

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22382Orig1s000

CHEMISTRY REVIEW(S)

NDA 22-382
Sprix™
(ketorolac tromethamine)
Nasal Spray

**Summary of the Basis for the Recommended Action
from Chemistry, Manufacturing, and Controls**

Applicant: ROXRO PHARMA, Inc.

Indication: Management of moderate to severe pain that requires analgesia at the opioid level.

Presentation: Sprix™ will be supplied in boxes containing 1 nasal spray bottle or 5 single-day nasal spray bottles. Each unit of Sprix™ contains a volume sufficient to deliver one day's supply, a maximum of eight doses of 100 µL (0.1 mL) sprays.

EER Status:	Recommendations:	Withhold
Consults:	EA -	Categorical exclusion provided
	CDRH-	N/A
	Statistics -	N/A
	Methods Validation -	Not recommended
	DMEPA-	Completed
	Biopharm-	N/A
	Microbiology -	Acceptable
	Pharm/toxicology -	N/A

Original Submission: 05-December-2008

Re-submissions: N/A

Post-Approval CMC PMC/PMR: None.

Background:

This is a 505(b)(1) application providing for a new dosage form (nasal spray). The reference approved drug for this product is Toradol (NDA 19-698) which was approved on November 30, 1989. The IND for ketorolac tromethamine nasal spray (62,829) was submitted on April 10, 2002, the EOP2 meeting was held on May 17, 2006 and the pre- NDA meeting was held on October 4, 2007.

Drug Substances:

The drug substance, ketorolac tromethamine, is currently marketed as Toradol® IV/IM (ketorolac tromethamine) injection (NDA 19-698) and Toradol® oral (ketorolac tromethamine) tablets (NDA 19-645).

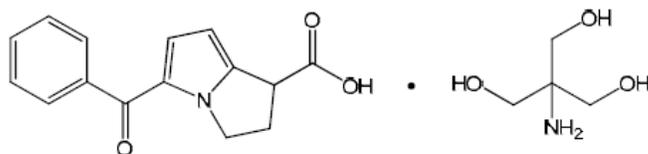
The drug substance, (ketorolac tromethamine USP) will be manufactured for commercial use by (b) (4)

(b) (4) with most of the CMC parameters provided in the (b) (4) Type II DMF No. (b) (4). A copy of the letter of authorization to reference DMF (b) (4) has been provided. The DMF was reviewed and found to be acceptable. In addition to the USP requirements, the drug substance will be tested for additional attributes ((b) (4) residual solvents, bacterial endotoxins).

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

Chemical Name: (±)-5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid, compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1)

Structural Formula



Molecular Formula:

C₁₉H₂₄N₂O₆

Molecular Weight: Ketorolac tromethamine: 376.41

Ketorolac (free acid): 255.27

The supporting shelf-life support (b) (4) storage re-test period for the drug substance.

Conclusion: The drug substances are satisfactory

Drug Product:

Sprix™ is an intranasal formulation of ketorolac tromethamine, a nonsteroidal anti-inflammatory drug indicated for short term (up to 5 days) management of moderate to severe pain. The drug product consists of a clear, colorless to yellow clear solution contained in a clear glass vial fitted with a metered (100 µL) multidose spray pump. Sprix™ will be supplied in boxes containing 1 nasal spray bottle or 5 single-day nasal spray bottles. Each unit of Sprix™ contains a volume sufficient to deliver one day's supply, a maximum of eight doses of 100 µL (0.1 mL) sprays. The product is not labeled as sterile and it is not formulated

to contain an antimicrobial. The drug product manufacturing is performed under (b) (4) conditions to produce a “low bioburden” spray.

The nasal spray solution is formulated as a low bioburden buffered solution at pH 7.2 containing the active ingredient (ketorolac tromethamine) and the compendial excipients edetate disodium (EDTA; (b) (4) monobasic potassium phosphate (b) (4), sodium hydroxide (b) (4) (b) (4) and sterile water for (b) (4) (b) (4)

Sprix™ is indicated for short term (up to 5 days) management of moderate to severe pain, as a single agent or in combination with opioids. The usual recommended dose for adult patients less than 65 years of age is one 15.75 mg ketorolac tromethamine spray in each nostril every 6 to 8 hours. The maximum daily dose should not exceed 126 mg. Each Sprix™ Nasal Spray vial contains one day’s supply of drug for administration of a maximum of eight 100 µL (0.1 mL) sprays. Before use for the first time, the pump must be properly activated (primed) by pressing down evenly and releasing the pump (actuating) 5 times. There is no further need to prime the pump again. After each use, the bottle should be stored in a cool, dry location out of direct sunlight. The patient is advised to discard each nasal spray bottle within 24 hours of administering the first dose, even though the bottle may still contain unused medication. The drug product will be labeled for long term storage at refrigerated (2° - 8°C) conditions, but may be maintained under ambient conditions during use.

Based on the submitted stability data, a shelf life of 24 months at refrigerated (2° - 8°C) temperatures and an in-use period of one day at ambient conditions is granted for the drug product.

Conclusion: The drug product is satisfactory.

Overall Conclusion:

From a CMC perspective, the application is not approvable based on the withhold recommendation from office of compliance with respect to drug product manufacturing site.

Ali Al-Hakim, Ph.D.
Branch Chief,
DPA I/ONDQA

1 page of draft labeling has been withheld in full as B(4) CCI/TS immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22382	ORIG-1	ROXRO PHARMA INC	KETOROLAC TROMETHAMINE NASAL SPRAY

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/s/

ALI H AL HAKIM
10/01/2009

NDA 22-382

**Sprix™
(ketorolac tromethamine)
Nasal Spray**

ROXRO PHARMA, Inc.

