CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207962Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approve

NDA 207962
Review #2

Drug Name/Dosage Form	**Ztlido™ (Lidocaine Topical System 1.8%)**
Strength	**1.8%**
Route of Administration	Topically
Rx/OTC Dispensed	Rx
Applicant	**Scilex Pharmaceuticals, Inc.**
US agent, if applicable	

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Erika England	OPQ/ONDP/DNDAPI/BII
Drug Product	Erika England	OPQ/ONDP/DNDAPI/BII
Process	James Norman	OPQ/OPF/DPAII/BV
Microbiology	N/A	OPQ/OPF/DPAII/BV
Facility	Cassandra Abellard	OPQ/OPF/DIA/BII
Biopharmaceutics	Kalpana Paudel	OPQ/ONDP/DB/BII
Regulatory Business Process Manager	Steve Kinsley	OPQ/OPRO
Application Technical Lead	Ciby Abraham	OPQ/ONDP
Laboratory (OTR)	N/A	
ORA Lead	Caryn McNab	ORA/OGROP
Environmental Assessment (EA)	N/A	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type II	(b) (4)	(b) (4)	Adequate	1/27/2017	Adequate. Reviewed by Erika E. Englund, Ph.D.
	Type IV			Only adequate to support NDA 207-962	1/16/2018	Reviewed by Erika E. Englund, Ph.D.
	Type IV			Adequate	11/09/2017	Adequate. Reviewed by Erika E. Englund, Ph.D.
	Type III			Adequate	12/27/2017	Reviewed by Erika E. Englund, Ph.D.
	Type III			Adequate	3/16/2016	Adequate. Reviewed by Erika E. Englund, Ph.D.
	Type III			Adequate	1/20/2016	Adequate. Reviewed by Erika E. Englund, Ph.D.

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation and Conclusion on Approvability

Based on the recommendations from drug substance, drug product, biopharmaceutics, process, and the office of compliance/CDRH-OC, we recommend approval from a Chemistry, Manufacturing, and Control (CMC) perspective.

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

N/A

II. A. Description of Drug Substance and Drug Product

The drug substance, Lidocaine is manufactured by [redacted] (b) (4) and is referenced in DMF# [redacted] (b) (4) (adequate, last reviewed 1/27/2017). Lidocaine is a white or almost white crystalline powder that is insoluble in water. Lidocaine is packaged [redacted] (b) (4) Lidocaine has a [redacted] (b) (4) month retest period when stored at [redacted] (b) (4) °C.

The drug product, Ztildo (lidocaine topical system) is manufactured by Oishi Koseido Co., Ltd. Ztildo contains 36 mg of lidocaine drug substance compounded in an anhydrous adhesive system intended for topical route of administration. The drug product comprises of an adhesive material containing lidocaine that is applied to a nonwoven cloth and covered with a polyethylene terephthalate release liner. The drug product contains 1.8% lidocaine in a 10 x 14 cm topical system, which can be cut into smaller sizes prior to removal of the release liner. Up to 3 topical systems may be applied for up to 12 hours in a 24 hour period. The applicant performed residual drug analysis on used patches (includes residuals from the skin and liners/envelopes) and a total of 18.44 mg of lidocaine was obtained for the 36 mg topical system.

Table 6.1 Summary of Residual Drug Analysis in Study SCI-LIDO-PK-002A

Component	Residual Drug (mg/patch)	
	Lidocaine Patch 1.8%	Lidoderm® Patch 5%
Used patches	17.70±2.96	521.3±48.05
Skin	0.53±0.21	4.37±1.69
Liners/envelopes	0.22±0.02	0.20±0.03
Total	18.44±2.94	525.9±48.02

] Appears this way on original

The extractables/leachables were reviewed and found adequate by Dr. Erika Englund. Below is a summary of her extractables/leachables review: "The extractables study was conducted with the release liner, cloth backing, adhesive (b) (4), and envelope striped with an excess of (b) (4) inks used in the commercial packaging (study (b) (4) 0353). The components were extracted in an oven at 40°C for 48 hours in two separate solvent systems: (1) 0.9% w/v saline solution and (2) 70:30 isopropyl alcohol and 0.9% saline. The extracts were then tested by GC-MS, LC-MS (positive and negative ion mode and UV detection) and ICP-OES (inductively coupled plasma optical emission spectrometry). The only elemental impurity above the PDE in the extractables study was (b) (4), and this was due to a suspected (b) (4) contamination (refer to document (b) (4) 053-01). The measured level of (b) (4) extracted from the iso-propanol and saline solution was (b) (4) mcg/system. This level of (b) (4) was not considered a potential safety issue by the non-clinical reviewer Armaghan Emami, Ph.D. No other elemental impurities were near the PDE. Since there were no elements detected in ICP-OES that were identified as a safety concern, the applicant's proposal to not use this analytical method in the leachables study is acceptable from a CMC perspective. The agency had agreed that various batches at different time points could be used to support the 24 month shelf life, and based on the totality of evidence new batches of drug product might not be necessary to be placed on stability for the current NDA review. Three different drug product batches were tested at 3 month, 18 month, and 38 month testing points. Three expired batches at the 55 month time point were tested. The individual components in the formulation were tested for residual monomers and dimers. The only two detected (above (b) (4) ppm) were (b) (4). In 2.3.P.2 the sponsor described that residual monomers were not detected in leachables analysis of the drug product. The description of the leachables/extractables study is adequate."

Dr. Le Zhang reviewed the in vivo adhesion study and found it to be adequate. Below is Dr. Le Zhang's conclusion on the in vivo adhesion study: "The study was suitably conducted for adhesion assessment (i.e. consistently spaced observations throughout wear period, no overlays, adhesive tapes, bandages or similar products were applied during the application period, etc.). The adhesion analysis included all topical systems from 54 subjects and no systems were removed early for unacceptable irritation or dropped out of the study before the end of the 12-hour application. The clinical study report for study SCI-LIDO-ADH-001 was provided in Section 5.3.5.4. A single lidocaine topical system (1.8%) applied over a predetermined fixed area on subject's left side or right side of the back (lower/mid back) according to randomization schedule and worn for the 12-hour study period. Adhesion assessment was done immediately after application (0 hour) and at 3, 6, 9 and 12 (before removal) hours after application with a window period ±15 minutes. The adhesion scores for all subjects are either 0 or 1, with 96% of 0's and 4% of 1's, indicating at least 75% adhesion for all systems at all times with 95% lower confidence limit 94.6%."

An expiry of 24 months at 25°C/ (b) (4) % RH is granted for Ztildo.

Final Risk Assessment

Executive Risk Assessment Summary

From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	Factors that can impact the CQA	Risk Ranking*	Risk Mitigation Approach	Risk Evaluation	Lifecycle Considerations/ Comments**
Assay, stability	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	-	N/A	
Physical stability (API)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	-	N/A	
Content uniformity	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	-	N/A	
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment	L	-	N/A	
In Vitro Dissolution	• Formulation • Raw materials • Process parameters • Scale/equipment • Site • Exclude major reformulations • Alcohol dose dumping	L	-	N/A	

*Risk ranking applies to product attribute/CQA

**For example, post marketing commitment, knowledge management post approval, etc.

Application Technical Lead Signature:

Ciby J. Abraham, Ph.D.
Quality Assessment Lead (Acting)
ONDP/DIV II/Branch IV

NDA 207962
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Recommendation: Approval
NDA: 207962

NDA 207962
Review #2

Drug Name/Dosage Form	**ZTlido™ (Lidocaine topical system 1.8%)**
Strength	**1.8%**
Route of Administration	**Topical System**
Rx/OTC Dispensed	**Rx**
Applicant	**Scilex Pharmaceuticals, Inc.**
US agent, if applicable	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. Referenced DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	REVIEW DATE	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	Adequate	01/27/2017	Reviewed by David Skanchy, Ph.D.
	IV			Only adequate to support NDA 207-962	01/16/2018	Reviewed by Erika E. Englund, Ph.D.
	IV			Adequate	11/09/2017	Reviewed by Erika E. Englund, Ph.D.
	III			Adequate	12/27/2017	Reviewed by Erika E. Englund, Ph.D.
	III			Adequate	3/16/2016	Reviewed by Erika E. Englund, Ph.D.
	III			Adequate	01/20/2016	Reviewed by Erika E. Englund, Ph.D.

