (5 mL Vial)

Akorn Pharmaceuticals

George Lunn, Ph.D.
Branch IV
Division of Pre-Marketing Assessment 2
Office of New Drug Quality Assessment

Chemistry Review Data Sheet

1. NDA or ANDA 022-186
2. REVIEW #: 3
3. REVIEW DATE: 7/10/2008
4. REVIEWER: George Lunn
5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Chemistry Review #1	04/JAN/2008
Chemistry Review #2	27/JUN/2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	8/July/2008

7. NAME & ADDRESS OF APPLICANT:

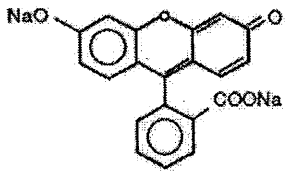
Name	Akorn Inc.
Address	2500 Middlebrook Drive Buffalo Grove, IL 60089-4694
Representative	Sam Boddapati, Ph.D.
Telephone	847-353-4909

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: AK-FLUOR®
   b) Non-Proprietary Name (USAN): Fluorescein Sodium
   c) Code Name/# (ONDC only): NA
   d) Chem. Type/Submission Priority (ONDC only):
      - Chem. Type: III (new strength)
      - Submission Priority: S
9. LEGAL BASIS FOR SUBMISSION: SBA for Funduscein-25 (Novartis, NDA 17-869), and Fluorescite 10% (Alcon, NDA 21-980)
10. PHARMACOL. CATEGORY: Diagnostic aid for ophthalmic angiography
11. DOSAGE FORM: Injection
12. STRENGTH/POTENCY: 10% (100 mg/mL) & 25% (250 mg/mL)/Normal adult dose is 500 mg

Chemistry Review Data Sheet

13. ROUTE OF ADMINISTRATION: Intravenous
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	Fluorescein Sodium
Chemical Name	Spiro[isobenzofuran-1(3*H*), 9'-[9*H*]xanthene]-3-one,3'6'-dihydroxy, disodium salt
CAS Reg. No.	518-74-8 (CAS 2321-07-5 for Fluorescein)
Molecular Formula	$C_{20}H_{12}Na_2O_5$
Molecular Weight	376.28
Structure Formula	



Chemistry Assessment Section

The Chemistry Review for NDA 22-186 Resubmission

Summary, Conclusion, and Recommendation

1. The applicant has adequately addressed both CMC deficiencies conveyed in the FDA letter dated July 2, 2008. The drug substance and drug product specifications are now satisfactory and are reproduced below.

2. An Establishment Evaluation Request was submitted and on 6/25/08 an Overall recommendation of Acceptable was made by S. Ferguson. The detailed EES report is given below.

From a CMC standpoint, NDA 22-186 is now recommended for approval.

8 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 1

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/s/

George Lunn
7/11/2008 07:56:12 AM
CHEMIST

Norman Schmuff
7/11/2008 09:29:21 AM
CHEMIST

Chemistry Review Data Sheet

NDA 22-186

AK-Fluor
(fluorescein sodium) Injection
25% (2 mL Vial) and 10% (5 mL Vial)

Akorn Pharmaceuticals

Ko-Yu Lo, Ph.D.
Branch IV
Division of Pre-Marketing Assessment 2
Office of New Drug Quality Assessment

Chemistry Review Data Sheet

1. NDA or ANDA 022-186
2. REVIEW #: 2
3. REVIEW DATE: 6/27/2008
4. REVIEWER: Ko-Yu Lo
5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Chemistry Review #1	04/JAN/2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Resubmission	28/March/2008

7. NAME & ADDRESS OF APPLICANT:

Name	Akorn Inc.
Address	2500 Middlebrook Drive Buffalo Grove, IL 60089-4694
Representative	Sam Boddapati, Ph.D.
Telephone	847-353-4909