**Joseph Leginus, PhD
Division of Pre-Marketing Assessment I, Branch II, ONDQA**

**For the Division of
Anesthesia, Analgesia and Rheumatology Products**

CHEMISTRY REVIEW #2

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Chemistry Review Data Sheet

1. NDA 22-382
2. REVIEW #: 2
3. REVIEW DATE: 07-Aug-2009
4. REVIEWER: Joseph Leginus, PhD
5. PREVIOUS DOCUMENTS:

Previous Documents

Original NDA
Amendment

Document Date

05-Dec-2008
29-Apr-2009

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

NDA Amendment
Amendment

Document Date

29-Jun-2009
04-Aug-2009

7. NAME & ADDRESS OF APPLICANT:

Name: Roxro Pharma, Inc.
Address: 535 Middlefield Road, Suite 180 Menlo Park, CA 94025
Representative: Roger Whiting, Ph.D.
Telephone: 650-947-9776

8. DRUG PRODUCT NAME/CODE/TYPE:

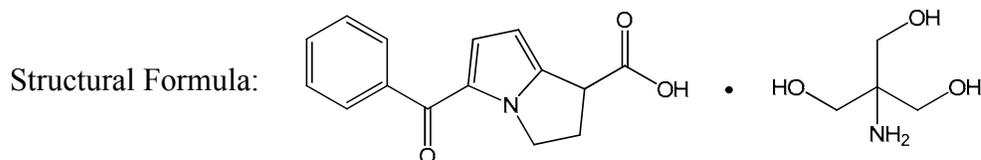
- a) Proprietary Name: SPRIX™ Nasal Spray
- b) Non-Proprietary Name (USAN): Ketorolac Tromethamine
- c) Code Name/# (ONDC only): CAS No.: 74103-07-4
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: Standard

Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: This NDA is submitted as a 505(b)(2) application.
10. PHARMACOL. CATEGORY:
Non-steroidal anti-inflammatory drug (NSAID) for short term (up to 5 days) management of moderate to severe pain that requires analgesia at the opioid level.
11. DOSAGE FORM: Nasal Spray
12. STRENGTH/POTENCY: 15% solution (weight/weight); 15.75 mg per 0.1 mL spray.
13. ROUTE OF ADMINISTRATION: Intranasal
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:

Chemical Name: (±)-5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid, compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1)



Molecular Formula: $C_{19}H_{24}N_2O_6$

Molecular Weight: Ketorolac tromethamine: 376.41
Ketorolac (free acid): 255.27

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Type	Holder	Item Referenced	Code ¹	Status ²	Date Review Completed	Comments
(b) (4)	2	(b) (4)	Ketorolac Tromethamine Drug Substance	1	Adequate	11-Oct-2006	Reviewed by R. D'Costa as adequate. Request pending for 2007 and 2008 annual reports.
	3		(b) (4)	1	Adequate	20-Aug-2004	Reviewed by Y. Yang
	3			1	Adequate	15-Dec-2005	Reviewed by J. Boal

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
NDA	19-645	Toradol® (ketorolac tromethamine) Tablets
NDA	19-698	Toradol® (ketorolac tromethamine) for Injection

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending		



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Pharm/Tox	Pending		Newton Woo
Biopharm	N/A		
Methods Validation	N/A		
EA	N/A		
Microbiology	Pending	4/21/2009	Robert Mello

19. ORDER OF REVIEW: N/A

The Chemistry Review for NDA 22-382

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 22-382 is considered to be approvable (AE) from a CMC perspective at this time.

- The EER for this NDA is currently pending. Acceptable cGMP recommendation is currently given for five establishments by the Office of Compliance and inspection outcomes are pending for three sites. Specifically, inspection has been performed for one site, inspection is assigned at one site and inspection is scheduled for one site. An acceptable cGMP recommendation is required for all manufacturing and testing facilities before approval.

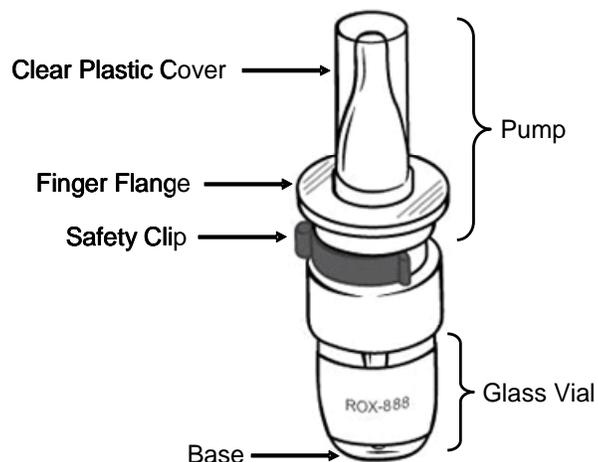
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not applicable.

II. Summary of Chemistry Assessments

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

Sprix™ is an intranasal formulation of ketorolac tromethamine, a nonsteroidal anti-inflammatory drug indicated for short term (up to 5 days) management of moderate to severe pain. The drug product consists of a clear, colorless to yellow clear solution contained in a clear glass vial fitted with a metered (100 µL) multidose spray pump. Sprix™ will be supplied in boxes containing 1 nasal spray bottle or 5 single-day nasal spray bottles. Each unit of Sprix™ contains a volume sufficient to deliver one day's supply, a maximum of eight doses of 100 µL (0.1 mL) sprays. The product is not labeled as sterile and it is not formulated to contain an antimicrobial. The drug product manufacturing is performed under (b) (4) conditions to produce a "low bioburden" spray.



