

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-430

CHEMISTRY REVIEW(S)



NDA 22-430

Lysteda™ (tranexamic acid) Tablets

Xanodyne Pharmaceuticals, Inc.

Gene W. Holbert, Ph.D.

Division of Reproductive and Urologic Products



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CHEMISTRY REVIEW



Chemistry Review Data Sheet

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Chemistry Review Data Sheet

1. NDA 22-430
2. REVIEW #: 1
3. REVIEW DATE: 18-SEP-2009
4. REVIEWER: Gene W. Holbert, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

None

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original

Amendment (BC)

Document Date

20-JAN-2009

14-APR-2009

24-APR-2009

04-JUN-2009

23-JUN-2009

30-JUN-2009

11-SEP-2009

15-SEP-2009

7. NAME & ADDRESS OF APPLICANT:

Name: Xanodyne Pharmaceuticals, Inc.

Address: One Riverfront Place
Newport, KY 41071-4563

Representative: Sabrina R. Girty, Assoc. Director, Regulatory Affairs

Telephone: 859-342-2088

8. DRUG PRODUCT NAME/CODE/TYPE:

a) **Proprietary Name:** Lysteda™

b) Non-Proprietary Name (USAN): tranexamic acid

c) Code Name/#: XP 12B-MR

Chemistry Review Data Sheet

d) Chem. Type/Submission Priority:

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (2)

10. PHARMACOL. CATEGORY: Hemostatic

11. DOSAGE FORM: Tablets,

CODE: 500

12. STRENGTH/POTENCY: 650 mg

13. ROUTE OF ADMINISTRATION: Oral

CODE: 001

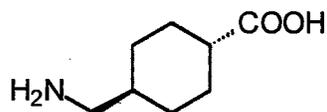
14. Rx/OTC DISPENSED: X Rx OTC

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:



$C_8H_{15}NO_2$
157.21

Tranexamic Acid



CHEMISTRY REVIEW



Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS: LOA DATE
					Adequate	3/6/2009 G Holbert	8/22/2008
					Adequate	03/22/2002 J Boa;	10/6/2008
					Adequate	4/22/2002 RP Frankewich	10/9/2008
					Adequate	3/10/1999 HS Khorshidi,	10/8/2008
					Adequate	9/1/1999 J Vidra	5/19/2008
					Adequate	2/24/2005 A Schroeder	10/7/2008
					Adequate	11/10/2003 S Pope	10/6/2008
					Adequate	8/15/1996	12/11/2008
					Adequate	9/7/1999 L Huang	10/6/2008
					Adequate	3/7/2005 G Holbert	1/5/2009

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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	SPONSOR
Tranexamic Acid 650 mg Modified Release Tablets	IND 68,096	Xanodyne Pharmaceuticals, Inc.
Cyklokapron 500 mg tablets	NDA 19-280 (discontinued)	Pharmacia & Upjohn
Cyklokapron Injectable 100 mg/mL	NDA 19-281	Pharmacia & Upjohn



CHEMISTRY REVIEW



Chemistry Review Data Sheet

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	21-SEP-2009	E. Johnson
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A		
DMEPA	Acceptable	06-JUN-2009 16-SEP-2009	Anne Crandall
EA	FONSI	27-MAR-2009	Raanan (Ron) Bloom,
Microbiology	N/A		



The Chemistry Review for NDA 22-430

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. All facilities involved are in compliance with cGMP, and labels have adequate information as required. Therefore, from a CMC perspective, this NDA is recommended for "Approval".

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

None.

II. Summary of Chemistry Assessments

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

Lysteda™ (tranexamic acid) tablets are white oval shaped tablets debossed on one side with XP-650. Each capsule contains 650 mg of tranexamic acid. Inactive ingredients include Microcrystalline Cellulose, Colloidal Silicon Dioxide, Pregelatinized Corn Starch, Povidone, Hypromellose, Stearic Acid and Magnesium Stearate. All excipients are compendial.

The product is packaged in _____ HPDE bottles containing ~, 30, 100 or 500 tablets respectively. The bottles are _____. The tablets are also packaged in PVC/_____. Each blister card contains six tablets. The blister cards are packaged in cardboard cartons.

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Lysteda™ (tranexamic acid) tablets are manufactured by _____

The manufacturing process consists of _____

b(4)

The drug product specification includes tests for Description, Tranexamic Acid Identification and Assay, Content Uniformity, Related Substances (individual and total), Dissolution and Hardness. Originally, the sponsor proposed multiple time points for dissolution acceptance criteria, but this was revised to a single time point criterion of NLT _____(Q) at 90 minutes.

