

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-536

CHEMISTRY REVIEW(S)

**Tradename
(indomethacin) for injection
NDA 22-536**

**Summary Basis for Recommended Action
From Chemistry, Manufacturing, and Controls**

Applicant: APP Pharmaceutical, LLC
1501 East Woodfield Road,
Schaumburg, IL 60173

Indication: Indicated to close a hemodynamically significant patent ductus arteriosus in premature infants.

Presentation: Lyophilized, white to yellow powder or plug supplied in a 3 cc vial as 1 mg indomethacin. The product is to be reconstituted prior to administration

EER Status: Acceptable, 22-Jun-09

Consults: Methods Validation – Revalidation by Agency was not requested.
EA – categorical exclusion granted
Microbiology: Acceptable

II. Summary of Chemistry Assessments

Drug Substance:

Indomethacin is a white to yellow, crystalline powder with a mol weight of 357.80 which is practically insoluble in water and slightly soluble in alcohol, chloroform and ether. The molecular formula is $C_{19}H_{16}ClNO_4$. Chemically, indomethacin is 1-(*p*-Chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic-acid. Indomethacin can exist in more than one polymorphic form. However, a thermodynamically stable (b)(4) is produced for this product. The CMC information for the drug substance is referenced to DMF (b)(4), held by (b)(4). The DMF was previously reviewed and found to be adequate to support NDA submissions. The applicant has provided specification for accepting the incoming lots of the drug substance. The specification includes test and acceptance limit for identification (IR, UV and X-ray), loss on drying, residue on ignition, heavy metals, residual solvents (GC), assay (HPLC), impurities (HPLC), microbial burden and bacterial endotoxin.

Conclusion: Acceptable.

Drug product: The drug product is a single –use, sterile, lyophilized powder that is reconstituted prior to administration. Excipients used in the formulation, sodium phosphate monobasic monohydrate, sodium phosphate dibasic anhydrous, sodium hydroxide, hydrochloric acid and water for injection are all compendial grade. The drug product manufacturing is fairly simple that involve (b) (4), filling and lyophilization. The drug product specification includes test and acceptance limit for description, pH, color, container/closure integrity, uniformity of dosage units by content uniformity, identification, assay (HPLC), impurities (HPLC), particulate matter, sterility, bacterial endotoxin and statement of compliance to <USP 467>. The specification also includes testing for reconstitution time, completeness of dissolution, clarity of solution, particulate matter and visual color for the reconstituted solution. All non-USP analytical procedures are adequately validated.

The microbiological quality of the product was reviewed by the NDMS reviewer and a final acceptable recommendation has been made by the reviewer.

Based on the available data a shelf life of 24 months may be granted for the product when stored under controlled room temperature.

Overall conclusion: The CMC related issues have been resolved. The application is recommended for approval from CMC perspective.

Additional Items: None

Ramesh Sood, Ph.D.
Branch Chief/DPA1/Branch 1/ONDQA

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22536	ORIG-1	APP PHARMACEUTICA LS LLC	INDOMETHACIN

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/s/

RAMESH K SOOD
03/18/2010

NDA 22-536

Indomethacin For Injection

APP Pharmaceuticals, LLC

Thomas M. Wong, Ph.D.
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment

Division of Cardiovascular and Renal Products
Review of Chemistry, Manufacturing, and Controls

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Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA 22-536
2. REVIEW #: 1
3. REVIEW DATE: Nov 24, 2009
4. REVIEWER: Thomas M. Wong, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

None

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original

CMC Amendment # 0003:

CMC Amendment # 0004:

Document Date

8 May 2009

8 Oct 2009

10 Nov 2009

7. NAME & ADDRESS OF APPLICANT:

Name: APP Pharmaceuticals, LLC

1501 East Woodfield Road

Address: Suite 300 East
Schaumburg IL 60173

Representative: Not Applicable

Telephone: (847) 969-2700

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: None
- b) Non-Proprietary Name (USAN): Indomethacin
- c) Code Name/#: N/A
- d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 3
 - Submission Priority: S

Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2) Indomethacin for Injection, 1 mg/vial.
10. PHARMACOL. CATEGORY: To close a hemodynamically significantly patent ductus arteriosus in premature infants.
11. DOSAGE FORM: Injection
12. STRENGTH/POTENCY: 1 mg/vial
13. ROUTE OF ADMINISTRATION: Intravenous
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:

USAN Name: Indomethacin, USP

Chemical name: 1-(*p*-Chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic-acidOther chemical name: 1*H*-Indole-3-acetic acid, 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-

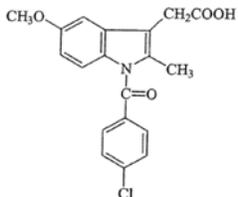
CAS registry number: 53-86-1

Company or lab code: None

Molecular Weight: 357.80

Structural formula: C₁₉H₁₆ClNO₄

Structure:



Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYP E	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	3	Adequate	17-Jun-2009	Reviewed by Sulene X Han and was found adequate
	III			4			Sufficient information in application
	III			4			
	III			3	Adequate	12-Nov-2006	Reviewed by Milagros Salazar Driver and was found adequate.

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)

Chemistry Review Data Sheet

Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Indocin® I.V., Ovation Pharmaceuticals	Not provided	Reference Listed Drug (RLD)

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	22-JUN-09	Office of Compliance
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A		
DMFPA	N/A		
EA	Acceptable/categorical exclusion	As per this review	Thomas M. Wong, Ph.D.
Microbiology	Pending		

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:

Executive Summary Section

The Chemistry Review for NDA 22-306

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The CMC of the drug product, Indomethacin for Injection 1 mg, has been reviewed and all deficiencies have been resolved. There is no CMC outstanding issues pending. At this time we are waiting for microbiology recommendation. A final memo will be deposited in the DARRTS once recommendation from microbiology review is obtained.

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

None at this time.

II. Summary of Chemistry Assessments

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

Drug product:

Indomethacin for injection is a cardiovascular drug and is indicated to close a hemodynamically significant patent ductus arteriosus in premature infants weighing between 500 and 1750 g when after 48 hours usual medical management (e.g., fluid restriction, diuretics, digitalis, respiratory support, etc.) is ineffective. The product is a sterile, lyophilized, white to yellow powder supplied as single dose vials containing 1 mg of indomethacin in a 3 c.c. vial. It is intended for I.V. injection upon reconstitution with water for injection or 0.9% sodium chloride injection. The reconstituted solution, pH 6.0 to 7.5, is clear, slightly yellow and essentially free from visible particles. Indomethacin for injection contains the following excipients: 0.29 mg monobasic sodium phosphate, 0.41 mg dibasic sodium phosphate, and 0.24 mg sodium hydroxide. The pH specification of the product does not meet the current USP standard. The applicant has incorporated the following statement in the carton label and the package insert: The pH of the product does not meet the USP monograph [FD&C Act Chapter V, SEC. 501. [21USC §351](b)]. Available 12 months stability data supports 24-month expiration dating period for the indomethacin for injection when stored at 25°C (77°F) and protect from light. Excursions permitted to 15° to 30°C (59° to 86°F).

Drug substance:

Detailed information of the drug substance is available in (b) (4). Indomethacin, USP, is a white to yellow crystalline powder with a molecular weight of 357.80. The molecular formula is C₁₉H₁₆ClNO₄. Chemically, indomethacin is 1-(*p*-Chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic-acid. It is practically insoluble in water, slightly soluble in alcohol, chloroform and in ether. Indomethacin exists in more than one polymorphic form. However, the thermodynamically stable (b) (4) is produced as confirmed by X-ray diffraction and IR spectrophotometry and the IR spectrum conforms to the IR spectrum of a similar preparation of USP indomethacin RS.