The drug substance, ketorolac tromethamine, is currently marketed as

Executive Summary Section

Toradol® IV/IM (ketorolac tromethamine) injection (NDA 19-698) and Toradol® oral (ketorolac tromethamine) tablets (NDA 19-645). All information with respect to the chemistry, manufacturing and controls of ketorolac tromethamine, USP is incorporated by reference to Drug Master File (b) (4)

(b) (4) Specifications are based on the USP monograph. In addition, the drug substance is tested for (b) (4) and controlled to NMT (b) (4) to limit (b) (4) (b) (4) (b) (4) Retest for the drug substance is (b) (4)

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

Sprix™ is indicated for short term (up to 5 days) management of moderate to severe pain, (b) (4). The usual recommended dose for adult patients less than 65 years of age is one 15.75 mg ketorolac tromethamine spray in each nostril every 6 to 8 hours. The maximum daily dose should not exceed 126 mg. Each Sprix™ Nasal Spray vial contains one day's supply of drug for administration of a maximum of eight 100 µL (0.1 mL) sprays. Before use for the first time, the pump must be properly activated (primed) by pressing down evenly and releasing the pump (actuating) 5 times. There is no further need to prime the pump again. After each use, the bottle should be stored in a cool, dry location out of direct sunlight. The patient is advised to discard each nasal spray bottle within 24 hours of administering the first dose, even though the bottle may still contain unused medication. The drug product will be labeled for long term storage at refrigerated (2°- 8°C) conditions, but may be maintained under ambient conditions during use.

C. Basis for Approvability or Not-Approval Recommendation

This is a 505(b)(2) application providing for a new dosage form (nasal spray). The reference approved drug for this product is Toradol (NDA 19-698) which was approved on November 30, 1989. The IND for ketorolac tromethamine nasal spray (62,829) was submitted on April 10, 2002, the EOP2 meeting was held on May 17, 2006 and the pre-NDA meeting was held on October 4, 2007.

The drug substance, (ketorolac tromethamine USP) will be manufactured for commercial use by (b) (4) with most of the CMC parameters provided in the (b) (4) Type II DMF No. (b) (4). A copy of the letter of authorization to reference DMF (b) (4) has been provided. The DMF was reviewed and found to be acceptable. In addition to the USP requirements, the drug substance will be tested for additional attributes ((b) (4) residual solvents, bacterial endotoxins). The (b) (4) test is included due to the (b) (4) (b) (4). The proposed acceptance criterion of NMT (b) (4) provides sufficient control over (b) (4) content in the drug substance when coupled with (b) (4) EDTA in the drug product.

Two impurities have been identified in the drug substance ("1-hydroxy" and "1-keto"), and both are adequately controlled at NMT 0.1%.

Executive Summary Section

The drug product is not labeled as sterile and it is not formulated to contain an antimicrobial. The drug product manufacturing is performed under (b) (4) conditions to produce a “low bioburden” spray. The multidose pump/cap packaging system is (b) (4). Vials are (b) (4). All batches manufactured at Hollister-Stier, the proposed commercial manufacturing facility, were formulated in (b) (4). Since the drug product was found to be photosensitive, (b) (4) which provide adequate protection from light. A label statement will be added to protect the drug product from light.

The nasal spray solution is formulated as a low bioburden buffered solution at pH 7.2 containing the active ingredient (ketorolac tromethamine) and the compendial excipients edetate disodium (EDTA; (b) (4), monobasic potassium phosphate (b) (4), (b) (4) sodium hydroxide (b) (4) and sterile water for injection (diluent). (b) (4)

The applicant states that osmolality is consistently controlled in the drug product, and, therefore, a specification for osmolality is unnecessary. However, the solution contains a (b) (4) (b) (4) (EDTA), which is a critical excipient to the formulation, (b) (4). Therefore, osmolality is a critical physicochemical property, characteristic of this particular drug product, and will need to be included in the drug product specifications.

The fill weight of 1.7 g (b) (4) per bottle represents an overfill of (b) (4) mg per bottle, corresponding to (b) (4) of ketorolac tromethamine (b) (4). The overfill represents a compromise to ensure an adequate volume for the recommend number of sprays (5 primes and 8 dosing) while minimizing potential patient abuse of remaining drug product.

A shelf life of 24 months at refrigerated (2° - 8°C) temperatures and an in-use period of one day at ambient conditions is granted for the drug product based on acceptable results from three sources:

- 1) 18 month real time stability data
- 2) 6 month accelerated stability data
- 3) Statistical extrapolation of the real time stability data for eight stability batches.

From a CMC perspective, the applicant has provided adequate documentation of the composition of the proposed drug product, control of ingredients, the manufacturing process, control of critical manufacturing steps and control of the finished product. Based

Executive Summary Section

on this information, the application is considered approvable. The deficiency comments outlined in the CMC IR letter dated May 13, 2009 have been adequately addressed by the applicant's 29-Jun-2009 and 04-Aug-2009 amendments. An acceptable GMP status is required for all manufacturing and testing facilities supporting this application. The EER for this NDA is currently pending. As of August 4, 2009, AC status is available for five establishments, inspection has been performed for one site, inspection is assigned for one site and inspection is scheduled for one site. Dr. Mello's review of the microbiology controls is pending. Labeling revisions will be finalized as part of the multidisciplinary review of the labeling.

III. Administrative

- A. Reviewer's Signature:** in DFS
- B. Endorsement Block:** in DFS
- C. CC Block:** in DFS

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- NDA 22382	----- ORIG 1	-----	----- KETOROLAC TROMETHAMINE NASAL SPRAY
NDA 22382	ORIG 1		KETOROLAC TROMETHAMINE NASAL SPRAY

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/s/

JOSEPH M LEGINUS
08/07/2009

ALI H AL HAKIM
08/07/2009

NDA 22-382

SprixTM
(ketorolac tromethamine)
Nasal Spray

ROXRO PHARMA, Inc.

Joseph Leginus, PhD
Division of Pre-Marketing Assessment I, Branch II, ONDQA

For the Division of
Anesthesia, Analgesia and Rheumatology Products

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Chemistry Review Data Sheet

1. NDA 22-382
2. REVIEW #: 1
3. REVIEW DATE: 22-June-2009
4. REVIEWER: Joseph Leginus, PhD
5. PREVIOUS DOCUMENTS:

Previous Documents

N/A

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedOriginal NDA
AmendmentDocument Date05-Dec-2008
29-Apr-2009

7. NAME & ADDRESS OF APPLICANT:

Name: Roxro Pharma, Inc.