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Chemistry Assessment Section

b(4)

The applicant has proposed the following expiration dating periods: bulk tablets, _____ months; 100 count bottles, 36 months; all other packaging configurations, 24 months, when stored at room temperature 25°C (77°F) (59-86° F); excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature]. Based on the available real time data, the proposed expiration dating periods are granted.

The drug substance is tranexamic acid, a white, odorless crystalline powder with a bitter taste. The drug substance is manufactured by _____
_____. The drug substance is described in DMF _____

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

Lysteda™ (tranexamic acid) tablets are indicated for the treatment of heavy menstrual bleeding (HMB, also called menorrhagia) and improvement of the associated limitations on social, leisure and physical activities.

The recommended dose of Lysteda is two 650 mg tablets taken three times daily (3900 mg) for a maximum of 5 days during menstruation. The product may be administered without regard to meals.

The product is contraindicated in patients with thromboembolic disease (deep vein thrombosis, pulmonary embolism and cerebral thrombosis) or history or risk of thromboembolism including retinal vein and artery occlusion.

C. Basis for Approvability or Not-Approval Recommendation

This NDA provided adequate information on the raw material controls, manufacturing process, specifications, and container/closure. It also provided sufficient stability data to assure identity, strength, purity and quality of the drug product during the shelf life. The Office of Compliance has issued an "Acceptable" overall recommendation for all the facilities involved. Labels have required information.

III. Administrative**A. Reviewer's Signature**

Signed electronically in DARRTS

B. Endorsement Block

Gene W. Holbert, Ph.D./18-SEP-2009

Moo-Jhong Rhee, Ph.D./25-SEP-2009

Nenita I. Crisostomo

56 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(4) Draft Labeling

§ 552(b)(5) Deliberative Process



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

APPENDIX

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application:	NDA 22430/000	Sponsor:	XANODYNE PHARMS INC
Org. Code:	580		1 RIVERFRONT PL
Priority:	P		NEWPORT, KY 410714563
Stamp Date:	30-JAN-2009	Brand Name:	TRANEXAMIC ACID 650MG MODIFIED RELEASE T
PDUFA Date:	30-OCT-2009	Estab. Name:	
Action Goal:		Generic Name:	TRANEXAMIC ACID
District Goal:	01-OCT-2009	Product Number; Dosage Form; Ingredient; Potency	

FDA Contacts:	J. MERCIER	Project Manager	301-796-0957
	G. HOLBERT	Review Chemist	301-796-1368
	D. CHRISTNER	Team Leader	301-796-1341

Overall Recommendation:	ACCEPTABLE	on 21-SEP-2009	by E. JOHNSON	(HFD-320)	301-796-3334
	WITHHOLD	on 07-JUL-2009	by E. JOHNSON	(HFD-320)	301-796-3334

Establishment:	CFN: _____	FEI: _____	
	✓	7	b(4)
DMF No:			AADA:
Responsibilities:	DRUG SUBSTANCE RELEASE TESTER		
Profile:	CONTROL TESTING LABORATORIES "ALSO" (DRUGS)	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	05-FEB-2009		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	CFN: _____	FEI: _____	
	✓	3	b(4)
DMF No:			AADA:
Responsibilities:	FINISHED DOSAGE RELEASE TESTER		
Profile:	CONTROL TESTING LABORATORY	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	06-FEB-2009		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Establishment: CFN: _____ FEI: _____
 DMF No: _____ AADA: _____
 Responsibilities: FINISHED DOSAGE RELEASE TESTER
 Profile: CONTROL TESTING LABORATORY OAI Status: NONE
 Last Milestone: OC RECOMMENDATION
 Milestone Date: 06-FEB-2009
 Decision: ACCEPTABLE
 Reason: BASED ON PROFILE

b(4)

Establishment: CFN: _____ FEI: _____
 DMF No: _____ AADA: _____
 Responsibilities: DRUG SUBSTANCE MANUFACTURER
 Profile: _____ OAI Status: NONE
 Last Milestone: OC RECOMMENDATION
 Milestone Date: 21-SEP-2009
 Decision: ACCEPTABLE
 Reason: DISTRICT RECOMMENDATION