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R.3 Environmental Assessment

Reviewer's Assessment:

In the original NDA, the reference to CFR 25.31(e) was submitted for the environmental assessment. This was not appropriate because this is for action on an IND. The following deficiency was sent in CR Letter #1:

The Environmental Assessment reference included in your submission is for the INDs. Provide an applicable CFR reference for the NDA, and include required information for the Environmental Assessment.

The applicant responded on 08/28/2017 and cited CFR 25.31(b) for the environmental assessment and calculated that the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 ppb. This response is adequate.

OVERALL ASSESSMENT AND SIGNATURES: DRUG PRODUCT

Reviewer's Assessment and Signature:

The responses to the deficiencies from CR Letter #1 are adequate. The requested shelf life of 24 months at 25°C/ (b) (4) % RH is adequate. This NDA is recommended for approval from a drug product perspective.

Erika E. Englund, Ph.D.

Secondary Review Comments and Concurrence:

I concur with Dr. Englund's assessment that the information on the drug product supports approval of the NDA.

Donna F. Christner, Ph.D.
Branch Chief (Acting)
DNDAPI

13-Jan-2018

Erika Englund

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Donna Christner

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Recommendation: Approval
NDA: 207962

NDA 207962
Labeling Review #2

Drug Name/Dosage Form	**ZTlido™ (Lidocaine topical system 1.8%)**
Strength	**1.8%**
Route of Administration	**Topical System**
Rx/OTC Dispensed	**Rx**
Applicant	**Scilex Pharmaceuticals, Inc.**
US agent, if applicable	

1) Immediate Container Label

(b) (4)

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Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	ZTlido (lidocaine topical system) 1.8%	Adequate. Refer to discussion of dosage form below.
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	1.8%	Adequate
Route of administration 21.CFR 201.100(b)(3))	Topical	Adequate
Net contents* (21 CFR 201.51(a))	1 topical system	Adequate
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	The inactive ingredients are listed: butylated hydroxytoluene, (b) (4) glycol, isostearic acid, mineral oil, polyisobutylene, silicon dioxide, styrene/isoprene/styrene block copolymer and terpene resin	Adequate
Lot number per 21 CFR 201.18	Space was provided on the pouch for lot number	Adequate
Expiration date per 21 CFR 201.17	Space was provided on the pouch for expiration date	Adequate
"Rx only" statement per 21 CFR 201.100(b)(1)	Rx only included on the pouch	Adequate
Storage	Storage conditions listed as 25 °C (77 °F), excursions permitted to 15-30 °C (59-86 °F)	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	NDC number listed as 69557-111-01 for the commercial product, and 69557-111-99 for the professional sample.	The PI lists NDC number as 69557-111-30. Which is the NDC for the container carton
Bar Code per 21 CFR 201.25(c)(2)***	Space was provided for the bar code on the commercial product pouch	Adequate
Name of manufacturer/distributor (21 CFR 201.1)	Scilex was listed on the pouch	Adequate
Others	The Professional Sample includes a statement that product is not for resale. Other information on pouch was the same.	Adequate

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.

**For solid oral dosage forms, CDER policy provides for exclusion of "oral" from the container label
**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion:

The immediate container labels from the 11/17/2017 amendment are copied above. The dosage form name was discussed with Yana Mille and Jibril Abdus- Samad from OPPQ. Jibril Abdus- Samad responded via e mail on 09/01/2017 that the dosage form should be described as a topical system. The applicant received an IR on 11/03/2017 that the labeling should be updated to describe the product as a topical system. The name now states "lidocaine topical system"; however, the content statement referred to "(b) (4)". The following comment was sent to the applicant to update the labeling to describe the contents as "1 topical system."

The content statements on the pouch and carton currently describe the number of (b) (4) The content statement should replace "(b) (4)" with "topical system."

The applicant sent the updated images of the pouches via e mail on 2/22/2018 (copied above). The requested changes were made, and this is adequate.

The NDC numbers were included on the pouches, cartons and PI. The NDC number on the commercial product carton is consistent with the NDC in the PI. This is adequate from a CMC perspective.

The strength for ZTlido is listed in terms of the concentration of lidocaine (1.8%) throughout the labeling. This is consistent with Lidoderm, which also lists the strength as a concentration (5% lidocaine). The representation of strength is adequate from a CMC perspective.

ZTlido is proposed to be bioequivalent to Lidoderm; however, the percentage of

lidocaine in the products is different. Refer to the clinical pharmacology review regarding the bioequivalence of the products. ZTlido contains 1.8% lidocaine, whereas Lidoderm contains 5 % lidocaine. The labeling group communicated on 01/03/2018 that there should be an equivalency statement on the product, similar to the salt equivalency statement. After further discussion with the OND and OPPQ groups, Jibril Abdus-Samad sent an e mail on 01/29/2018 that OPPQ's recommendation is to include an equivalency statement that specifically describes Lidoderm. The recommended equivalency statement is copied below.

One ZTlido (lidocaine topical system) 1.8% provides equivalent lidocaine exposure to one Lidoderm® (lidocaine patch 5%).

OPPQ recommended that this labeling statement be placed on the container label and carton labeling. (b) (4) . The justification was that the equivalency statement provides additional information about exposure comparison to Lidoderm for dosage recommendations. The following comment was sent to the applicant to include the equivalency statement on the container and carton labeling:

Include the equivalency statement below on the container label and carton labeling. Refer to the comments from the PI for the location of the equivalency statement in the PI.

**One ZTlido (lidocaine topical system) 1.8% provides equivalent lidocaine exposure to one Lidoderm® (lidocaine patch 5%).*

In the updated pouch image sent on 2/22/2018, the applicant made the requested change. This is adequate.

2) Carton Labeling

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Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	ZTlido (lidocaine topical system) 1.8%	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))	1.8%	Adequate
Net contents (21 CFR 201.51(a))	3 pouches (professional sample) or 30 pouches for the commercial product	Adequate
Lot number per 21 CFR 201.18	Lot number included on carton	Adequate
Expiration date per 21 CFR 201.17	Expiration date included on carton	Adequate
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(d)(2)]	The inactive ingredients are listed: butylated hydroxytoluene, (b) (4) glycol, isostearic acid, mineral oil, polyisobutylene, silicon dioxide, styrene/isoprene/styrene block copolymer and terpene resin	Adequate
Sterility Information (if applicable)	The product is not sterile	Adequate
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)	Rx only is included on the carton	Adequate
Storage Conditions	Storage conditions listed as 25 °C (77 °F), excursions permitted to 15-30 °C (59-86 °F)	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	The NDC Code on the commercial product is 69557-111-30, and is 69557-11-03 on the professional sample	Adequate
Bar Code per 21 CFR 201.25(c)(2)**	Space was provided for the bar code on the commercial product carton	Adequate
Name of manufacturer/distributor	Scilex was listed on the carton	Adequate
"See package insert for dosage information" (21 CFR 201.55)	Carton states: "for dosage and full prescribing information, please read accompanying product information"	Adequate
"Keep out of reach of children" (optional for Rx,	The carton states to keep out of reach of children, pets, and others	Adequate

required for OTC)		
Route of Administration (not required for oral, 21 CFR 201.100(d)(1) and (d)(2))	Topical Route of administration	Adequate

The labeling from the 11/17/2017 amendment is copied above. The storage conditions and inactive ingredients for the PI are consistent with the pouch and carton. The equivalency statements were added to the carton, and the content was updated to list "topical systems" instead of "(b) (4)". Refer to the discussion above concerning replacing the word "(b) (4)" with "topical system" in the content statement. In addition, refer to the comment above about the equivalency statement. This is adequate.

In the previously submitted labeling, the cartons included a space for the lot and expiration date. In the carton labeling that was subsequently submitted, the lot number and expiration date were not included. The following comment was sent:

We acknowledge that previously the carton labeling included the lot and expiration date; however, the 11/17/2017 carton labeling did not include this information. Include the lot number and expiration date on the cartons.

The updated cartons images received via e mail on 2/22/2018 included the recommended changes. This is adequate.

PI:

The PI submitted on 11/17/2017 had updated the dosage form to lidocaine topical system, as requested on 11/03/2017. Refer to the discussion of the dosage form above. Only a single strength is available, and only the 1.8% topical system is described in Dosage forms and strengths. This is adequate.

The description section of the PI describes the product as a "(b) (4)" This section also describes the total quantity of lidocaine in the system (36 mg) and lists all of the inactive ingredients. This information is consistent with the

information submitted to the NDA.