Specification of the drug substance is in place. There are two actual impurities arising from the synthesis of the drug substance, namely, (b) (4) and (b) (4).

(b) (4) The HPLC testing method is an alternative method which is

Executive Summary Section

different from the USP regulatory methods and has been validated. The available stability data supports a 5 year expiry dating.

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

Indomethacin for injection is a sterile, lyophilized, white to yellow powder product. Upon reconstitution with water for injection or 0.9% sodium chloride injection, it is administered intravenously for the indication of closing a hemodynamically significant patent ductus arteriosus in premature infants weighing between 500 and 1750 g.

Indomethacin for injection is supplied as single dose vials containing 1 mg of indomethacin in a 3 c.c. vial. Each vial is individually packed in a carton. The drug product is to be stored at 25°C (77°F) with excursions permitted to 15° to 30°C (59° to 86°F). Protect from light. The product number is 605903 and the NDC is 63323-659-03.

C. Basis for Approvability or Not-Approval Recommendation

From a CMC perspective, APP Pharmaceuticals, LLC, has submitted sufficient and appropriate information to support the approval of the drug product, Indomethacin for Injection.

III. Administrative

A. Reviewer's Signature

See electronic signatures in DFS.

B. Endorsement Block

Chemist Name: Thomas M. Wong, Ph.D.

Branch Chief Name: Ramesh Sood, Ph.D.

Project Manager Name:

C. C Block

See DFS.

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22536	ORIG-1	APP PHARMACEUTICA LS LLC	INDOMETHACIN

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/s/

THOMAS M WONG
11/24/2009

RAMESH K SOOD
11/24/2009

Initial Quality Assessment Branch I

OND Division:	Division of Cardiovascular and Renal Products
NDA:	22-536
Applicant:	APP Pharmaceuticals, LLC
Letter Date:	08 May 2009
Status Date:	12 May 2009
PDUFA Date:	12 Mar 2010
Tradename:	None
Established Name:	Indomethacin for injection
Dosage Form:	Sterile lyophilized solid, 1 mg/vial
Route of Administration:	Intravenous injection
Indication:	To close hemodynamically significant patent ductus arteriosus in premature infants
Assessed by:	Kasturi Srinivasachar
ONDQA Fileability:	Yes

Summary

This 505(b)(2) NDA, in eCTD format, is for a lyophilized formulation of indomethacin for injection. The reference listed product is Ovation Pharmaceutical's Indocin IV, NDA 18-878. The route of administration, dosage form and strength of the proposed drug product are the same as those for Indocin IV. The RLD uses indomethacin sodium salt as the drug substance whereas this NDA uses indomethacin free acid. The RLD has no other excipients other than water for injection which is removed during lyophilization. In this NDA, the sodium salt of indomethacin is formed in situ with sodium hydroxide and phosphate buffers are used to maintain the pH between (b) (4) in the manufacturing procedure. Hydrochloric acid may also be used for final pH adjustment to 7.2. There is no IND application associated with this NDA and no meetings have been held with the Applicant.

Drug Substance

Indomethacin is a white to yellow crystalline powder which is practically insoluble in water and slightly soluble in alcohol, chloroform and ether. All CMC information for this drug substance is cross-referenced to (b) (4), held by the manufacturer, (b) (4). This DMF has been previously reviewed and found to be adequate. The last review, dated Feb. 18, 2009, was of an annual report. There is an USP monograph for indomethacin. Regulatory specifications have been provided by the Applicant which follow USP except for the use of an alternate HPLC method for assay, the inclusion of specified impurities and tests for microbial bioburden and bacterial endotoxins. (b) (4) are the residual solvents which are monitored. It is claimed that indomethacin manufactured by (b) (4) is the thermodynamically stable crystalline (b) (4) which conforms to the USP indomethacin RS by X-ray diffraction pattern and IR spectrum. The retest period for the drug substance is set not to exceed the manufacturer's expiration of 5 years.