Address: 535 Middlefield Road, Suite 180 Menlo Park, CA 94025

Representative: Roger Whiting, Ph.D.

Telephone: 650-947-9776

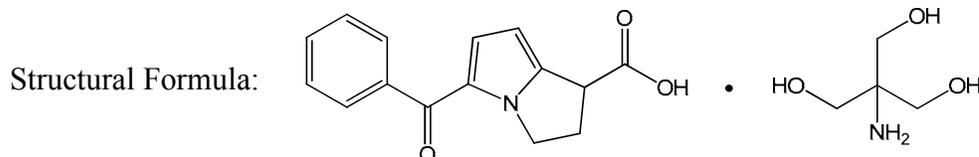
8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: SPRIX™ Nasal Spray
- b) Non-Proprietary Name (USAN): Ketoro1ac Tromethamine
- c) Code Name/# (ONDC only): CAS No.: 74103-07-4
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: This NDA is submitted as a 505(b)(2) application.
10. PHARMACOL. CATEGORY:
Non-steroidal anti-inflammatory drug (NSAID) for short term (up to 5 days) management of moderate to severe pain that requires analgesia at the opioid level.
11. DOSAGE FORM: Nasal Spray
12. STRENGTH/POTENCY: 15% solution (weight/weight); 15.75 mg per 0.1 mL spray.
13. ROUTE OF ADMINISTRATION: Intranasal
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:

Chemical Name: (±)-5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid, compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1)



Molecular Formula: $C_{19}H_{24}N_2O_6$

Molecular Weight: Ketorolac tromethamine: 376.41
Ketorolac (free acid): 255.27

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Type	Holder	Item Referenced	Code ¹	Status ²	Date Review Completed	Comments
(b) (4)	2	(b) (4)	Ketorolac Tromethamine Drug Substance	1	Adequate	11-Oct-2006	Reviewed by R. D'Costa as adequate. Request pending for 2007 and 2008 annual reports.
	3	(b) (4)	(b) (4)	1	Adequate	20-Aug-2004	Reviewed by Y. Yang
	3	(b) (4)	(b) (4)	1	Adequate	15-Dec-2005	Reviewed by J. Boal

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
NDA	19-645	Toradol® (ketorolac tromethamine) Tablets
NDA	19-698	Toradol® (ketorolac tromethamine) for Injection

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending		
Pharm/Tox	Pending		Newton Woo

Chemistry Review Data Sheet

Biopharm	N/A		
Methods Validation	N/A		
EA	N/A		
Microbiology	Pending	4/21/2009	Robert Mello

19. ORDER OF REVIEW: N/A

The Chemistry Review for NDA 22-382

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 22-382 is considered to be approvable (AE) from a CMC perspective at this time.

- Comments forwarded to the applicant in IR letter dated May 13, 2009 need to be adequately addressed prior to the approval of the application.
- The EER for this NDA is currently pending. Acceptable cGMP recommendation is currently given for four establishments by the Office of Compliance and inspection outcomes are pending for 4 sites. Specifically, inspection has been performed for one site, inspection is assigned for two sites and inspection is scheduled for one site. An acceptable cGMP recommendation is required for all manufacturing and testing facilities before approval.

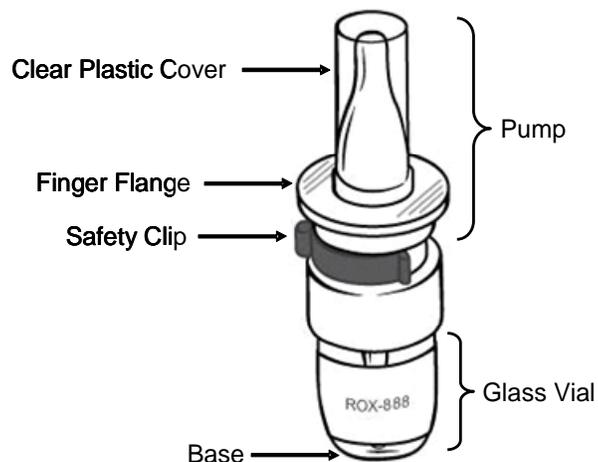
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not applicable.

II. Summary of Chemistry Assessments

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

Sprix™ is an intranasal formulation of ketorolac tromethamine, a nonsteroidal anti-inflammatory drug indicated for short term (up to 5 days) management of moderate to severe pain. The drug product consists of a clear, colorless to yellow clear solution contained in a clear glass vial fitted with a metered (100 µL) multidose spray pump. Sprix™ will be supplied in boxes containing 1 nasal spray bottle or 5 single-day nasal spray bottles. Each unit of Sprix™ contains a volume sufficient to deliver one day's supply, a maximum of eight doses of 100 µL (0.1 mL) sprays. The product is not labeled as sterile and it is not formulated to contain an antimicrobial, therefore, drug product manufacturing is performed under (b) (4) conditions.



Executive Summary Section

The drug substance, ketorolac tromethamine, is currently marketed as Toradol® IV/IM (ketorolac tromethamine) injection (NDA 19-698) and Toradol® oral (ketorolac tromethamine) tablets (NDA 19-645). All information with respect to the chemistry, manufacturing and controls of ketorolac tromethamine, USP is provided by reference to Drug Master File (b) (4) (b) (4)

(b) (4) Specifications are based on the USP monograph. In addition, the drug substance is tested for (b) (4) and controlled to NMT (b) (4) to limit (b) (4) (b) (4). Retest for the drug substance is (b) (4)

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

Sprix™ is indicated for short term (up to 5 days) management of moderate to severe pain, (b) (4). The usual recommended dose for adult patients less than 65 years of age is one 15.75 mg ketorolac tromethamine spray in each nostril every 6 to 8 hours. The maximum daily dose should not exceed 126 mg. Each Sprix™ Nasal Spray vial contains one day's supply of drug for administration of a maximum of eight 100 µL (0.1 mL) sprays. Before use for the first time, the pump must be properly activated (primed) by pressing down evenly and releasing the pump (actuating) 5 times. There is no further need to prime the pump again. After each use, the bottle should be stored in a cool, dry location out of direct sunlight. The patient is advised to discard each nasal spray bottle within 24 hours of administering the first dose, even though the bottle may still contain unused medication. The drug product will be labeled for long term storage at refrigerated (2°- 8°C) conditions, but may be maintained under ambient conditions during use.