In the how supplied section, the NDC number for the 30 topical system carton is listed, and storage at USP controlled room temperature is described for the product. This information is consistent with information included in the NDA.

The container closure system is described as child-resistant envelopes in section 16. The container closure system for this product is a sealed envelope, which is opened with scissors. Lidoderm is also supplied in child resistant sealed envelopes that are cut open with scissors. The description of the product in the PI is adequate.

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature:

The applicant included the recommended edits to the labeling. The labeling is adequate from a CMC perspective.

Erika E. Englund, Ph.D.

Secondary Review Comments and Concurrence:

I concur with Dr. Englund's assessment that the labeling is adequate fron the CMC perspective.

Donna F. Christner, Ph.D.
23-Feb-2018

Erika Englund

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Donna Christner

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Quality In Vivo Adhesion Assessment

NDA No.:	207962
Date Received by FDA:	08/28/2017
Drug Name:	ZTlido™ (Lidocaine topical system 1.8%)
Indication:	Relief of pain associated with post-herpetic neuralgia
Sponsor:	Scilex Pharmaceuticals Inc.
Review Type:	In vivo Adhesion Assessment
Review Finished:	01/04/2018
TDWG Reviewer:	Le Zhang, Ph.D.
Consults:	Office of Biostatistics Statistical Review: Biometrics Division VI 10/03/2017– Meiyu Shen, Ph.D. and Chao Wang, Ph.D.
CONCLUSION AND QUALITY RECOMMENDATION:	From a quality perspective, the formulation and product design of the drug product used in clinical study SCI-LIDO-ADH-001 demonstrates adequate in vivo adhesion.

Background: The purpose of this review is to assess the in vivo adhesion performance of ZTlido™ (lidocaine topical system 1.8%). On behalf of Scilex Pharmaceuticals Inc. (Scilex), Clinipace Worldwide resubmitted this 505(b)(2) New Drug Application for ZTlido™ (lidocaine topical system 1.8%) for the treatment of pain associated with post-herpetic neuralgia (PHN) in response to the Complete Response Letter (CRL) received on May 10, 2016. The resubmission was received by FDA on August 28, 2017.

Study SCI-LIDO-DERM-001 (DS103214): A Multi-center Phase I, Repeat Insult Patch Test and Adhesion of Lidocaine Topical System 1.8% and its Comparator Lidocaine Patch 5% (Lidoderm®) in Healthy Subject was conducted for NDA 207-962. The 74-day letter dated September 22, 2015 pointed out the deficiency about the adhesion data in this study. To address the deficiency regarding to the adhesion and to support the adhesion of the proposed formulation, the sponsor conducted Study SCI-LIDO-ADH-001 ((b) (4) Study No. A15.0168), an open label, single-treatment, single-period, single-application, adhesion performance study of lidocaine topical system 1.8% in healthy, adult, human subjects. The study was conducted in accordance with advisement received October 15, 2015. In the advisement received October 15, 2015, it noted, "There is no need for a Lidoderm study group in the same study." Therefore, there is no reference product in Study SCI-LIDO-ADH-001.

The adhesion analysis included all topical systems from 54 subjects and no systems were removed early for unacceptable irritation or dropped out of the study before the end of the 12-hour application. The clinical study report for study SCI-LIDO-ADH-001 was provided in Section 5.3.5.4. A single lidocaine topical system (1.8%) applied over a predetermined fixed area on subject's left side or right side of the

back (lower/mid back) according to randomization schedule and worn for the 12-hour study period. Adhesion assessment was done immediately after application (0 hour) and at 3, 6, 9 and 12 (before removal) hours after application with a window period ±15 minutes. The drug product was checked for degree of adhesion by the trained scorer according to the scoring system recommended in the FDA guidance, Assessing Adhesion with Transdermal Delivery Systems and Topical Patches for ANDAs (hereafter referred to as the Guidance):

- 0: ≥90% adhered (essentially no lift off the skin),
- 1: ≥75% to < 90% adhered (some edges only lifting off the skin),
- 2: ≥50% to < 75% adhered (less than half of the TDS lifting off the skin),
- 3: > 0% to < 50% adhered (not detached, but more than half of the TDS lifting off the skin without falling off),
- 4: = 0% adhered (TDS detached; completely off the skin).

Reviewer's Assessment: The study was suitably conducted for adhesion assessment (i.e. consistently spaced observations throughout wear period, no overlays, adhesive tapes, bandages or similar products were applied during the application period, etc.) It is notable the study design differs from that laid out in the Product Specific Draft Guidance for Lidocaine topical patches (i.e. BE draft guidance for lidocaine topical systems followed by generic applicants). That guidance, refers specifically to lidocaine 5% as it is the only currently approved strength for any lidocaine topical system. ZTlido consists of an adhesive system containing 1.8% lidocaine (36 mg lidocaine in the proposed formulation) in a single-layer adhesive. Bioequivalence (BE) between ZTlido (1.8%) and Lidoderm (5%) has been established.

Statistical Consult for Adhesion Evaluation:

A statistical consult was requested to assess the adhesion data of SCI-LIDO-ADH-001. Information from the study was assessed by the Office of Biostatistics. Refer to the Biostatistics Consult response dated Dec. 29, 2017 for full details.

statistical_review.pdf

In summary:

- The adhesion scores for all subjects are either 0 or 1, with 96% of 0's and 4% of 1's, indicating at least 75% adhesion for all systems at all times with 95% lower confidence limit 94.6%.

• The point estimate of the proportion of subjects having at least 90% adhesion, i.e., adhesion score being 0, throughout the study, is 87.04% with 95% lower confidence limit 79.52%. The sponsor claimed that "greater than 90% of subjects had 90% adhesion". However, the analysis performed by the Office of Biostatistics showed that the claim is not correct.

• At each of 0, 3, 6, 9, 12 hour, the point estimate of the probability of a system having adhesion score 0 point is greater than 90%. However, the 95% lower confidence limit is below 90% at hour 9 and hour 12.

• The following criterion for assessing adhesion is recommended. For given significance level = 0.05, the probability of a system having a maximum adhesion score being 0 and 1 throughout the entire wear period should be at least 75% and 90% respectively. This requires the 95% lower confidence limit for the probability of a system with a maximum adhesion score being 0 and 1 be greater than 75% and 90% respectively. The data of this adhesion study supports that proposed product passes the criteria.

Individual adhesion scores for all subjects at Right side of the back of Study SCI-LIDO-ADH-001 are listed in the following table:

Individual adhesion scores for all subjects at Right side of the back of Study SCI-LIDO-ADH-001

Subject	Site	0hr	3hr	6hr	9hr	12hr
(b) (4)						

Individual adhesion scores for all subjects at Left side of the back of Study SCI-LIDO-ADH-001 are listed in the following table:

Individual adhesion scores for all subjects at Left side of the back of Study SCI-LIDO-ADH-001

Subject	Site	0hr	3hr	6hr	9hr	12hr
(b) (4)						

The sponsor stated in their report that the primary endpoint of adhesion was the Cumulative Adhesion Score (CAS) during the 12-hour application period (i.e. the CAS for a specific subject was the sum of the adhesion scores recorded immediately after the drug product had been applied (0 hour) +3, +6, +9, and +12 hours after application). Descriptive statistics (e.g. mean, standard deviation, median, minimum and maximum) on CAS was generated. Mean CAS (i.e. score obtained by dividing the CAS with total number of observations) was provided. Descriptive statistics (e.g. mean, standard deviation, median, minimum and maximum) on mean CAS was generated.

Reviewer's Assessment: Usually the CAS and the Mean CAS are not good indication of adhesion since different combinations of adhesion scores could yield the same CAS. However, the adhesion scores for all subjects in this study are either 0 or 1. Just for this study, the CAS and the Mean CAS are directly related to the percentage of adhesion score of 1 in all the observations.