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Establishment: CFN: _____ FEI: _____
 DMF No: _____ AADA: _____
 Responsibilities: DRUG SUBSTANCE RELEASE TESTER
 FINISHED DOSAGE MANUFACTURER
 FINISHED DOSAGE RELEASE TESTER
 FINISHED DOSAGE STABILITY TESTER
 Profile: TABLETS, PROMPT RELEASE OAI Status: NONE
 Last Milestone: OC RECOMMENDATION
 Milestone Date: 18-MAR-2009
 Decision: ACCEPTABLE
 Reason: DISTRICT RECOMMENDATION

b(4)



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Establishment: CFN: _____ FEI: _____ **b(4)**
 ✓ _____ ✓ _____
 DMF No: _____ AADA: _____
 Responsibilities: FINISHED DOSAGE RELEASE TESTER
 Profile: CONTROL TESTING LABORATORY OAI Status: NONE
 Last Milestone: OC RECOMMENDATION
 Milestone Date: 06-FEB-2009
 Decision: ACCEPTABLE
 Reason: BASED ON PROFILE

Establishment: CFN: _____ FEI: _____ **b(4)**
 ✓ _____ ✓ _____
 DMF No: _____ AADA: _____
 Responsibilities: FINISHED DOSAGE OTHER TESTER
 Profile: CONTROL TESTING LABORATORY OAI Status: NONE
 Last Milestone: OC RECOMMENDATION
 Milestone Date: 06-FEB-2009
 Decision: ACCEPTABLE
 Reason: BASED ON PROFILE

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22430	ORIG-1	XANODYNE PHARMACEUTICS INC	TRANEXAMIC ACID 650MG MODIFIED RELEASE T
NDA-22430	ORIG-1	XANODYNE PHARMACEUTICS INC	TRANEXAMIC ACID 650MG MODIFIED RELEASE T

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

/s/

GENE W HOLBERT
09/24/2009

MOO JHONG RHEE
09/24/2009
Chief, Branch III

Initial Quality Assessment
Branch III
Pre-Marketing Assessment Division II

OND Division: Division of Reproductive and Urologic Products
NDA: 22-430
Applicant: Xanodyne Pharmaceuticals, Inc.
Stamp Date: 02-Feb-2009
PDUFA Date: 30-Jul-2009 **PRIORITY**
Trademark: Lysteda
Established Name: Tranexamic Acid
Dosage Form: Modified-release tablets
Route of Administration: Oral
Indication: Treatment of heavy menstrual bleeding (menorrhagia) and the amelioration of symptoms associated with menorrhagia, including limitations on social, leisure, and physical activities

PAL: Donna F. Christner, PhD

	YES	NO
ONDQA Fileability:	x	<input type="checkbox"/>
Comments for 74-Day Letter	x	<input type="checkbox"/>

Summary and Critical Issues:

A. Summary

The drug product is a modified-release tablet which is white, oval-shaped, debossed with XP 650 on one side. The tablets are 950 mg in weight and contain 650 mg tranexamic acid. The drug product will be packaged in 5 commercial configurations. Daily dose is 2-650 mg tablets, 3 times/day, for a total daily dose of 3.9 g.

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The drug product is for the treatment of heavy menstrual bleeding (menorrhagia) and the amelioration of symptoms associated with menorrhagia, including limitations on social, leisure, and physical activities.

B. Critical issues for review

The sponsor states that _____ and _____ are the manufacturers of the drug substance. Sponsor has provided batch release data comparing the drug substance from the two different sources. In addition, they have provided dissolution results comparing tablets prepared with both APIs. The comparison data will need to be carefully reviewed to determine if the APIs are comparable. In addition, if the _____ API will be used for commercial distribution, a LOA to reference the DMF for CMC information should be provided.

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For the drug product, the individual impurity acceptance criteria are set based on ICH guidelines, but it may not be appropriate to set the total limit based on addition. This is not only a CMC review issue, but will also be discussed with the toxicology reviewer. The sponsor should clarify if these impurities are only drug substance process impurities and are therefore not controlled in the drug product, or if these are also degradation products and are included in the Related Substances specification under "Individual Unknowns".

Dissolution specifications will need to be carefully reviewed to see if they have been appropriately set.

C. Comments for 74-Day Letter

Clarify if the _____ API will be used for commercial distribution. If so, information on the manufacturing site and a LOA to reference the DMF for CMC information should be provided

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Clarify if impurities A, B, C and D are only drug substance process impurities and are therefore not controlled in the drug product, or if these are also degradation products and are included in the drug product Related Substances specification under "Individual Unknowns".