C. Basis for Approvability or Not-Approval Recommendation

This is a 505(b)(2) application providing for a new dosage form (nasal spray). The reference listed drug (RLD) for this product is Toradol (NDA 19-698) which was approved on November 30, 1989. The IND for ketorolac tromethamine nasal spray (62,829) was submitted on April 10, 2002, the EOP2 meeting was held on May 17, 2006 and the pre-NDA meeting was held on October 4, 2007.

The drug substance, (ketorolac tromethamine USP) will be manufactured for commercial use by (b) (4) with most of the CMC parameters provided in the (b) (4) Type II DMF No. (b) (4). A copy of the letter of authorization to reference DMF (b) (4) has been provided. The DMF was reviewed and found to be acceptable. In addition to the USP requirements, the drug substance will be tested for additional attributes (b) (4) residual solvents, bacterial endotoxins). The (b) (4) test is included due to the (b) (4). The proposed acceptance criterion of NMT (b) (4) provides sufficient control over (b) (4) content in the drug substance when coupled with (b) (4) EDTA in the drug product.

Executive Summary Section

Two impurities have been identified in the drug substance (“1-hydroxy” and “1-keto”), and both are adequately controlled at NMT 0.1%.

The drug product is not labeled as sterile and it is not formulated to contain an antimicrobial, therefore, drug product manufacturing is performed under (b) (4) conditions. The multidose pump/cap lots are (b) (4) Vials are (b) (4) All batches manufactured at Hollister-Stier, the proposed commercial manufacturing facility, were formulated in (b) (4)

Since the drug product was found to be photosensitive, (b) (4) which provide adequate protection from light. A label statement will be added to protect the drug product from light.

The nasal spray solution is formulated as a low bioburden buffered solution at pH 7.2 containing the active ingredient (ketorolac tromethamine) and the compendial excipients edetate disodium (EDTA; (b) (4) monobasic potassium phosphate (b) (4) (b) (4) sodium hydroxide (b) (4) and sterile water for (b) (4)

The applicant states that osmolality is consistently controlled in the drug product, and, therefore, a specification for osmolality is unnecessary. However, the solution contains a (b) (4) (b) (4) (EDTA), which is a critical excipient to the formulation, (b) (4) Therefore, osmolality is a critical physicochemical property, characteristic of this particular drug product, and will need to be included in the drug product specifications.

The fill weight of 1.7 g (b) (4) per bottle represents an overfill of (b) (4) per bottle, corresponding to (b) (4) of ketorolac tromethamine (b) (4) The overfill represents a compromise to ensure an adequate volume for the recommend number of sprays (5 primes and 8 dosing) while minimizing potential patient abuse of remaining drug product.

A 24 months expiry period for the drug product was requested, however, the level of 1-keto impurity is anticipated to exceed its qualified level (1.0%) prior to 24 months under the recommended storage conditions. Real time stability data is available to support an expiry date of (b) (4) at refrigerated (2° - 8°C) temperatures and an in-use period of one day at ambient conditions.

Executive Summary Section

From a CMC perspective, the applicant has provided adequate documentation of the composition of the proposed drug product, control of ingredients, the manufacturing process, control of critical manufacturing steps and control of the finished product. Based on this information, the application is considered approvable. The deficiency comments outlined in the CMC IR letter dated May 13, 2009 do not include approvability issues, but rather request additional justification and clarification. Also, an acceptable GMP status is required for all manufacturing and testing facilities supporting this application. The EER for this NDA is currently pending. As of May 18, 2009, AC status is available for four establishments, inspection has been performed for one site, inspection is assigned for two sites and inspection is scheduled for one site. Dr. Mello's review of the microbiology controls is pending.

III. Administrative

- A. Reviewer's Signature:** in DFS
- B. Endorsement Block:** in DFS
- C. CC Block:** in DFS

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

/s/

Joseph Leginus
6/22/2009 08:42:07 AM
CHEMIST
Revisions incorporated as discussed.

Ali Al-Hakim
6/22/2009 11:21:29 AM
CHEMIST

Initial Quality Assessment
Division of Pre-Marketing Assessment I, Branch II
Office of New Drug Quality Assessment
Division of Anesthesia, Analgesia and Rheumatology Products

OND Division:	Anesthesia, Analgesia and Rheumatology	
NDA:	22-382	
Applicant:	ROXRO Pharmaceuticals	
Stamp date:	December 5, 2008	
PDUFA Date:	October 5, 2009	
Trademark:	Sprix	
Established Name:	Ketorolac Tromethamine Nasal Spray	
Dosage Form:	Nasal Spray (15% w/w)	
Route of Administration:	Intranasal	
Indication:	Short term (up to 5 days) management of pain	
Pharmaceutical Assessment Lead:	Danae D. Christodoulou, Ph.D.	
	YES	NO
ONDQA Fileability:	<u>√</u>	_____
Comments for 74-Day Letter:	_____	<u>√</u>

Summary, Critical Issues and Comments

A. Summary

The application is filed as a 505(b)(2), non-priority NDA with 10-month review clock, based on the approved NDAs, Toradol® IV/IM (ketorolac tromethamine) injection (NDA 19-698) and Toradol® oral (ketorolac tromethamine) tablets (NDA 19-645).