Individual Cumulative & Mean adhesion scores of all subjects are provided in the following table:

Individual Cumulative & Mean adhesion scores of all subjects

Subject	Site	Cumulative Adhesion Score	Mean Adhesion Score
(b) (4)			

Subject	Site	Cumulative Adhesion Score	Mean Adhesion Score
[redacted]			

(b) (4)

R= Right side of the back

L= Left side of the back

Descriptive Statistics of Cumulative and Mean adhesion scores of Lidocaine (N=54) and Subjects with meaningful degree of detachment (i.e. score ≥3) are shown in the following table:

Descriptive Statistics of Cumulative and Mean adhesion scores of Lidocaine (N= 54)

Statistics	Cumulative Adhesion Score	Mean Adhesion Score
N	54	54
Minimum	0	0
Maximum	4	1
Mean	0.22	0.04
SD	0.691	0.138
CV(%)	311.1	311.1

Subjects with meaningful degree of detachment (i.e. score ≥ 3):

Site*	No. of Subjects	Proportion of Subjects (%)
R	0	0
L	0	0

** R- Right side of the back; L- Left side of the back.*

Reviewer's Assessment: Although the unofficial gold standard of 90% of all patients having at least 90% adhesion for the duration of wear was not achieved by the proposed drug product, 100% of the population had greater than 75% adhesion at all time points, 100% of the population had mean adhesion score less than 1, and there were no reports of meaningful degree of detachment. The adhesion data supports that the proposed drug product passes the criteria of the probability of a system having a maximum adhesion score being 0 and 1 throughout the entire wear period (i.e. greater than 90% and 75% area adherence respectively), for a given significance level of 0.05.

Overall Recommendation: From a quality perspective, the formulation and product design of the drug product used in clinical study SCI-LIDO-ADH-001 demonstrates adequate in vivo adhesion. As such, quality control parameters (such as (b) (4) release and stability acceptance criterion, (b) (4) specifications) should be based on this clinical batch's in vitro data to ensure adequate product performance batch to batch.

Le Zhang, Ph.D.
OPQ/OLDP/DPMA1/Branch II
01/04/2018

Caroline Strasinger, Ph.D.
OPQ/ONDP/DNDPII/Branch V
01.04/2018

Le Zhang

Digitally signed by Le Zhang
Date: 1/05/2018 10:00:40AM
GUID: 594abf46003a4cb7cc12cf6cfd6d8751

Caroline Strasinger

Digitally signed by Caroline Strasinger
Date: 1/05/2018 10:31:22AM
GUID: 5051dfdd000013b995075b4d54108ed8

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DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Manufacturing & Quality
Physical Medicine, Orthopedic, Neurology, Dental

Date: January 25, 2018

To: Cassandra Abellard, OMPT/CDER/OPQ/OPF/DIA/IABII
Cassandra.abellard@fda.hhs.gov

Julia Pinto, OMPT/CDER/OPQ/ONDP/DNDPII/NDPBIV
Julia.pinto@fda.hhs.gov

Office of Combination Products at combination@fda.gov

RPM: Steven Kinsley

Through: Kendra Y. Jones, Lead Consumer Safety Officer,
DPLC, OC, CDRH

From: Robert Kang, POND, DMQ, OC, CDRH

Applicant: Scilex Pharmaceuticals, Inc.
301 Linden Drive, Ste 300
Malvern, PA 19355
FEI#: 3012645358

Application # NDA 207962

Consult # ICC1700742

Product Name: ZTlido

Combination Product Intended Use: Relief of pain associated with post-herpetic neuralgia (PHN)

Pre-Approval Inspection: **Yes**

Documentation Review: **No Additional Information Required**

Final Recommendation: **Approvable**

The Office of Compliance (OC) at the Center for Devices and Radiological Health (CDRH) received a consult request from CDER to evaluate the applicant's compliance with applicable Quality System Requirements for the approvability of NDA 207962.

PRODUCT DESCRIPTION

The drug product, lidocaine patch, 1.8%, consists of lidocaine drug substance compounded in an anhydrous adhesive patch (NCI Code: C42968) intended for cutaneous route of administration (NCI Code: C38675). The drug product comprises an adhesive material containing 1.8% lidocaine is applied to a nonwoven cloth and covered with a polyethylene terephthalate separator. The release liner is removed prior to application to the skin. The size of the patch is 10 cm x 14 cm. Each adhesive patch contains 36 mg of lidocaine (18 mg per gram adhesive or 1.8%) in an anhydrous base.

REGULATORY HISTORY

The following facilities was identified as being involved in the manufacturing and/or development of the ZTlido in NDA 207962:

1. **Oishi Koseido Co., Ltd.**
   2539-1 Yamaura-Machi
   Tosu, Saga Japan
   FEI# 3010166685

Responsibility – Drug product manufacture; Drug product QC release and testing; Drug product stability testing; Packaging

Inspectional History – An analysis of the firm's inspection history over the past 2 years showed that an initial inspection was conducted from 01/25/2016 to 01/29/2016. The inspection covered drug GMP and was classified OAI.

Inspection Recommendation:

An inspection is required because:

- The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and,
- A recent medical device inspection of the firm has not been performed.

2. **Scilex Pharmaceuticals, Inc.**
   301 Lindenwood Drive, Ste 300
   Malvern PA 19355-1774
   FEI# 3012645358

Responsibility – Drug product applicant/ specification developer

Inspectional History – An analysis of the firm's inspection history over the past 2 years showed it has never been inspected.

Inspection Recommendation:
An inspection is not required because:

- The firm is not responsible for major activities related to the manufacturing and/or development of the final combination. The firm is the licensed initial importer of the combination product, but does not perform any manufacturing activities.

DOCUMENTATION REVIEW
The application was searched for documents pertaining to applicable 21 CFR part 820 regulations for this combination product.

(b) (4)

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RECOMMENDATION

The Office of Compliance at CDRH has completed the evaluation of application NDA207962 and has the following recommendations:

Application NDA207962 is approvable from the perspective of the Medical Device Regulations.

Pre-approval inspections were conducted at two facilities noted below and both were classified NAI with no 483 observations. The inspection report indicated that the Quality System was covered and no deficiencies identified. The areas covered included Product Specifications and Testing, Annual Product Review, Change Control, and Deviations/Investigations (Non-Conformances) which included CAPA. However, it did not specifically discuss (b) (4)

[redacted] (b) (4) It is recommended that the next scheduled inspection (pre or post) cover [redacted] (b) (4) for medical devices.

In addition, the report indicated that process validation (PV) was not completed at the time of the inspection although a draft PV protocol was available for review. The decision for approval in light of an incomplete PV report is deferred to CDER.

Facilities Inspected:

a. Combination Product Contract Manufacturer
   Oishi Koseido Co., Ltd.
   2539-1 Yamaura-Machi
   Tosu, Saga, Japan
   FEI: 3010166685
b. Quality Control Testing Laboratory
   1 Chrome 933 Hon-Machi
   Tosu, Saga, Japan
   FEI: 3006786747

_____

Prepared: RKang: 10/5/17; 11/6/17
Reviewed: KJones: 10/25/17
IR Response Review: RKang: 1/25/18

CTS No.: ICC1700742
NDA 207962

Review Cycle Meeting Attendance:
Month/Day/Year
Month/Day/Year
Month/Day/Year

Inspectional Guidance

CDRH recommends a preapproval inspection under the applicable Medical Device Regulations of
Oishi Koseido Co., Ltd.
2539-1 Yamaura-Machi
FEI: 3010166685

A comprehensive baseline Level 2 inspection is recommended focusing on Management Responsibility (21 CFR 820.20), Purchasing Controls (21 CFR 820.50), CAPA (21 CFR 820.100), Final Acceptance Activities (21 CFR 820.80), and Design Controls (21 CFR 820.30)

Additionally, evaluate the manufacturing activities associated with the manufacturing/assembly of the finished combination product, including in process and final acceptance activities.

REGULATORY STRATEGY

The establishment inspection report (EIR) for the firm should be shared with CDRH (The EIR should be assigned to CDER and then sent to CDRH as a consult for review). If the inspection is being classified Official Action Indicated (OAI), the District should consider recommending appropriate regulatory action with consultation from CDER and CDRH and whether the violation is drug or device related.

Questions regarding this consult should be referred to one of the following individuals:

Primary Contact
Robert Kang, Compliance Officer
POND/DMQ/OC/CDRH
Office of Compliance, WO66 RM 3432
Phone: 301-796-6614

Secondary Contacts (if Primary is unavailable and a timely answer is required)
Kendra Y. Jones
DPLC/OC/CDRH
Office of Compliance, WO66 RM 3631
Phone: 301-796-3917

THIS ATTACHMENT IS NOT TO BE PROVIDED TO THE FIRM OR SHOWN TO THEM DURING THE INSPECTION. THIS ATTACHMENT CONTAINS PREDECISIONAL INFORMATION

BIOPHARMACEUTICS

Product Background:

NDA/ANDA: NDA-207962-ORIG-1-RESUB-24

Drug Product Name / Strength: Lidocaine patch 1.8% (ZTlido™)

Route of Administration: Topical

Applicant Name: Scilex Pharmaceuticals, Inc.