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: AK-FLUOR®
   b) Non-Proprietary Name (USAN): Fluorescein Sodium
   c) Code Name/# (ONDC only): NA
   d) Chem. Type/Submission Priority (ONDC only):
      - Chem. Type: III (new strength)
      - Submission Priority: S
9. LEGAL BASIS FOR SUBMISSION: SBA for Funduscein-25 (Novartis, NDA 17-869), and Fluorescite 10% (Alcon, NDA 21-980)
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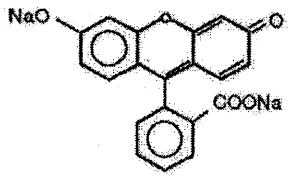
Chemical Name	Spiro[isobenzofuran-1(3*H*), 9'-[9*H*]xanthene]-3-one,3'6'-dihydroxy, disodium salt
CAS Reg. No.	518-74-8 (CAS 2321-07-5 for Fluorescein)
Molecular Formula	$C_{20}H_{12}Na_2O_5$
Molecular Weight	- 376.28
Structure Formula	



Chemistry Assessment Section

The Chemistry Review for NDA 22-186 Resubmission

This resubmission contains the applicant's response addressing all the deficiencies in the FDA letter dated February 6, 2008. Responses to the CMC deficiencies are evaluated in the Review Note Section.

Summary, Conclusion, and Recommendation

1. The applicant has adequately addressed 7 out of the 9 CMC deficiencies conveyed in FDA letter dated February 6, 2008. DS specification and DP specification are outstanding at this time.
   a) Regarding DS specification (Deficiency #2): Acceptance Criteria (AC) for Impurity (Related Substances) was recommended in the 2/6/2008 FDA letter. The applicant states that DS specification is currently being tightened and the revision will be provided to the Agency by end of June. The applicant should revised the DS specification according to FDA recommendation (see draft Chemistry letter).
   b) Regarding DP specification (Deficiency #4(iii)): It is recommended the stability AC for degradant [redacted] and for Related Substances (Total) be tightened to NMT [redacted]% and [redacted]% respectively (see draft chemistry letter). b(4)

2. CGMP inspection deficiencies are currently being addressed by HFD-320.

From a CMC standpoint, NDA 22-186 is approvable pending the resolution of review deficiencies 1a and 1b, and CGMP inspection deficiencies.

7 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 2

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/s/

Ko-yu Lo
6/30/2008 01:42:30 PM
CHEMIST

Norman Schmuff
7/9/2008 09:36:15 AM
CHEMIST

NDA 22-186

AK-Fluor
(fluorescein sodium) Injection
25% (2 mL Vial) and 10% (5 mL Vial)

Akorn Pharmaceuticals

Ko-Yu Lo, Ph.D.
Branch IV
Division of Pre-Marketing Assessment 2
Office of New Drug Quality Assessment

Table of Contents

Chemistry Review Data Sheet

1. NDA ~~or ANDA~~ 022-186

2. REVIEW #: 1

3. REVIEW DATE: 1/4/2008

4. REVIEWER: Ko-Yu Lo

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	06/APR/2007
Amendment	22/AUG/2007

7. NAME & ADDRESS OF APPLICANT:

Name	Akorn Inc.
Address	2500 Middlebrook Drive Buffalo Grove, IL 60089-4694
Representative	Sam Boddapati, Ph.D.
Telephone	847-353-4909

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      - Chem. Type: III (new strength)
      - Submission Priority: S
9. LEGAL BASIS FOR SUBMISSION: SBA for Funduscein-25 (Novartis, NDA 17-869), and Fluorescite 10% (Alcon, NDA 21-980)
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Chemical Name	Spiro[isobenzofuran-1(3*H*), 9'-[9*H*]xanthene]-3-one,3'6'-dihydroxy, disodium salt
CAS Reg. No.	518-74-8 (CAS 2321-07-5 for Fluorescein)
Molecular Formula	$C_{20}H_{12}Na_2O_5$
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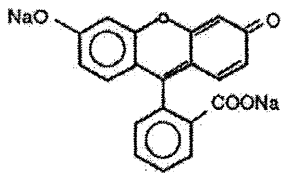
Structure Formula	



Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			1 & 4	Adequate		
	III			4	Adequate		
	III			4	Adequate		

b(4)

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

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND		

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Withhold	11/21/07	Office of Compliance
Pharm/Tox			
Biopharm			
LNC			
Methods Validation			
OPDRA			
EA	Exclusion Acceptable	1/4/08	Ko-Yu Lo
Microbiology	Approvable pending the Resolution of product quality microbiology deficiencies	1/4/08	Stephen E. Langille

The Chemistry Review for NDA 22-186

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

CGMP compliance status for the drug substance manufacturing facility (. ——— ————————) and drug product manufacturing facilities (Akorn Inc, Decatur IL) was found not acceptable. FDA Office of Compliance has recommended a "Withhold" action for NDA 22-186. The compliance issue must be addressed before this application is approved. b(4)

CMC deficiencies found in Module 3 of NDA 22-186 are not considered to be approvability issues. The CMC section of the NDA is acceptable pending the resolution of these review deficiencies.

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

N/A

II. Summary of Chemistry Assessments

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

Drug Substance

Fluorescein is yellowish to red fine crystalline powder soluble in ———— to form a bright green fluorescence appearing red by transmitted light. Fluorescein is insoluble in water. b(4)

The drug substance Fluorescein USP is manufactured by ———— Chemistry, Manufacturing, and Controls (CMC) for Fluorescein USP is cross-referencing to ——— II DMF ——. Flourescein is ———————— ——— Structure of fluorescein is established by the ———— ———————— Impurities found in ——— Fluorescein USP includes: ———————— ———————— unknowns. ——— has performed an analysis for Fluorescein USP assay (via ——— on 70 lots over a 2 year period. Assay values were within the USP Acceptance Criteria (AC) of 97.0-102.0%. b(4)

Current USP monograph for Fluorescein specify a max 2.0% for total impurity, but does not test for individual related compounds. Akorn has developed a validated HPLC analytical procedure (RD291) to determine fluorescein, and related substances in bulk drug substance. RD291 is also used to determine fluorescein sodium, and related substances in the drug product. Comparison of RD291 with current USP methods for Fluorescein and Fluorescein Sodium Injection show RD291 has better precision. The proposed drug substance specification includes: [redacted]. As adverse reactions had been reported in 2004-2006 for products containing fluorescein, it is recommended that the proposed acceptance criteria (AC) for related substances (individual and total) be tightened based on [redacted] available data. The DS specification will be established after discussion with the applicant. b(4)

Fluorescein drug substance is manufactured at [redacted]. CGMP compliance status for this facility is found not acceptable. A "Withhold" action is recommended by FDA Compliance Office. b(4)

Drug Product

Marketing Background

The drug product, AK-FLUOR® (fluorescein sodium) Injection 25% (250 mg/mL, 2 mL vial) and 10% (100 mg/mL,5 mL vial) is a sterile clear aqueous solution with dark reddish orange color. Akorn has been marketing AK-FLUOR 25% and 10% for a number of years under grandfather status as listed in the DESI-2 product lists. Akorn also sold AK-FLUOR 10% (5 mL ampoules distributed by Norartis) in Europe. For the years of 2004 to 2006 several serious unexpected adverse drug events were reported, primarily in France using fluorescein sodium 10% injection in ampoules. b(4)

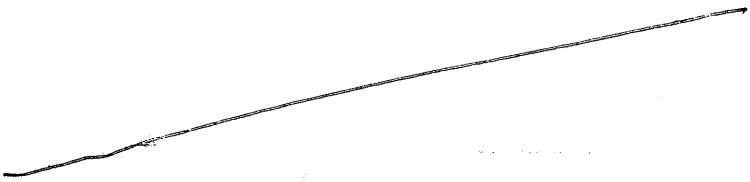
[redacted] *Approximate [redacted] flakes was recovered from AK-FLUOR vial lot 11333. Both ampoule and vial samples show no visible particulates when examined using a stereomicroscope and pass USP particulate matter test.*

To prevent these particles from entering into the body, Akorn included in the package insert (revised May 2006) for the use of [redacted]. The same statement is included in the proposed labeling for this NDA b(4)

AK-FLUOR is currently manufactured in glass vials only and discontinued the manufacturing of this product in glass ampules as of 12/31/2006.