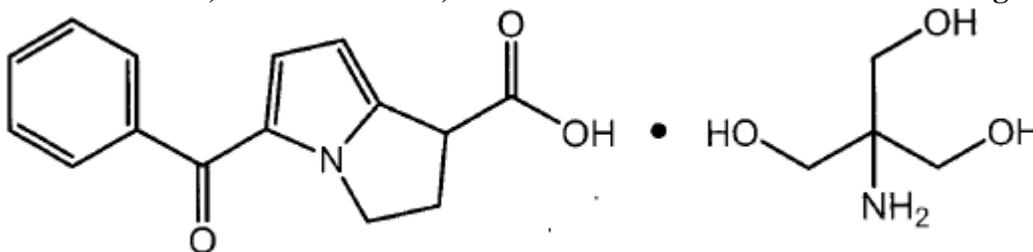
The drug substance, ketorolac tromethamine, is manufactured by (b) (4) and referenced to Drug Master File (DMF) (b) (4). A Letter of Authorization (LoA) has been provided. Ketorolac is a potent NSAID analgesic, a COX inhibitor resulting in reduced synthesis of prostaglandins, thromboxanes and prostacyclin. Ketorolac may influence actions of other substances, such as P and FAAH, related to pain mechanisms.

The drug product is formulated as a non-sterile, "low bioburden" aqueous solution for intranasal administration of 15.75 mg/ml, pH 7.2, in USP Type I clear bottle, with an attached metered pump/snap on closure (b) (4) for intranasal delivery. The drug product is intended for administration in eight actuations over a one-day period, with 15.75 mg ketorolac tromethamine per actuation per nostril, to provide a dose of 31.5 mg (two sprays). Based on 18-month real time stability data, a 24-month shelf-life is proposed for the product.

B. Review, Comments and Recommendations

Drug Substance Ketorolac Tromethamine

Molecular Structure, Chemical Name, Molecular Formula and Molecular Weight



1H-Pyrrolyzine-1-carboxylic acid, 5-benzoyl-2,3-dihydro, (±),
compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1: 1)
Molecular formula: C₁₉H₂₄N₂O₆ (C₁₅H₁₃NO₃-C₄H₁₁NO₃)
Molecular weight: 376.41

As discussed above, ketorolac tromethamine is manufactured by (b) (4) and referenced to Drug Master File (b) (4). Specifications are based on the USP monograph. In addition, the drug substance is tested for (b) (4) content, residual solvents and bacterial endotoxin. Residual (b) (4) ion is controlled to NMT (b) (4) to limit (b) (4). Details regarding the manufacturing process, characterization and impurities are referenced to DMF (b) (4). This DMF has been reviewed previously and found adequate. Potential impurities/degradants are listed in Table 1, below, and are controlled at NMT 0.1%. The acceptance criteria for other individual impurities and total impurities have been reduced to (b) (4) and (b) (4) as agreed with the Division (pre-NDA correspondence of 10/4/2007). The proposed drug substance specifications should be assessed as per ICH Q3A(R2) in consultation with the Toxicology division. Regarding the (b) (4) limit of NMT (b) (4) the firm conducted a spiking study on the proposed commercial formulation (containing (b) (4) EDTA) with (b) (4) concentrations up to (b) (4) in the drug product, corresponding to (b) (4) in the drug substance. The applicant claimed that in the presence of the (b) (4) EDTA in the drug product, a limit of NMT (b) (4) in the drug

substance was sufficient to (b) (4). This should be assessed upon review. Note that the applicant did not comment on the nasal cavity content of (b) (4) and its impact on the (b) (4).

Microbial testing is performed by (b) (4) as per USP<1111>, and validation studies are included in the DMF. In addition, the drug substance complies with NMT (b) (4) bacterial endotoxins. This is the USP requirement for injectable ketorolac tromethamine, at the same daily dose as the proposed spray. The microbiological attributes of the drug substance should be assessed in consultation with the Microbiology division.

Table 1. Potential impurities in Ketorolac Tromethamine

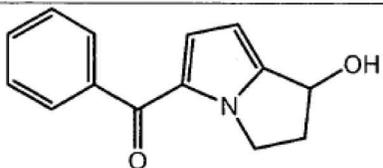
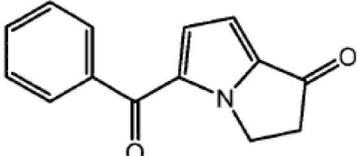
Table 2.3.S.3-1. Structures of Potential Drug Substance Impurities/Degradants	
Name(s)	Structure
(±)-5-benzoyl-1-hydroxy-2,3-dihydro-1H-pyrrolizine (1-hydroxy compound)	
(±)-5-benzoyl-1-keto-2,3-dihydro-1H-pyrrolizine (1-keto compound)	

Table 2. Drug Substance Specifications (b) (4)

Table 2.3.S.4-1. Drug Substance Specifications ^a	
Test	Method
Description	Visual inspection
Identification A (IR)	Current USP monograph
Identification B (UV)	Current USP monograph
Identification C (FLC)	Current USP monograph
Melting point	Current USP monograph
pH	Current USP monograph
Loss on drying	Current USP monograph
Residue on ignition	Current USP monograph
Heavy metals	Current USP monograph
Chromatographic purity	Current USP monograph
Assay (b) (4)	Current USP monograph USP <730> ^c
Residual solvents	USP <467>
Microbial limits ^b	USP <61>
Bacterial endotoxins	USP <85>

^a Results for all tests except Identification A may be taken from the supplier certificate of analysis, with confirmation by full testing upon receipt at the drug product manufacturing site for one batch at routine intervals.

^b The microbiological quality of the drug substance has been determined by the supplier via validation studies described in their DMF.

^c Further details regarding (b) (4) analysis are provided in Section 3.2.S.4.2.

Batch analyses

Batch analysis results are included in the NDA for 9 batches. The (b) (4) and microbial limits have not been reported for three batches manufactured prior to 2004. Impurities of re-analysed batches (analysis performed by ROXRO) meet the revised acceptance criteria for impurities.

