CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-044 / S-008

Trade Name: Indium In-111 Oxyquinoline

Generic Name:

Sponsor: GE Healthcare

Approval Date: August 8, 1990

Indications: For the extension of the maximum time –sterilization.

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APPROVAL LETTER

10.1

AUG 8 1990

NDA 19-044/S-008

Amersham Corporation
2636 South Clearbrook Drive
Arlington Heights, Illinois 60005-4692

Attention: John H. Waterman
Manager, Scientific and Regulatory Affairs

Dear Mr. Waterman:

Reference is made to your supplemental new drug application dated September 15, 1989 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for indium In 111 oxyquinoline.

The supplemental new drug application provides for the extension of the maximum time between the opening of the first sterile item employed in the manufacture of the product and [redacted] (b) (4) sterilization from [redacted] (b) (4).

We have completed our review of this supplemental new drug application and it is approved, effective on the date of this letter.

We remind you that you must comply with the requirements set forth under 21 CFR 314.80 and 314.81 for an approved NDA.

Sincerely yours,

Eric B. Sheinin, Ph.D.
Supervisory Chemist
Division of Medical Imaging,
Surgical and Dental Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
NDA 19-044/S-008
HFD-160/Div File
HFD-160/CSO/Lange
HFD-160/Ruby/Sheinin
HFD-160/Stone
R/D Endorsed by:
S. Lange 7.31.90
E. Ruby 8.03.90
E. Sheinin, Ph.D. 8.03.90 E Ruby for E Sheinin 07 Aug 90
F/T by: RCannon 8.03.90
Wang 0469B

APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

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CHEMISTRY REVIEW(S)

APR 2 1990

CHEMIST'S REVIEW

Organization
HFD-160

NDA Number
19-044

Name and Address of Applicant
Amersham Corporation
2636 South Clearbrook Dr.
Arlington Heights, IL 60005-4692
(312) 593-6300

AF Number

Supplements
Number Date
S-008 15Sep89

Name of Drug

Non-Proprietary Name
Indium In-111 Oxyquinoline

Supplement Provides For:
To extend from [redacted] (b) (4) the maximum time between the opening of the first sterile item employed in the manufacture of the product and [redacted] (b) (4) sterilization.

Pharmacological Category
diagnostic radiopharmaceutical

How Dispensed
Rx

Related NDA/DMF

Dosage Form
injectable solution

Potency
about 1 mCi In-111;
and 50 ug 8-hydroxyquinoline

Chemical Name and Structure
complex of 8-hydroxyquinoline and In-111 [redacted] (b) (4)

Comments
The supplement is based on data collected with the LAL bacterial endotoxins test (see REVIEW NOTES). A supplement (S-006) was submitted 22Mar89 to allow for use of this test in place of the pyrogen (rabbit) test. Supplement S-006 is still under review (we are awaiting the result of a consultive microbiology review).

Conclusions and Recommendations
Supplement S-008 is approvable pending the approval of S-006.

Reviewer
E. Ruby 30Mar90
Eric Ruby, Chemist, HFD-160

~~Date Completed~~
30March90

Orig. NDA 19-044/S-008
HFD-160/Div. File
HFD-160/ERuby
HFD-160/FStone
HFD-161/SLange
R/D Init. by: ESheinin/ 4-2-90
F/T by: ERuby

C:\RUBY.03\19044S08.CR1

REVIEW NOTES

(b) (4)

[redacted]

C:\RUBY.03\19044S08.CR1

05Apr90 Addendum – this submission was forwarded to HFD-160 supv. microbiologist Peter Cooney for consultative review. Dr. Cooney stated that he did not have any objection to the supplement from the microbiology point of view and that a microbiology review was not required.

E-Rey 05Apr90

EBSheinin 4-5-90

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PHARMACOLOGY REVIEW(S)

PHARMACEUTICALS

QUALITY ASSURANCE AND REGULATORY AFFAIRS

15 June 1989

Extension of the [redacted] (b) (4) applied to the manufacturing process for Indium (In^{111}) oxyquinoline IN15PA.