Review Recommendation: **Adequate**

Review Summary:
The proposed drug product, Lidocaine patch 1.8% (ZTlido™) is indicated for the treatment of pain associated with post-herpetic neuralgia (PHN). NDA 207962 was originally submitted on July 10, 2015. The drug release method (Apparatus 5 with water at 32 °C) was found to be acceptable during the review of original submission. However, the complete in vitro drug release stability data for 12 units of the registration lots were not submitted and hence determination of release specifications was pending. A deficiency was sent to provide these data in Agency's Complete Response (CR) letter dated May 10, 2016. On August 28, 2017, the Applicant responded to the deficiency in the current resubmission. The Applicant has provided all the requested in vitro release data. However, the Applicant's release specifications are found to be unacceptable and following specifications are recommended for the release of lidocaine from ZTlido™ patch based on the data provided. The Applicant was requested to acknowledge their acceptance of the following recommended acceptance criteria in the November 3, 2017 Information Request (IR) letter:

10 Minutes	(b) (4) %
30 Minutes	(b) (4) %
120 Minutes	NLT (b) (4) %
180 Minutes	NLT (b) (4) %

The Applicant has provided in vitro skin permeability data in response to a Drug Product deficiency that addressed the potential permeation enhancer capability of (b) (4) excipients. The skin permeability study is found to be acceptable.

On November 17, 2017, the Applicant responded to the above deficiency. The Applicant has accepted the Agency recommended dissolution specifications for Lidocaine patch.

The Applicant's response is acceptable.

List Submissions being reviewed (table): Dissolution data and acceptance criteria

Application 207962 - Sequence 0021 - 0021 (24) 08/28/2017 ORIG-1 /Multiple Categories/Subcategories

Application 207962 - Sequence 0023 - 0023 (26) 11/17/2017 ORIG-1 /Multiple Categories/Subcategories

Highlight Key Outstanding Issues from Last Cycle:

The following deficiency was communicated to the Applicant in the first review cycle:

The FDA recommends implementation of the following in vitro drug release specifications for your drug product based on the submitted data:

10 Minutes (b) (4)%

30 Minutes (b) (4)%

120 Minutes NLT (b) (4)%

180 Minutes NLT (b) (4)%

Acknowledge your acceptance of the above recommended specifications and update the drug product specification tables and other relevant parts of your NDA accordingly.

The Applicant responded to the above deficiency on November 17, 2017. The Applicant has accepted the Agency's recommended acceptance criteria.

Concise Description Outstanding Issues Remaining: None

Drug Release Method and Acceptance Criteria

The Applicant's proposed in vitro release method is provided below. The method was found to be acceptable in the original submission review.

Apparatus	5
Medium	Water
Volume	500 mL
Temperature	32 ± 0.5°C
Rotation speed	50 rpm
Sampling time points (commercial release):	(b) (4) minutes
Replacement volume	4 mL

The proposed drug release acceptance criteria are provided below.

(b) (4) (b) (4)%

(b) (4)%

(b) (4) NLT (b) (4)%

Drug release profiles:

The Applicant provided the following drug release profiles in the original submission.

(b) (4)

However, the complete in vitro drug release stability data of the registration lots were not submitted in the original submission and the following deficiency was communicated to the Applicant in the CR letter:

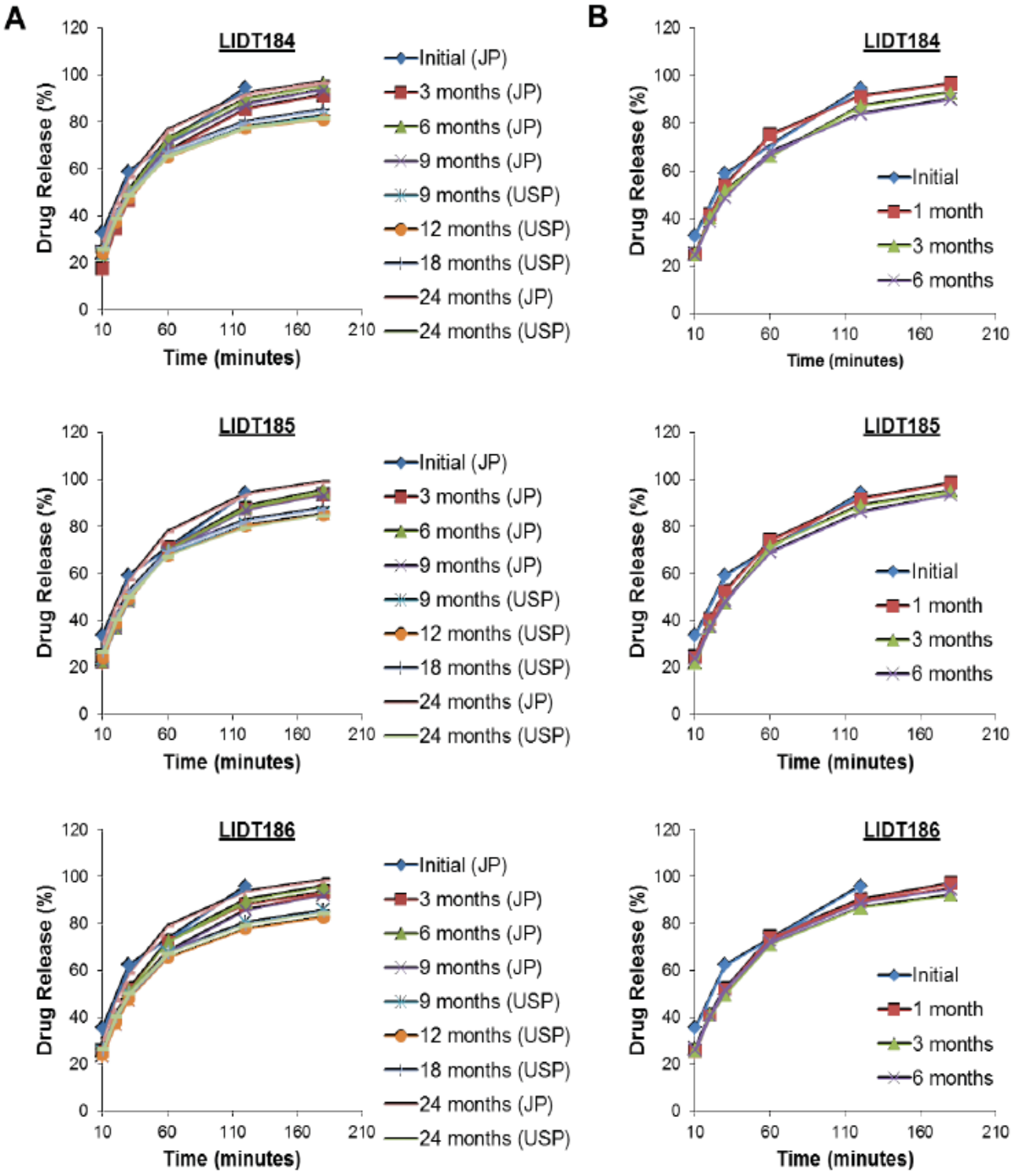
The complete in vitro drug release stability data (individual, mean, standard deviation, and profiles) for at least 12 units of the registration lots were not submitted. To address this deficiency, provide the complete in vitro drug release stability data (individual, mean, standard deviation, and profiles) for at least 12 units of the registration lots.

The Applicant responded to the above deficiency on August 28, 2017 and has submitted the requested data. The in vitro drug release stability results of each registration lot are provided in the Pharmaceutical Development report as identified in the tables below.