AK-FLUOR® 10% & 25% were formulated to match the reference listed drug (RLD) Fluorescite® Injection 10% (5 mL vial by Alcon). AK-FLUOR® contains USP grade

fluorescein (API) and NF/USP grade excipients (NaOH, HCl and Water for Injection). The product is formulated at pH [redacted]. The manufacturing process include the following steps: (i) [redacted] b(4)



The proposed DP specification includes: Fluorescein sodium assay, related substances, pH, ID, sterility, product appearance, container appearance, bacterial endotoxin, and particulate matter. Current USP monograph for Fluorescein Injection test for Assay, ID, pyrogen and pH ([redacted]). It is recommended that the DP specification be revised to (i) add a test for osmolality, (ii) modify the AC for product appearance, and (iii) tighten the AC for Related Substances (individual and total). The DP specification will be established after discussion with the applicant with the update stability data. b(4)

Although [redacted] of AK-FLUOR prior to use could eliminate potential [redacted] Akorn should provide the following to ensure product/packaging compatibility (i) [redacted] and impurity profile in packaging compatibility samples stored under accelerated conditions, and (ii) leachables on the packaging compatibility samples stored under accelerated conditions. b(4)

Akorn provides 6 months long-term stability data on 1 exhibit lot and up to 36 months long-term stability data on 6 production lots to support a 24 months expiry for AK-FLUOR Injection. It is recommended that the following be amended to the NDA: (i) an NDA stability protocol to described how product stability at accelerated and long term storage conditions is studied, and (ii) stability update on exhibit lots/supporting annual lots at 25°C/60%RH, 40°C/25%RH (accelerated condition), 30°C/65%RH (intermediate conditions if applicable), [redacted] We recommend 3 exhibit lots to be placed on the NDA stability protocol. Expiration dating for the drug product will be determined when these data are available to the FDA. b(4)

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

AK-FLUOR® 10% (100 mg/mL) and AK-FLUOR® 25% is indicated in diagnostic fluorescein angiography or angioscopy of the retina and iris vasculature.

Dosage and Administration

The normal adult dose of AK-FLUOR® 10% is 500 mg (100 mg/mL) and of AK-FLUOR® 25% is 500 mg (250 mg/mL) via intravenous administration.

For children, the dose should be calculated on the basis of 35 mg for each ten pounds of body weight (7.7 mg/kg body weight)

C. Basis for Approvability or Not-Approval Recommendation

CGMP compliance status for the drug substance manufacturing facility ([redacted]) and drug product manufacturing facilities (Akorn Inc, Decatur IL) was found not acceptable. The Office of Compliance has recommended a "Withhold" action for NDA 22-186. The compliance issue must be addressed before this application is approved. b(4)

AK-FLUOR is claimed to be a Fluorescein Injection USP product. Information submitted in the CMC section meet the requirement for current USP monograph for Fluorescein drug substance and Fluorescein Injection. However, the NDA data were evaluated based on Agency's current CMC quality standard for a drug submitted in an NDA and found to have deficiencies on the drug substance and drug product. These deficiencies are not considered to be approvability issues.

The CMC section is acceptable pending the resolution of CMC review deficiencies.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date:
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

38 Page(s) Withheld

1 Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 3

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/s/

Ko-yu Lo
1/10/2008 07:50:59 PM
CHEMIST

Norman Schmuff
1/10/2008 08:12:26 PM
CHEMIST