Summary

The results obtained by LAL 5000 assay of Indium oxyquinoline (IN15PA) have shown that there is no significant risk incurred by extending the time between start of manufacture and [redacted] (b) (4) sterilisation of the dispensed product within the limits of [redacted] (b) (4). Even in the worst case condition of [redacted] (b) (4) delay before [redacted] (b) (4) the final product the level of endotoxin in the product did not rise above 0.05 EU/ml. This may be compared with the product release specification of not more than [redacted] (b) (4) EU/ml.

I D Faulkner

RIDFIN15

PHARMACEUTICALS

QUALITY ASSURANCE AND REGULATORY AFFAIRS

Justification for extension of the [redacted] applied during the production of Indium In111 Oxyquinoline

A time limit of [redacted] from opening the first sterile item to [redacted] sterilisation of the product was documented in NDA#19-044. This has been standard practice at Amersham and time limits for production operations are a requirement of CGMP specified in 21CFR 211.111. [redacted]. The attached report documents a study of the effect of extending the time from start of manufacture to [redacted] sterilisation by [redacted] on the bacterial endotoxin concentration in the product. Even after [redacted], the bacterial endotoxin concentration was less than 0.1% of the specification limit and consequently an extension of the time limit from [redacted] is justified.

Rjbloxy

Introduction

Permission has been requested to relax the time span of the production process for Indium oxyquinoline (IN15PA). The current dossier instruction specifies that the time elapsed from opening the first sterile reagent to completion of (b) (4) and (b) (4) sterilization by (b) (4). Normal pharmaceuticals practice is that such operations should be completed within the working day. (b) (4). The introduction of the LAL 5000 quantitative assay for endotoxin allows the effect of the increased elapsed time to be monitored as well as providing evidence of the safety margin for the product relative to the final pack specification of not more than (b) (4) EU/ml. A formal experiment was designed comparing the effect of elapsed time on the level of endotoxin in the final product vial with that produced in the product vials (b) (4) and released for sale.

The level of endoxotin routinely found in finished product since introduction of the test provides further evidence of the inherent stability of the process.

Experimental Design

The study was set up to cover production over the week 22-26 May 1989. A sample vial was removed before (b) (4) of the final product and stored overnight at room temperature. This vial was then tested as an 'unknown' alongside the final pack release test of the same batch of product. By this means any change in endotoxin level could be directly compared against the product standard curve for that batch formulation. The assays were carried out in accordance with the requirements of the LAL 5000 test method SOP AL/QC033.

Results

The levels of endotoxin found in the final pack vials and stored (b) (4) vials from each of the three batches are summarised in Table I.

Table I

Assay No.	IN15PA Lot No.	Endotoxin level in final pack vial EU/ml	Process Time	Endotoxin level in stored vial EU/ml.	Process Time
8905036	756 AA	(b) (4)	(b) (4)	(b) (4)	(b) (4)
8905039	757 AA				
8905040	758 AA				

The levels of endotoxin found in routine manufacture since the introduction of the quantitative limulus test are summarised in Table II.

Table II

Assay No.	Indium Oxine Batch No.	Endotoxin content EU/ml (specification ≯ (b) (4) EU/ml
8903027	730 AA/1	(b) (4)
8903026	731 AA	
8903029	732 AA	
8903034	733 AA	
8903036	734 AA	
8904005	735 AA	
8904009	736 AA	
8904011	737 AA	
8904016	738 AA	
8904019	739 AA	
8904023	740 AA	
8904028	741 AA	
8904030	742 AA	
8904032	743 AA	
8904037	744 AA	
8904039	744/1AA	
8904039	745 AA	
8904042	746 AA	
8905006	747 AA	
8905006	748 AA	
8905008	749 AA	
8905013	750 AA	
8905016	751 AA	
8905018	752 AA	
8905023	753 AA	
8905029	754 AA	

* Duplicate assay tubes 1.68, 0.002 probable operator error, Product release specification ≯ (b) (4) EU/ml.