Drug substance stability

The drug substance is supported by 60 months stability data, referenced to DMF (b) (4). The proposed retest date is (b) (4).

Drug product

The drug product is formulated as a multidose, low-bioburden aqueous solution of ketorolac tromethamine in a Type I clear glass bottle, filled to contain NLT 1.7 g (b) (4) per bottle, with an attached 100 µL metered pump/snap on closure for intranasal administration. The drug product should be administered in eight actuations in a one day period. The solution does not contain novel excipients.

Table 3. Quantitative composition for ketorolac tromethamine nasal spray, is provided below.

Table 2.3.P.1-1. Drug Product Unit Composition					
Ingredient	mg/spray ^a	Amount (b) (4)	mg/bottle ^c		Function (b) (4)
			8 sprays	(b) (4)	
Drug Substance:					
Ketorolac Tromethamine USP	15.75	(b) (4)	126.0	(b) (4)	(b) (4)
Excipients:					
Edetate Disodium USP	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Monobasic Potassium Phosphate NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Sodium Hydroxide NF	pH 7.2	(b) (4)	pH 7.2	(b) (4)	(b) (4)
(b) (4) Water for Injection USP	q.s. ad	(b) (4)	q.s. ad	(b) (4)	(b) (4)
Total	105	(b) (4)	840.0	(b) (4)	(b) (4)

^a Based on a nominal spray of 100 µL (=105 mg) per actuation.

(b) (4)

Manufacturing Process:

The proposed commercial manufacturer is Hollister-Stier Laboratories, LLC, located in Spokane, WA. Developmental batches of the drug product were manufactured by (b) (4)

(b) (4) and batch 7029A of Hollister-Stier, but subsequently was (b) (4). The multidose pump/cap system was (b) (4)

All vials were (b) (4). The commercial manufacturing process at Hollister-Stier includes (b) (4) in (b) (4)

The suitability of the manufacturing process and microbiological assurance of the low bioburden solution should be assessed in consultation with the Microbiology division.

The proposed commercial batch size is (b) (4) approximately a (b) (4) scale-up of the (b) (4) registration batches. Batch formula is shown in Table 4, below.

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Process validation:

The applicant will perform process validation on three consecutive batches at the proposed commercial scale.

Pharmaceutical Development:

The drug substance, ketorolac tromethamine, is well-characterized and used in other drug products. Since the drug product is formulated as an aqueous solution, the particle size, morphic form and other solid state properties of the drug substance are not expected to impact the bioavailability of the drug. Critical attributes of the drug product are: the concentration of ketorolac tromethamine (target 15%w/w), concentration of EDTA (b) (4) pH (7.2). Critical attributes to drug product performance are the spray characteristics, e.g., pump delivery, spray content uniformity, droplet size distribution and spray geometry. (b) (4)

(b) (4). Antimicrobial preservatives have not been used based on the proposed limited fill and use of the spray. An overfill of less than (b) (4) of solution per bottle is used for the proposed commercial drug product presentation to ensure the delivery of adequate doses. A justification for this overfill is provided in a characterization study (Table 2.3.P.2-4) describing the effect of fill weight upon tail off characteristics of the spray. The adequacy of the overfill weight for optimal delivery and minimal residual should be assessed upon review.

(b) (4)

Batch Number	Amount (wt % in water)			Buffer System	Container Closure System
	Ketorolac Tromethamine	EDTA	Other Ingredients		
ROX1/019/F	0	(b) (4)	----	(b) (4)	(b) (4)
ROX1/020/F*	15		----		
ROX1/024/F	0		----		
ROX1/025/F*	15		----		
ROX1/026/F	0		----		
ROX1/027/F*	15		----		
7133	15		----		

*Proposed commercial presentation. ** Proposed commercial container closure system.

The results of the above characterization studies should be assessed as per the 2002 FDA Guidance recommendations “*Nasal Spray and Inhalation Solution, Suspension and Spray Drug Products – CMC Documentation*”.

The applicant provided analytical data for assay, pH, osmolality, pump delivery (% target), impurities and bioburden (CFU/g) for their development batches. Osmolality was determined to remain constant during development, (0.56 – 0.64 Osm/kg) and a specification was not deemed necessary for end-product testing. The firm’s justification and supporting data should be assessed for the need of the osmolality specification for the drug product.

The leachables/extractables evaluation study and rationale for specification should be assessed in consultation with the Toxicology division. No detectable quantities of leachables have been observed in the stability samples, up to 18 months of upright and horizontal/inverted storage at 5°C and 6 months of upright and horizontal/inverted storage at 25°C/60% RH. Accordingly, drug product leachables will be routinely controlled exclusively via pump extractables testing.

Integrity of the container/closure system regarding microbiological attributes (in-use and shelf life) should be assessed in consultation with the Microbiology division.

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Analytical methods are based on compendial procedures with the exception of:

- Identification, Assay, Impurities and Degradation Products (LM-RO001-001)
- Tromethamine (LM-RO001-015)
- EDTA (LM-RO001-002)
- Pump Delivery and Spray Content Uniformity (LM-RO001-003)
- Spray Pattern (LM-RO001-016)
- Droplet Size Distribution (LM-RO001-004)

Methods Validation, according to ICH Q2(R1), are provided in the submission and should be assessed.

Batch analysis data:

Batch analysis data are included for 8 drug product batches, (b) (4) 7029A, 7066, 7087, 7090, 7133, 7278, 7279, 7304. Product conforms to specifications. Note, that levels of individual and total impurities at release are (b) (4) respectively, for all batches.