Drug Product

This is a sterile lyophilized product containing 1 mg indomethacin in a 3mL vial. Excipients used in the formulation, sodium phosphate monobasic monohydrate, sodium phosphate dibasic anhydrous, sodium hydroxide, hydrochloric acid and water for injection are all compendial grade. The product is manufactured by APP in Puerto Rico using standard procedures for a sterile lyophilized dosage form. Indomethacin is initially dissolved in water for injection containing the (b) (4) while maintaining a pH between (b) (4)

The pH is then adjusted to 7.2

The container/closure is a 3 mL Type I glass vial with 13 mm stopper and 13 mm flip cap aluminum crimp seal.

The product specification contains the usual test attributes for a sterile lyophilized solid. There is an USP monograph for indomethacin for injection which is based on indomethacin sodium drug substance. The APP product meets these specifications except for pH and so will not be labeled with the USP designation. The Applicant will use an in-house method rather than the USP method for assay and impurities. Stability data have been provided for 3 full-scale batches stored under accelerated and long term conditions. 6 months' accelerated and long term data are available for all batches. 9 and 12 months' data have been submitted for two of the batches at 25°C/60% RH. It is stated that updated stability data for 12 months will be submitted in an amendment as soon as they are available. A 2 year expiry is proposed.

Critical Review Issues

Drug substance

- It is stated that indomethacin has different morphic forms which can be distinguished by X-ray diffraction and IR spectroscopy. Do these forms exhibit different solubilities and does the manufacturing process consistently produce only one form?
- Should the HPLC method for assay be designated an alternate method in the specification since the USP method is considered the regulatory method?
- Is the proposed limit for (b) (4) justified from a safety perspective?
- It is not clear why the two degradation products, (b) (4) and (b) (4) - (b) (4) are specified with different limits since both are formed simultaneously by hydrolysis of indomethacin.
- What is the retest period for the drug substance? It is claimed that the manufacturer has assigned an expiration date of 5 years.

Drug Product

- Since this is a parenteral dosage form, the major critical issue is sterility assurance of the product after manufacture and maintenance of sterility over the shelf-life. These aspects are expected to be covered by the microbiology reviewer.
- Are all excipients tested for residual solvents or is certification provided that no organic solvents are used their manufacture?
- Is the justification provided for excluding determination of water content at release or on stability acceptable?
- Should reconstitution time be part of the specification?

- Is it sufficient to state “ meets specifications” for the batch results for Uniformity of Dosage Units?
- Is the ^{(b) (4)} limit for Total Impurities acceptable?
- Is the pH range of 6.0-7.5% justified considering the release and stability data and the finding that the product is most stable in the pH range 7.0-7.5?
- It is stated that the Container/Closure Integrity test will be performed in the stability studies in lieu of sterility –is this acceptable? Is the ICP method adequate for this purpose? (These issues may be covered in the Microbiology review).
- There is no provision for testing under accelerated conditions in the post-approval stability protocol for the first 3 commercial batches.

Labeling

- The ^{(b) (4)} statement on the container labels does not seem to be relevant to this product –it is relevant to the RLD where the 1 mg strength refers to indomethacin whereas the sodium salt is used in the formulation.
- The PI gives the structure of indomethacin sodium salt ^{(b) (4)} for the drug substance. This is not correct since indomethacin is the drug substance for this NDA and the sodium salt is only formed in situ.
- The storage conditions on the labels should be revised to reflect current practice.

Comments and Recommendations

The application is fileable. Manufacturing, testing and packaging facilities have been entered into EES and the reviewer should verify the accuracy and completeness of the entries. A microbiology reviewer has been assigned to this NDA. A single CMC reviewer is recommended for this application.

Kasturi Srinivasachar
 Pharmaceutical Assessment Lead
Ramesh Sood, Ph.D.
 Branch Chief

Jun. 18, 2009
 Date
Jun. 18, 2009
 Date

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/s/

Kasturi Srinivasachar
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CHEMIST

Ramesh Sood
6/18/2009 12:44:51 PM
CHEMIST