Submit a copy of the blister card. Clarify whether the HDPE bottles will be packaged in cartons, and if so, carton labels should be provided.

Please be aware that "Modified Release Tablets" is not a recognized dosage form for purposes of labeling. "Extended Release Tablets" may be more appropriate for our product, but final determination will be made during the NDA review and will be conveyed with other carton and container label comments.

Provide the individual dissolution data points in tabular form for the following graphs in Section 3.2.P.2. In addition, state what dissolution method was used.

- *Figure 2 on page 12*
- *Figure 8 on page 21*
- *Figure 9 on page 22*

D. Recommendation:

This NDA is fileable from a CMC perspective. A single CMC reviewer, Gene Holbert, Ph.D., has been assigned. There are three comments to be conveyed in the 74-day letter.

Donna F. Christner, Ph.D.

NDA Number: 22-430

Applicant: Xanodyne

Stamp Date: 02-Feb-2009

Drug Name: Lysteda

NDA Type:

On initial overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	Comment
1	Is the section legible, organized, indexed, and paginated adequately?	X		
2	Are ALL of the manufacturing and testing sites (including contract sites) identified with full street addresses (and CFNs, if applicable)?	X		
3	Is a statement provided to indicate whether each manufacturing or testing site is ready for inspection or, if not, when it will be ready?	X		
4	Is a statement on the Environmental Impact provided as required in 21 CFR 314.50(d)(1)(iii)?	X		An Environmental Analysis is provided
5	Is information on the Drug Substance provided as required in 21 CFR 314.50(d)(1)(i)?	X		DMF _____
6	Is information on the Drug Product provided as required in 21 CFR 314.50(d)(1)(ii)?	X		
7	If applicable, has all information requested during the IND phases, and at the pre-NDA meetings been included?	X		
8	Have draft container labels and package insert been provided?	X		
9	Have all DMF References been identified?	X		
10	Is information on the investigational formulations included?	X		
11	Is information on the Methods Validation included?	X		
12	If applicable, is documentation on the sterilization process validation included?	X		N/A

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IS THE CMC SECTION OF THE APPLICATION FILEABLE? yes

If the NDA/BLA is not fileable from chemistry, manufacturing, and controls perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Donna F. Christner, PhD
Pharmaceutical Assessment Lead

19-Feb-2009
Date

Moo-Jhong Rhee, PhD
Branch Chief

Date

DMF	Holder	Description	LOA	Status
			Yes	Updates since last review in April 2000. Will require review.
			Yes	Updates since last review in August 1996. May require review. See ONDC Policies on Bottles /Blisters*
			Yes	Updates since last review in October 2003. May require review.
			Yes	
			Yes	Updates since last review in September 1999. May require review
			Yes	Adequate on 25-Jul-2008 by J. Chang for NDA
			Yes	Updates since last review in September 1999. May require review
			Yes	Updates since last review in September 2000. May require review.
			Yes	Updates since last review in March 2005. May require review. See ONDC Policies on Bottles and Blisters*
			Yes	Updates since last review in October 2003. May require review. See ONDC Policies on Bottles and Blisters*

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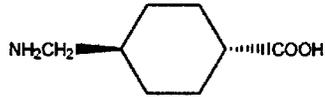
*Policy on the Review of Container Closure Systems for Solid Oral Drug Products (Bottles), 26-Apr-2001
 Policy on the Review of Blister Container Closure Systems for Oral Tablets and Hard Gelatin Capsules, 29-May-2002

DRUG SUBSTANCE

Full information on tranexamic acid is provided in DMF — The sponsor has provided the following information in the NDA;

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Structural Formula:



Compendial Name: Tranexamic acid
Chemical Name(s): *trans*-4-(Aminomethyl)cyclohexanecarboxylic acid
CAS Registry Number: 1197-18-8

The following facilities are responsible for manufacture and testing of the drug substance:

Manufacturing Site: [redacted] b(4)

DMF Holder: [redacted] b(4)

The following table lists the contract laboratories used when testing Tranexamic Acid.

Contract Testing Facility	Contact
[redacted]	Director, Regulatory Submissions
CFN# [redacted] Ready for Inspection	Telephone: [redacted] Fax: [redacted] Email: [redacted]
[redacted]	QA Manager

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Comment: The EER was submitted on 04-Feb-2009 by Gene Holbert.

The drug substance is controlled by the following specifications:

The specifications for Tranexamic Acid (Code 984) are based on the specifications outlined in the EP, JP and vendor's specifications. There is no monograph for the Tranexamic Acid in the current USP.