Location of Drug Release Data (Summary, Individual Data, and Profiles)

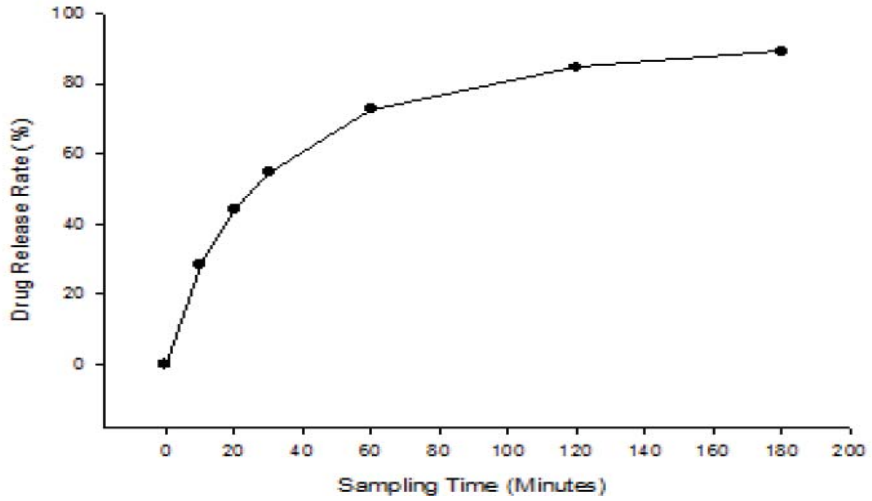
Study	Registration Lots			Clinical Lot
	LIDT184	LIDT185	LIDT186	LIDT187
Release Data (individual and mean)	Table 3.2.P.2.2.41			Table 3.2.P.2.2.52
Summary Stability Data	Table 3.2.P.2.2.42			-
Stability Data (individual, mean, and SD)				
Accelerated	Table 3.2.P.2.2.43	Table 3.2.P.2.2.46	Table 3.2.P.2.2.49	-
Long-term (JP)	Table 3.2.P.2.2.44	Table 3.2.P.2.2.47	Table 3.2.P.2.2.50	-
Long-term (USP <724>)	Table 3.2.P.2.2.45	Table 3.2.P.2.2.48	Table 3.2.P.2.2.51	-
Profiles	Figure 3.2.P.2.2.20			Figure 3.2.P.2.2.21

In vitro Drug Release Profiles of the Registration Lots



In vitro drug release profiles (n=18) of the Registration Lots (LIDT184 – top panel, LIDT185 – middle panel, LIDT186 – bottom panel) after storage at (A) controlled room temperature or (B) accelerated stability conditions for the indicated time periods. Samples stored at controlled room temperature were analyzed by either the JP drug release method or the USP <724> commercial drug release method, as indicated. Samples stored under accelerated stability conditions were analyzed by the JP drug release method.

In Vitro Drug Release Profile of the Clinical Lot (LIDT187)



Summary Drug Product Release Data (JP: 32ºC; Clinical Lot)

Lot Number	Vessel	% Release (Minutes)						
		0	10	20	30	60	120	180
LIDT187	1							(b) (4)
	2							
	3							
	4							
	5							
	6							
	7							
	8							
	9							
	10							
	11							
	12							
	13							
	14							
	15							
	16							
	17							
	18							
	19							
	20							
	21							
	22							
	23							
	24							
	Average	**0.0**	**28.4**	**43.9**	**54.6**	**72.6**	**84.7**	**89.2**
	SD	**0.00**	**2.48**	**3.00**	**2.90**	**3.40**	**3.54**	**3.42**

The Applicant also provided drug release data for batch 21510A that has been used in new BE study SCI-LIDO-PK-002A.

Lidocaine Patch 1.8% Drug Product Release Data (Lot 21510A)

Vessel Number	Drug Release (% Lidocaine)						
	0 minutes	10 minutes	20 minutes	30 minutes	60 minutes	120 minutes	180 minutes
1							(b) (4)
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15							
16							
17							
18							
Average	**0.0**	**30.9**	**46.8**	**58.2**	**76.6**	**88.0**	**91.8**
SD	**0.00**	**2.14**	**2.74**	**3.15**	**3.99**	**4.08**	**3.94**

Based on the data, the Applicant's proposed drug release specifications are too liberal. The following deficiency was sent to the Applicant.

The FDA recommends implementation of the following in vitro drug release specifications for your drug product based on the submitted data:

10 Minutes (b) (4) %

30 Minutes (b) (4) %

120 Minutes NLT (b) (4) %

180 Minutes NLT (b) (4) %

Acknowledge your acceptance of the above recommended specifications and update the drug product specification tables and other relevant parts of your NDA accordingly.

The Applicant has accepted the Agency's recommended acceptance criteria.

In Vitro Permeation Studies

The Applicant has provided In Vitro Permeation Studies results in response to the following deficiency (by drug product reviewer) that was communicated in the CR letter (see Appendix 1):

The justification provided in the December 18, 2015, (section 3.2.P.5.1-) (b) (4)

[redacted] *is inadequate. To address this deficiency, provide justification for why* [redacted] *Provide controls of* [redacted] *in the drug product specifications or additional justification for not testing these in the specifications.*

The skin permeation results were reviewed and are described below.

[redacted]

Human cadaver skin study

To assess the permeation enhancement potential [redacted] on the drug, *in vitro* skin permeation testing was performed on human cadaver skin (3 donors and 2 anatomic sites/donor) over 12 hours with patches manufactured with: [redacted] as shown in the table below. In addition to test patches, a solution of lidocaine dissolved in dimethyl sulfoxide (DMSO) (31.5 µg/µL) was tested as a positive control, given DMSO is a well-established skin permeation enhancer for lidocaine.

Formulation of lidocaine patch test articles

Component	Composition (%)		
	Patch I (No [redacted]) Lot 27605A	**Patch II (Target Levels) Lot 07606A**	**Patch III (x2 Target [redacted]) Lot 09606A**
Dipropylene glycol	[redacted]		
Isostearic acid			
Lidocaine			
Mineral oil			
Polyisobutylene (1,100,000 g/mol)			
Polyisobutylene (55,000 g/mol)			
Silicon dioxide			
Butylated hydroxytoluene			
Terpene resin			
Styrene/isoprene/styrene block copolymer			
Manufacturing dates:	MAY 2016	JUN 2016	JUN 2016

To assess the *in vitro* permeation of lidocaine, patches were applied to dermatomed human skin placed on a vertical glass Franz cell with Sorensen buffer as the receptor fluid. This static cell system was selected to achieve sufficiently high enough permeated drug concentrations in the

receptor fluid within the range of the HPLC analytical method. Sorensen buffer was selected as the receptor fluid based on it being well-established for skin permeation study and it was used in previous nude mouse Franz cell study design (Oishi Report 2016[1]), which allows for comparisons across studies. The dosing period was established at 12 hours consistent with the intended labeled dosing period for the product in the treatment of PHN pain. A validated HPLC method with UV detection was used to determine the permeation rate of the drug through skin and residual drug remaining in the patch at the end of the permeation.

Details of the skin permeation experimental design are outlined in the table below.

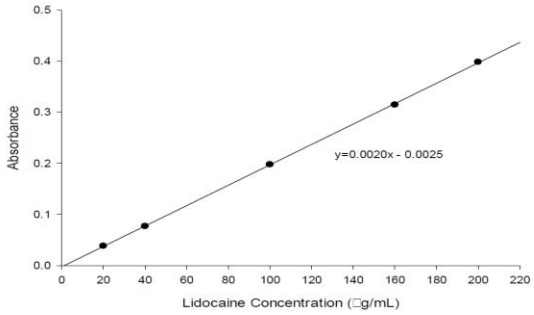
Skin Permeation Experimental Design

Cell	25 mm clear jacketed 4.91 cm^2 vertical Franz cell with flat ground joint, 20 mL receptor volume, stir bar, and clamp ((b) (4))
Receptor fluid	Sorensen buffer at pH 7.4 with 50 µg/mL gentamycin sulfate. Stirred at 37°C.
Stirring speed	600 rpm
Skin	
Species	Human cadaver skin, dermatomed ((b) (4) (b) (4))
Skin surface temperature	32°C
Skin surface area	5 cm^2
Skin storage	0-4°C in plastic bags until use (within 14 days)
Skin integrity	Transepidermal water loss (TEWL) measured with Delfin VapoMeter at 15 minutes prior to topical application. Skin with a value higher than 20 AU were replaced. (du Plessis J 2013)
Formulations	(I) (II) (III) (b) (4) All patches were cut to 4.91 cm^2 (r = 1.25 cm) using a punch Total applied dose: 1.26 mg lidocaine
Positive control	DMSO (1.26 mg lidocaine/40 µL DMSO) (Total applied dose: 1.26 mg lidocaine) Lidocaine: (b) (4) (Lot 557)
Dose	Single application
Patches (I, II, and III)	4.91 cm^2
DMSO control	40 µL
Duration	
Pre-incubation	~1 hour
Dose exposure (permeation period)	12 hours
Sampling	
Time points	0, 2, 4, 8, and 12 hours (all patch samples and DMSO control)
Procedure	1.0 mL aliquot of receptor fluid is withdrawn with a 1.0 cc lock dispensing syringe with 19G blunt tip fill needle 10 cm tubing length through the sampling outlet from the receiving chamber. The same volume of fresh receptor fluid was reinjected into the chamber.
Sample storage	Freezer at -25°C
Used patch storage	Freezer at -25°C

[1]Oishi Koseido Co. Ltd. Pharmaceutical Development Center. "Final Report: Comparative studies on the skin permeability of Lidocaine from ZTlido containing various levels of the (b) (4)." (2016).