Conclusion

The level of endotoxin in the finished product vial of Indium oxyquinoline is consistently low and relatively insensitive to elapsed time of the process of manufacture. The ability of the formulation to support growth of gram negative bacteria which could contribute to the endotoxin level in the finished product is probably diminished by the presence of a surface active agent, ' (b) (4). There is relatively little available nutrient in the formulation and the routine observation of levels of endotoxin at or below the limit of detection of the assay supports this view.

Given these circumstances and the retention of the LAL 5000 assay as a release test on the finished product then relaxation of the process timescale from (b) (4) is justified, retaining an adequate safety margin for the process.

Similar relaxation is recommended for any process where a hostile environment eg, very low or very high pH is maintained. It is advisable that tight control be retained for any process where nutrients are present or where the product is administered by the intrathecal route of injection.

RIDFIN15

Note:- pH range for NDA 19-044
In-111 oxine is 6.5 - 7.5
- Product is administered I.V.

Department of Health, Education and Welfare
December 23, 1986

5. Date change to be implemented:

Therefore, based on the foregoing reasons the proposed modifications to the processing controls, which will provide increased assurance that the drug product Indium In 111 Oxyquinoline Solution has the chemical purity it is represented to possess, will be implemented on 5 January 1987.

Should you have any questions, please do not hesitate to contact the undersigned.

Sincerely,

Donald E. Baker
Manager, Medical Regulatory Affairs

DEB:ve

Attachments

CENTER FOR DRUG EVALUATION AND RESEARCH

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ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Amersham Corporation
2636 South Clearbrook Drive
Arlington Heights, Illinois 60005-4692
(312) 593-6300

ORIGINAL

SCS-008

Amersham

15 September 89

Division of Medical Imaging and
Surgical-Dental Drug Products [HFD-160]
Room 18B-08
5600 Fishers Lane
Rockville, MD 20857

Re: NDA #19-044 - Indium ^{111}In Oxyquinoline
Supplement - EXPEDITED REVIEW REQUESTED

Gentlemen:

Please refer to our approved New Drug Application for Indium ^{111}In Oxyquinoline, identified above.

This New Drug Application Supplement, for which expedited review is requested, provides for revision of the Manufacturing Methods Section to increase the elapsed time permitted between opening the first sterile item employed in manufacture to (b) (4) sterilization, from (b) (4), (b) (4).

The (b) (4) imposed by the original NDA reflected routine manufacturing procedure at the time of filing (1983). Since that time, two significant events have occurred: (b) (4) (b) (4)

Amersham International has performed a study of the effect of extending the time from start of manufacture of Indium ^{111}In Oxyquinoline to (b) (4) sterilization of the finished product by (b) (4), on bacterial endotoxin concentration in the finished product. This study demonstrates that, even after (b) (4), the bacterial endotoxin concentration is less than 0.1% of the NDA specification, supporting the extension provided for by this Supplement.

A copy of the study report follows, accompanied by justification statement prepared by Amersham International.

Please contact me should you have any questions or comments concerning this Supplement. We appreciate your prompt attention to this submission.

Yours truly,

Jack Waterman

John H. Waterman
Manager, Scientific & Regulatory Affairs

JHW:mcs

25800

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001
Expiration Date; August 31,1989.

FOR FDA USE ONLY	
DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS.