Table 3.2.S.4.1

Specification	Acceptance Criteria	Method	Procedure
*Description	Odorless white crystals or crystalline powder.	Visual- JP	RMP0984 P001
Identification	IR conforms to RS or reference spectrum	Infrared USP Method	RMP0984 RMPG039
pH		pH meter USP Method	RMP0984 RMPG002
Clarity and Color of Solution	The solution is clear and colorless	Visual- JP	RMP0984
	NMT	General USP Method	RMP0984 RMPG009
	NMT	Method I, USP	RMP0984 RMPG005
*Related Substances Impurity I	NMT	HPLC- JP	RMP0984
Impurity II	NMT	HPLC- JP	RMP0984
Unspecified Impurities (each)	NMT	HPLC- JP	RMP0984
Total Impurities	NMT	HPLC- JP	RMP0984
*Loss on Drying	NMT	General USP Method	RMP0984 RMPG003
Residue on Ignition	NMT	General USP Method	RMP0984 RMPG004
*Assay		HPLC- JP	RMP0984
ANNUAL MANUFACTURER VALIDATION TESTING			
Residual Solvent	NMT NMT	Gas Chromatography USP Method	RMP0984
Particle Size**			BTC94

* Testing required for reassay

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The sponsor has identified the following process impurities in the drug substance:

Impurities Tranexamic Acid

Common Name	Other Name(s)	Name	Process Impurity or Degradant
Impurity A			Process Impurity
Impurity B			Process Impurity
Impurity C			Process Impurity
Impurity D			Process Impurity

b(4)

The sponsor has submitted batch analysis of typical batches, but all other information is cross-referenced to the DMF.

Comment: The DMF will require review.

DRUG PRODUCT

The drug product is a modified-release tablet which is white, oval-shaped, debossed with XP 650 on one side. The tablets are 950 mg in weight and contain 650 mg tranexamic acid. The drug product will be packaged in the following commercial configurations:

- _____
- _____ bottles containing 30 tablets b(4)
- _____ bottles containing 100 tablets
- _____ bottles containing 500 tablets
- _____ blisters containing _____ and 6 tablets/blister b(4)

The tablets are of the following composition:

Table 1: Composition of the Tranexamic Acid Modified-Release Tablets

Component	Code #	Reference	Pharmaceutical Function	Quantity Per Tablet
Tranexamic Acid			Active	650.00 mg
Microcrystalline Cellulose NF		NF		
Colloidal Silicon Dioxide		NF		
Pregelatinized Corn Starch		NF		
Povidone		USP		
Hypermellose		USP		
Stearic Acid		NF		
Magnesium Stearate		NF		
Total				

Excipients are of compendial grade and are controlled by compendial methods. There are no novel excipients in the formulation.

Comment: Information is adequate for review

PHARMACEUTICAL DEVELOPMENT

The sponsor has provided a Pharmaceutical development section. They state that there have been no changes to the formulation, method of manufacture or equipment class made between manufacturing the Registration Stability and Clinical Supply batches and the intended commercial product batches.

The sponsor states that _____ and _____ are the manufacturers of the drug substance. Sponsor has provided batch release data comparing the drug substance from the two different sources. In addition, they have provided dissolution results comparing tablets prepared with both APIs.

Comment: The sponsor should clarify if the _____ API will be used for commercial distribution. If so, a LOA to reference the DMF for CMC information should be provided.

In the early development phase, the sponsor investigated immediate release tablets, delayed-release tablets and modified release tablets. These were compared in a number of clinical studies, and the decision was made to develop the modified release formulation. The sponsor investigated the effect of the following minor changes on the dissolution profile of the tablets:

- ~~_____~~ b(4)
- Impact of different drug substance suppliers
- Impact of debossing

None of these changes were shown to impact the release characteristics of the dosage form.

The sponsor also investigated the impact of the pH of the dissolution media on the release profile and the effect of different ratios of alcohol in the dissolution media on the release profile. For the pH of the dissolution media, only the pH 6.8 Phosphate buffer was shown not to be equivalent. Acid pH gave f2 values above 50. For the alcohol study, Levels of 5%, 10% and 20% gave f2 values over 50, while the 40% alcohol solution gave an f2 value of 26. However, the release curve was much slower than the other media, indicating that dose dumping does not occur with this formulation.