(b) (4)

Stability:

Stability testing of the drug product was performed at 5°C, 15°C, and 25°C/60% RH (accelerated). Longest data are provided up to 18 months under long term storage conditions (5°C) and 6 months under accelerated (25°C/60% RH). Stability data include horizontal and inverted configurations, photostability conducted as per ICH Q1B Option 2, temperature cycling by cycling every 12 hours from -10°±2°C to 40°±2°C for 4 weeks (horizontal and upright orientation, uncontrolled humidity, light shielded), with testing at t=1, 2 and 4 weeks. Stability protocols are provided. No significant trends have been observed on stability, individual and total impurities/degradants remained ≤ 1 and no differences have been observed between upright and inverted storage configurations. The applicant proposed 24 months expiration dating based on 18 month real time stability data at 2-8°C on registration batches, and statistical analysis evaluation using SlimStat Version 4.3.0 software. Limiting attribute was the 1-keto degradant with estimated shelf-life of 29 months. The proposed expiration dating should be assessed as per ICH Q1E.



Comparability Protocol:

A comparability protocol for inclusion of a (b) (4) in the manufacture of the commercial drug product, (b) (4)

is proposed in the NDA.

(b) (4) would be more extensive than the

(b) (4) The (b) (4)

(b) (4)

(b) (4) The drug

(b) (4)

product batches will be prepared from a

The revised presentation would not result in any modified label claims other than those related to the product description and expiry period/storage conditions. Any additional changes beyond those provided above would be discussed with the Agency prior to submission.

Labeling

Labeling information on the container labels and packaging insert should be assessed with respect to CMC information. SPL labeling should be requested from the applicant.

C. Critical issues for review and recommendation

During assessment of the CMC information provided in this NDA, the primary reviewer should consider addressing issues identified above and other related ones, summarized here, for their impact on drug product quality and performance throughout the shelf-life:

1. The drug substance DMF (b) (4) should be assessed.
2. Suitability of the proposed drug substance specifications for ketorolac tromethamine should be assessed as per ICH Q3(R) and ICH Q3B(R), in consultation with the Toxicology division.
3. Suitability of the manufacturing process, which includes (b) (4) processing, should be assessed in consultation with the Microbiology division. In addition, specifications and microbiological integrity of the drug substance, drug product for in-use and shelf life duration should be evaluated accordingly.
4. Hold times of intermediates and (b) (4) from manufacturing conditions should be assessed.
5. Method Validation for the non-compendial methods (HPLC) for the drug product.
6. In-process controls and scale-up of the manufacturing process should be assessed.
7. Bridging/comparability studies of the device during development and assessment of spray characteristics for changes of the pump and vial and impact on drug product performance should be assessed.
8. Specifications (in-process and end product testing) for critical attributes of drug product performance, e.g., pH, osmolality (justification for no specification), pump delivery, spray characteristics, fill weight, etc.
9. Specifications for drug product impurities/degradants as discussed in 2 above, for the drug substance.
10. Compatibility of the container closure with the solution and leachables/extractables evaluation in consultation with the Toxicology division.
11. Suitability of the container/closure system, evaluation of specifications and priming/repriming, tail-off characteristics.
12. Proposed expiration dating of 24 months, including storage orientations and statistical analysis evaluation.
13. Proposed comparability protocol to upgrade the manufacturing process for inclusion of (b) (4) (b) (4)

D. Comments for 74-day Letter:

None

- E. **Recommendation for fileability:** The NDA is fileable based on pre-NDA agreements, sufficient number of primary stability batches, and 18 month real time stability data at 5°C, accelerated 25°C/60% RH. The NDA is suitable for evaluation and assessment based on FDA and ICH guidelines for submitting CMC information for New Drug Applications.

Recommendation for Team Review: The NDA is not recommended for team review. The drug substance is not an NME, the formulation does not include novel excipients and the manufacturing process for the drug product does not present complexity, nor significant development. The device performance characteristics have

been tested according to the FDA Guidance on Nasal Sprays. In addition, the primary stability batches are representative of the commercial process.

Consults:

Since the drug product is a “low bioburden” nasal solution for limited (one day) use, microbiology consult was initiated.

Specifications for impurities and leachables/extractables evaluation should be assessed in consultation with the Toxicology reviewer.

Statistical analysis consult was not deemed necessary, since a sufficient body of real time data has been included in the NDA and no significant trends on stability have been observed.

Danae D Christodoulou, Ph.D.
Pharmaceutical Assessment Lead

3/5/2009
Date

Ali Al-Hakim, Ph.D.
Branch II Chief, ONDQA

3/6/2009
Date

Fileability Template

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	√		
2	Is the section indexed and paginated adequately?	√		
3	On its face, is the section legible?	√		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full <u>street</u> addresses and CFNs?	√		
5	Is a statement provided that all facilities are ready for GMP inspection?	√		
6	Has an environmental assessment report or categorical exclusion been provided?	√		Categorical exclusion requested 21CFR 25.31(a)
7	Does the section contain controls for the drug substance?	√		
8	Does the section contain controls for the drug product?	√		
9	Has stability data and analysis been provided to support the requested expiration date?	√		Stability data have been provided with statistical analysis
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		Pre-NDA 10/4/2007 IND 62,829
11	Have draft container labels been provided?	√		
12	Has the draft package insert been provided?	√		
13	Has a section been provided on pharmaceutical development/ investigational formulations section?	√		
14	Is there a Methods Validation package?	√		
15	Is a separate microbiological section included?	√		“low bioburden” solution
16	Have all consults been identified and initiated?	√ N/A N/A N/A N/A √		Pharm/Tox Statistics OCP/CDRH/CBER LNC DMETS/ODS Microbiology

Have all DMF References been identified? Yes (√) No ()

DMF Number	Holder	Description	LoA Included	Status
(b) (4) Type II	(b) (4)	Ketorolac Tromethamine	Yes	Adequate
(b) (4) Type III	(b) (4)	(b) (4)	Yes	pending
(b) (4) Type III	(b) (4)	(b) (4)	Yes	pending

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/s/

Danae Christodoulou
3/6/2009 01:17:52 PM
CHEMIST
Initial Quality Assessment

Ali Al-Hakim
3/6/2009 01:27:31 PM
CHEMIST