NOTE: No application may be filed unless a completed application form has been received *(21 C.F.R. Part 314).*

NAME OF APPLICANT	DATE OF SUBMISSION
Amersham Corporation	15 Sept. 89
ADDRESS *(Number, Street, City, State and Zip Code)*	TELEPHONE NO. *(Include Area Code)*
2636 S. Clearbrook Drive Arrlington Heights, IL 60005	312-593-6300
	NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued)
	19-044

DRUG PRODUCT

ESTABLISHED NAME *(e.g., USP/USAN)*	PROPRIETARY NAME *(If any)*
Indium Oxine	Indium In 111 Oxyquinoline Solution

CODE NAME *(If any)*	CHEMICAL NAME
IN.15PA	Indium In 111 Oxyquinoline Solution

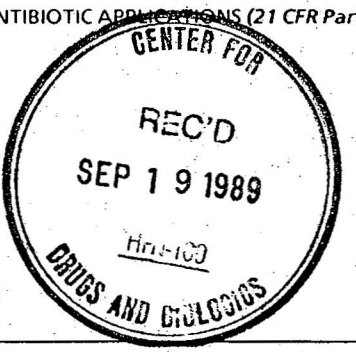
DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
Sterile, non-pyrogenic, isotonic aqueous solution	Intravenous	Single dose

PROPOSED INDICATIONS FOR USE

For the radiolabeling of autologous leucocytes

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, AND DRUG MASTER FILES *(21CFR 314.420)* REFERRED TO IN THIS APPLICATION:

N/A



INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

[X] THIS SUBMISSION IS A FULL APPLICATION *(21 CFR 314.50)* [ ] THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION
Indium In 111 Oxyquinoline	Amersham Corporation

STATUS OF APPLICATION *(Check one)*

[ ] PRESUBMISSION
[ ] ORIGINAL APPLICATION
[ ] AN AMENDMENT TO A PENDING APPLICATION
[ ] RESUBMISSION
[X] SUPPLEMENTAL APPLICATION

PROPOSED MARKETING STATUS *(Check one)*

[X] APPLICATION FOR A PRESCRIPTION DRUG PRODUCT *(Rx)*
[ ] APPLICATION FOR AN OVER - THE - COUNTER PRODUCT *(OTC)*

FORM FDA 356h (3/87)

CONTENTS OF APPLICATION	
This application contains the following items: *(Check all that apply)*	
1. Index	
2. Summary (21 CFR 314.50 (c))	
3. Chemistry, manufacturing, and control section (21 CFR 314.50 (d) (1))	
4. a. Samples (21 CFR 314.50 (e) (1)) (Submit only upon FDA's request)	
b. Methods Validation Package (21 CFR 314.50 (e) (2) (i))	
c. Labeling (21 CFR 314.50 (e) (2) (ii))	
i. draft labeling *(4 copies)*	
ii. final printed labeling (12 copies)	
5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2))	
6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3))	
7. Microbiology section (21 CFR 314.50 (d) (4))	
8. Clinical data section (21 CFR 314.50 (d) (5))	
9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b))	
10. Statistical section (21 CFR 314.50 (d) (6))	
11. Case report tabulations (21 CFR 314.50 (f) (1))	
12. Case reports forms (21 CFR 314.50 (f) (1))	
13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))	
14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))	
15. OTHER *(Specify)* Support Data	X

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit these safety update reports as follows: (1) 4 months after the initial submission, (2) following receipt of an approvable letter and (3) at other times as requested by FDA. If this application is approved, I agree to comply with all laws and regulations that apply to approved applications, including the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211.
2. Labeling regulations in 21 CFR 201.
3. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
4. Regulations on making changes in application in 21 CFR 314.70, 314.71, and 314.72.
5. Regulations on reports in 21 CFR 314.80 and 314.81.
6. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the controlled substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

NAME OF RESPONSIBLE OFFICIAL OR AGENT	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	DATE
John H. Waterman, Manager Scientific and Regulatory Affairs	John H Waterman	15 Sept. 89
ADDRESS *(Street, City, State, Zip Code)* Amersham Corporation 2636 S. Clearbrook Drive Arlington Heights, IL 60005		TELEPHONE NO. *(Include Area Code)* 312-593-6300

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec.1001.)

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