Comment: During the filing meeting, the Clinical Pharmacology reviewer, Dr. Hyunjin Kim, PhD., wanted to request additional information on the dissolution profiles for the changes outlined above. Through collaboration with Dr. Kim and Dr. Holbert, the following comment was included in the 74-day letter:

Provide the individual dissolution data points in tabular form for the following graphs in Section 3.2.P.2. In addition, state what dissolution method was used.

- *Figure 2 on page 12*
- *Figure 8 on page 21*
- *Figure 9 on page 22*

MANUFACTURING

The sponsor has provided the following flow chart for the manufacturing process. They have also included a table containing a narrative.

┌

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The sponsor manufactures

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Comment: Information is adequate for review

The following facilities are involved in the manufacture of the drug product:

Table 1: Facilities Involved in the Manufacture, Packaging and Testing of Tranexamic Acid Modified-Release Tablets, 650 mg

Manufacturing Site	Contact	Tasks Performed
[Redacted] CFN# [Redacted]	Director, Regulatory Submissions Telephone: [Redacted] Fax: [Redacted] Email: [Redacted]	[Redacted]
[Redacted] Site	Director, Regulatory Submissions Telephone: [Redacted] Fax: [Redacted] Email: [Redacted]	[Redacted]
Testing Sites:	Contact	
[Redacted] CFN# [Redacted]	Director, Regulatory Submissions Telephone: [Redacted] Fax: [Redacted] Email: [Redacted]	[Redacted]
[Redacted]	Associate Director, Quality Assurance	[Redacted]
[Redacted]	Director, Quality Assurance	[Redacted]
[Redacted]	Bioburden and General Microbiology Manager	[Redacted]
[Redacted]	Manager, Specialty & Applied Chemistry	[Redacted]
[Redacted]	QA Manager	[Redacted]

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Comment: The EER was submitted on 04-Feb-2009 by Gene Holbert.

SPECIFICATIONS

The drug product quality is controlled by the following specifications.

Table 1: Finished Product Specifications for Tranexamic Modified-Release Tablets, 650 mg

Test	Specifications
	MF 1036B
Description	White to off-white, oval shaped, plain on one side and "XP650" debossed on the other side
<i>Analytical Procedure</i>	<i>(RDMF1036B) Visual</i>
Identification	RT of the peaks in the sample solutions must correspond with RT of standards.
<i>Analytical Procedure</i>	<i>(RDMF1036B)</i>
ASSAY: Tranexamic Acid 650 mg	_____
<i>Analytical Procedure</i>	<i>(RDMF1036B)</i> <i>HPLC</i>
RELATED SUBSTANCES	
Individual Unknowns Total Related Substances	NMT _____ NMT _____
<i>Analytical Procedure</i>	<i>(RDMF1036B)</i> <i>HPLC</i>
CONTENT UNIFORMITY: Tranexamic Acid 650 mg	USP Limits*
<i>Analytical Procedure</i>	<i>(RDMF1036B)</i>
DISSOLUTION: Tranexamic Acid 650 mg	15 minutes NMT _____ 45 minutes _____ 90 minutes NLT _____
<i>Analytical Procedure</i>	<i>(RDMF1036B)</i> <i>HPLC</i>
Hardness	_____
<i>Analytical Procedure</i>	<i>(FPPG003)</i>
Residual Solvents	Product complies with USP <467>, Option 1

b(4)

b(4)

b(4)

b(4)

b(4)

*USP Limits for Content Uniformity are as follows:

SI: for 10 tablets, AV ≤ 15.0 SII: for 30 tablets, AV ≤ 25.0, no dosage units less than _____ or more than _____