The average saturated solubility of lidocaine in Sorensen buffer is 5.3640 mg/mL. Sample solutions from the skin permeation study are within the soluble range of drug in Sorensen buffer if they are <5.360 mg/mL. Maximum concentration of lidocaine measured in the receptor fluid was 0.063 mg/mL, well below the saturation point. The stability and solubility data are provided below.

Lidocaine Sorenson Buffer Solubility (Calibration Curve)



Lidocaine Saturated Solubility in Sorensen Buffer

Buffer	Dilution	Absorbance (ABS)	Lidocaine Concentration (µg/mL)	Saturated Solubility (mg/mL)	Average Saturated Solubility (mg/mL)
Sorensen (pH 7.4)	1/40	0.2633	132.90	5.3160	5.3640
		0.2666	134.55	5.3820	
		0.2672	134.85	5.3940	

Lidocaine Stability in Sorenson Buffer

Time	Average Recovery (%)	
	0.25 µg/mL	50.0 µg/mL
Initial	100.0%	100.0%
2 Weeks	103.9%	106.9%
4 Weeks	98.5%	103.6%

Dermatomed human cadaver skin was obtained from two anatomical sites: thigh and trunk (abdomen and/or chest) from three donors. All skin thickness was within the desired range of 0.22±0.04 mm (trunk) and 0.38±0.03 mm (thigh). Skin was not used if older than 14 days, damaged, or had irregularities (scar tissue, holes, birthmarks, etc.). No skin was accepted from donors with hepatitis, HIV, or AIDS. The trunk skin was all collected from the upper abdomen area.

Analytical method

Lidocaine HPLC Method

High Performance Liquid Chromatograph	Agilent HP 1100 or equivalent
Column	XTerra® RP15 5 µm, 15 x 3.9 mm (Waters or equivalent)
Column temperature	40°C
Mobile phase	Solution A and acetonitrile (3:2)
Solution A	Dissolved 9.7 g potassium dihydrogenphosphate and dilute with water to 1900 mL. Adjusted with 40% w/w sodium hydroxide to pH 8.0 and dilute to volume (2000 mL) with water. Filtered through 0.5 µm membrane filter.
Flow rate	0.9 mL/minute
Injection volume	20 µL
Detector	UV at 230 nm
System suitability	≤2.0% RSD
Standard	Lidocaine analytical standard
Supplier	(b) (4)
Lot number	SLBJ7206V
Storage condition	Room temperature

The method was fully validated for the nude mouse model study with the following parameters: specificity, limit of detection (LOD), limit of quantitation (LOQ), linearity, accuracy, range, precision (repeatability and intermediate), stability of injection sample solution, and system suitability. A summary of validation results is presented below.

Lidocaine HPLC Method Validation Summary

Specificity	Lidocaine is adequately resolved from components of Sorensen buffer and placebo (see Figure 3.3, Figure 3.4, Figure 3.5, and Figure 3.6)			
Range	0.125 – 50 µg/mL (1 – 200% of target concentration of 25 µg/mL)			
Linearity				
Correlation coefficient	0.9999			
y-intercept (bias)	666			
Slope	47409			
Limit of quantitation	0.2203% (0.055µg/mL)			
Limit of detection	0.0727% (0.018µg/mL)			
Accuracy and precision				
% Recovery (n=3/concentration)	0.25 µg/mL	2.50 µg/mL	25.00 µg/mL	50.00 µg/mL
	95.4%	93.4%	95.8%	95.7%
Average recovery	94.9%			
95% Confidence interval	-6.1 ≤δ≤ -3.8			
Standard deviation	1.45			
RSD	1.53%			
90% Confidence interval (of standard deviation)	1.0 ≤δ≤ 2.5			
Intermediate precision				
Average	94.8%			
Standard deviation	2.22			
RSD	2.34%			
90% confidence interval of standard deviation	1.49 ≤δ≤ 4.63			
Solution stability				
Stock solution	1 week (3-8°C)			
Sample solution	24 hours (ambient)			

The method was further qualified for use in the human skin permeability study with additional analysis of LOQ, linearity and precision. Limit of quantitation was determined to be 0.25 µg/mL. The method was linear over the concentration range of 0.25 to 50 µg/mL with a correlation coefficient of 1.000. The method is precise at 50 µg/mL with a 0.6% RSD.

The adequacy of the study design was assessed for feasibility by assessing permeation of lidocaine from all three test patches and DMSO control. The feasibility assessment confirmed (1) that the levels of permeated lidocaine from the three patches are within range of the analytical method (i.e., observed between ~18 to ~180 µg/cm^2 between 2 to 12 hours) and (2) the DMSO provides for a positive control (i.e., observed between ~110 to ~225 µg/cm^2).

Results

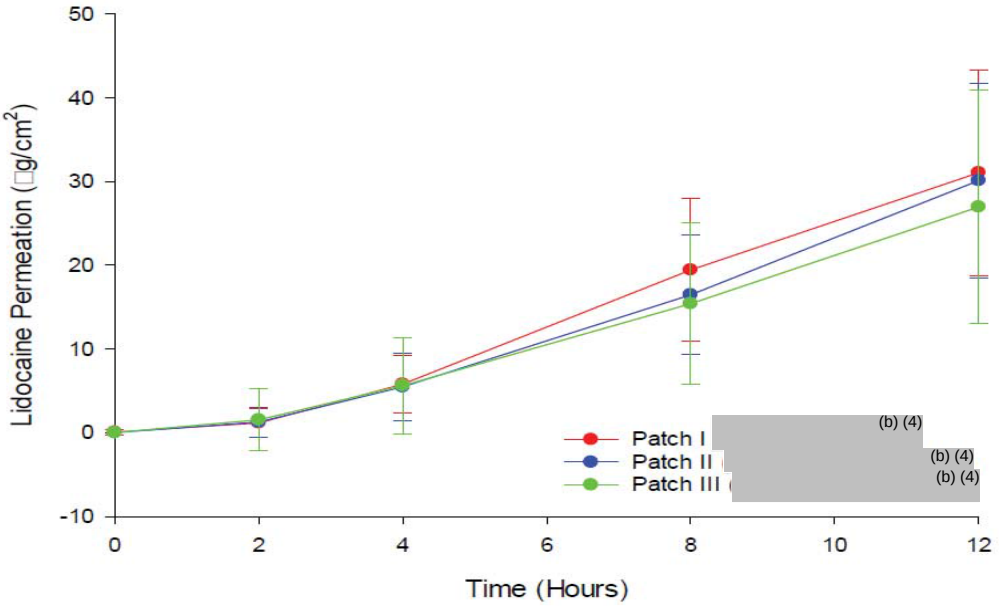
Before dosing, skin integrity was verified by transepidermal water loss (TEWL), a widely used indicator for measuring skin barrier function. Integrity data for all skin samples are summarized in the table below. All results are below the established threshold of 20 AU.

Summary Skin Integrity Data (TEWL)

Donor	Anatomic Site	Transepidermal Water Loss (AU)			
		Patch I ((b) (4) Free)	Patch II (Target (b) (4))	Patch III (x2 Target (b) (4))	DMSO Control
Donor 1	Thigh	3.5±0.1	3.2±0.0	3.3±0.4	3.2±0.3
	Trunk	3.6±0.7	3.2±0.3	3.5±0.6	3.2±0.4
Donor 2	Thigh	3.5±0.3	3.5±0.4	3.7±0.2	3.8±0.3
	Trunk	5.8±1.2	5.9±0.5	5.2±0.6	5.2±0.6
Donor 3	Thigh	3.4±0.3	3.6±0.2	3.5±0.4	3.6±0.3
	Trunk	4.1±0.4	4.3±0.2	4.3±0.2	4.6±0.3

A summary of the cumulative skin permeation and flux from all three donors is presented in figures and tables below. Analysis of variance (ANOVA) results for the log-transformed indicated no site by-treatment interaction; therefore, the main effect of treatment was reported.