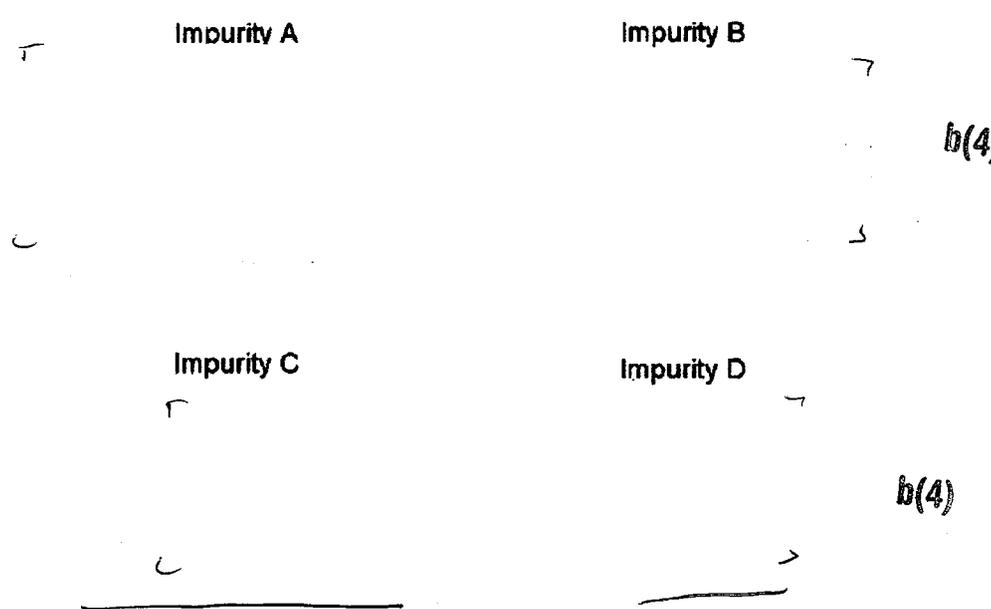
The sponsor has provided a copy of the analytical procedures and the validation reports. Batch analysis is also provided. The sponsor provides the following information concerning related substances.

Table 3: Identifiable Impurities in Tranexamic Acid Modified-Release Tablets, 650 mg

Common Name	Other Nomenclature	Name	Process Impurity or Degradant
Impurity A			Process Impurity
Impurity B			Process Impurity
Impurity C			Process Impurity
Impurity D			Process Impurity

b(4)

Figure 3. Tranexamic Acid Impurities



b(4)

b(4)

The sponsor has provided the following justification for the impurity specification:

Related Substance: The individual unknown related substances specification is NMT _____ each in accordance with the ICH guidelines. The TDI is _____ so the identification threshold is the reporting limit and the limit of quantitation will be _____. The total related substances specification is NMT _____ based on the drug substance total related substances specifications.

b(4)

Comment: While the individual impurity acceptance criteria are set based on ICH guidelines, it may not be appropriate to set the total limit based on addition. This is not only a CMC review issue, but should also be discussed with the toxicology reviewer. The sponsor should clarify if these impurities are only drug substance process impurities and are therefore not controlled in the drug product, or if these are also degradation products and are included in the Related Substances specification under "Individual Unknowns".

Dissolution specifications will need to be carefully reviewed to see if they have been appropriately set.

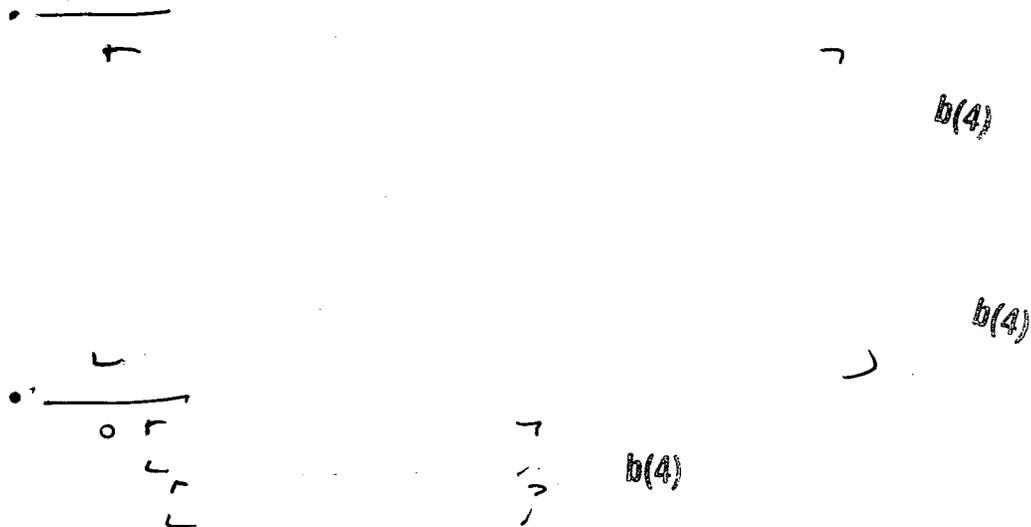
CONTAINER CLOSURE SYSTEM

Drug product is packaged either in HDPE bottles or blisters. Information is provided in the application and referenced DMFs.

Comment: Information is adequate for review

STABILITY

The sponsor has submitted an extensive stability package. They request a 36 month expiration dating period for the 100-count bottle and a 24 month expiration dating period for the 6, 30, and 500 count bottle and the blister pack, based on the following data:



- 30 count bottle
 - 1 lot of drug product
 - 24 months at 25°C/60% RH
 - 12 months at 30°C/65% RH
 - 6 months at 40°C/75% RH
 - 3 lots of drug product
 - 12 months at 25°C/60% RH
 - 12 months at 30°C/65% RH
 - 6 months at 40°C/75% RH
 - 1 lot of drug product split between debossed and non-debossed
 - Debossed: 3months at 25°C/60% RH and 40°C/75% RH
 - Non-debossed: 3months at 25°C/60% RH
- 100 count bottle
 - 1 lot of drug product
 - 48 months at 25°C/60% RH
 - 12 months at 30°C/65% RH
 - 6 months at 40°C/75% RH
 - 3 lots of drug product
 - 36 months at 25°C/60% RH
 - 12 months at 30°C/65% RH
 - 6 months at 40°C/75% RH

- 1 lot of drug product
 - 24 months at 25°C/60% RH
 - 12 months at 30°C/65% RH
 - 6 months at 40°C/75% RH
- 3 lots of drug product
 - 12 months at 25°C/60% RH
 - 12 months at 30°C/65% RH
 - 6 months at 40°C/75% RH
- 1 lot of drug product split between debossed and non-debossed
 - Debossed: 3months at 25°C/60% RH and 40°C/75% RH
 - Non-debossed: 3months at 25°C/60% RH
- 500 count bottle
 - 1 lot of drug product
 - 24 months at 25°C/60% RH
 - 12 months at 30°C/65% RH
 - 6 months at 40°C/75% RH
 - 3 lots of drug product
 - 12 months at 25°C/60% RH
 - 12 months at 30°C/65% RH
 - 6 months at 40°C/75% RH
 - 1 lot of drug product split between debossed and non-debossed
 - Debossed: 3months at 25°C/60% RH and 40°C/75% RH
 - Non-debossed: 3months at 25°C/60% RH
- PVC blister
 - 1 lot of drug product
 - 24 months at 25°C/60% RH
 - 12 months at 30°C/65% RH
 - 6 months at 40°C/75% RH
 - 3 lots of drug product
 - 12 months at 25°C/60% RH
 - 12 months at 30°C/65% RH
 - 6 months at 40°C/75% RH
 - 1 lot of drug product split between debossed and non-debossed
 - Debossed: 3months at 25°C/60% RH and 40°C/75% RH
 - Non-debossed: 3months at 25°C/60% RH
-  blister
 - 1 lot of drug product
 - 24 months at 25°C/60% RH
 - 12 months at 30°C/65% RH
 - 6 months at 40°C/75% RH
 - 3 lots of drug product
 - 12 months at 25°C/60% RH
 - 12 months at 30°C/65% RH
 - 6 months at 40°C/75% RH
- Bulk storage
 - 1 lot of drug product for 6 months at 25°C/60% RH
 - 3 lots of drug product for 12 months at 25°C/60% RH
 - 1 lot of drug product split between debossed and non-debossed
 - Debossed for 3months at 25°C/60% RH
 - Non-debossed for 3months at 25°C/60% RH

b(4)

Comment: Information is adequate for review

LABELING

Container labels are provided for all HDPE bottles and the carton label is provided for the blister packages. A copy of the blister card is not provided and should be submitted. The PI contains adequate information to review from the CMC standpoint, including the DLDE table.

***Comment:** A copy of the blister card should be submitted. Clarification should be provided on whether the HDPE bottles will be packaged in cartons, and if so, carton labels should be provided.*

Discussions were held with the primary reviewer, Gene Holbert, Ph.D., after the filing meeting concerning the dosage form name. The following comment was included in the 74-day letter.

***Comment:** Please be aware that "Modified Release Tablets" is not a recognized dosage form for purposes of labeling. "Extended Release Tablets" may be more appropriate for our product, but final determination will be made during the NDA review and will be conveyed with other carton and container label comments.*

ENVIRONMENTAL ASSESSMENT

An EA has been provided and has been consulted to the Office of Pharmaceutical Science.

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

/s/

Donna Christner
4/13/2009 09:33:32 AM
CHEMIST

Hard copy signed on 27-Feb-2009.

Moo-Jhong Rhee
4/13/2009 10:19:06 AM
CHEMIST
Chief, Branch III