Comparison of Skin Permeation across All Donors and Anatomic Sites for Three Test Patches



Summary Mean Human Skin Permeation Parameters (Non-transformed)

Formulation (Treatment)	N	Cumulative Lidocaine ($\mu g \cdot h/cm^2$) [±SD]	J_{max} ($\mu g/cm^2/h$) [±SD]
Patch I (b) (4)	24	31.06 (12.25)	3.06 (1.51)
Patch II (b) (4)	24	29.75 (11.51)	2.91 (1.04)
Patch III (b) (4)	24	27.05 (13.99)	2.55 (1.10)
DMSO control	24	177.03 (63.91)	17.98 (7.61)

Results of Tukey Analysis for Log-transformed Maximum Flux Data

Formulation (Treatment)	Geometric Mean ($\mu g/cm^2/h$)	95% Confidence Interval	
		Lower Limit	Upper Limit
Patch I	2.78	2.19	3.51
Patch II	2.73	2.16	3.46
Patch III	2.27	1.80	2.88
DSMO	14.73	11.64	18.64

Comparison	Ratio (%)	Lower Limit (%)	Upper Limit (%)	Tukey Result
Patch I/ Patch II	101.8	65.8	157.5	NS
Patch III/Patch II	83.3	53.8	128.9	NS
Patch I/Patch III	122.2	79.0	189.2	NS
DSMO/Patch I	530.0	342.2	820.0	Sig
DSMO/Patch II	539.5	348.7	834.8	Sig
DSMO/Patch III	647.9	418.7	1002.7	Sig

NS: not significant ($p >= 0.05$)

Sig: significant ($p < 0.05$)

Results of Tukey Analysis for Log-transformed Cumulative Permeation

Formulation (Treatment)	Geometric Mean ($\mu g/cm^2 \cdot h$)	95% Confidence Interval	
		Lower Limit	Upper Limit
Patch I	27.9	22.1	35.3
Patch II	27.6	21.9	34.9
Patch III	23.3	18.5	29.5
DSMO	149.2	118.0	188.6

Comparison	Ratio (%)	Lower Limit (%)	Upper Limit (%)	Tukey Result
Patch I/ Patch II	101.1	65.3	156.3	NS
Patch III/Patch II	84.4	54.5	130.6	NS
Patch I/Patch III	119.8	77.4	185.3	NS
DSMO/Patch I	533.9	344.9	826.1	Sig
DSMO/Patch II	539.6	348.7	834.9	Sig
DSMO/Patch III	639.4	413.2	989.5	Sig

NS: not significant ($p >= 0.05$)

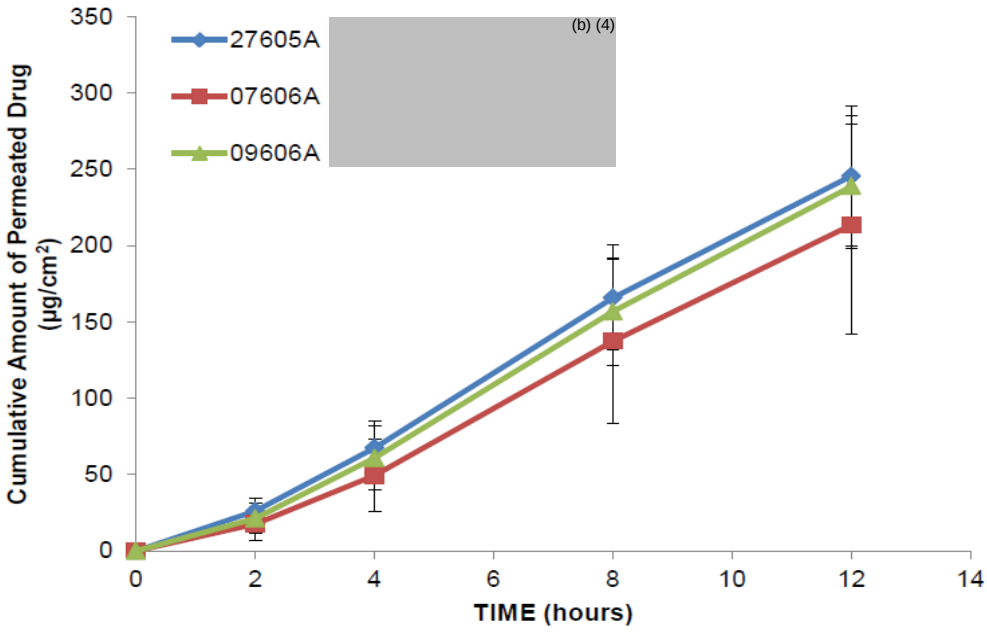
Sig: significant ($p < 0.05$)

The data show cumulative skin permeation of 27.05±13.99 to 31.06±12.25 $\mu g \cdot h/cm^2$ across the three test patches and flux (Jmax) between 2.55±1.10 to 3.06±1.15 $\mu g/cm^2/h$ over the 12-hour administration period. There were no statistically significant differences for either parameter between the three patch formulations. The details of human skin permeation study report are provided in Attachment 3.2.P.2.2a. All skin permeation results were consistent between donors and anatomical sites with the expected level of variability associated with *in vitro* studies.

Mouse skin study

An experiment was also conducted using mouse skin, which confirms the results from the human skin study (provided in Section 3.2.P.2.2.1.4 of Pharmaceutical Development Report). The summary results are provided below.

Effect of [redacted] (b) (4) Concentration on Lidocaine Permeation through Mouse Skin



Summary Mean Mouse Skin Permeation Parameters

Formulation (Treatment)	N	Cumulative Lidocaine (µg·h/cm²) [±SD]	J_{max} (µg/cm²·h) [±SD]
Patch I (b) (4)	6	245.71 (46.12)	22.3 (4.2)
Patch II (b) (4)	6	213.54 (71.89)	20.0 (6.4)
Patch III (b) (4)	6	238.89 (40.83)	22.0 (3.2)

(b) (4)

The results across both the human and mouse studies verify that (b) (4) utilized within the formulation (b) (4) do not act as skin permeation enhancers. The Applicant's in vitro permeability studies are acceptable. However, the final determination on whether the controls for either (b) (4) are necessary in the drug product specification will be made by Drug Product Reviewer.

Primary Biopharmaceutics Reviewer Name and Date: Kalpana Paudel, Ph.D.10/26/2017; 12/01/2017

Secondary Reviewer Name and Date: Kelly M. Kitchens, Ph.D., 11/02/2017; 12/08/17

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Kalpana Paudel

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Kelly Kitchens

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Date: 12/11/2017 10:45:59AM
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Recommendation:
NDA: 207962

NDA 207962
Review #1

Drug Name/Dosage Form	**Ztlido™ (Lidocaine patch 1.8%)**
Strength	**1.8%**
Route of Administration	Cutaneous Patch
Rx/OTC Dispensed	Rx
Applicant	**Scilex Pharmaceuticals, Inc.**
US agent, if applicable	

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	**Erika England**	OPQ/ONDP/DNDAPI/BII
Drug Product	**Erika England**	OPQ/ONDP/DNDAPI/BII
Process	**James Norman**	OPQ/OPF/DPAII/BV
Microbiology	**Daniel Schu**	OPQ/OPF/DPAII/BV
Facility	**Quallyna Porte**	OPQ/OPF/DIA/BII
Biopharmaceutics	**Haritha Mandula/Kelly Kitchens**	OPQ/ONDP/DB/BII
Regulatory Business Process Manager	Steve Kinsley	OPQ/OPRO
Application Technical Lead	**Ciby Abraham**	OPQ/ONDP
Laboratory (OTR)		
ORA Lead	Paul Perdue	ORA/OGROP
Environmental Assessment (EA)		

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type II	(b) (4)	(b) (4)	Adequate	2/26/2016	Adequate. Reviewed by Erika E. Englund, Ph.D.
	Type IV			Deficient	3/16/2016	**Deficient** Reviewed by Erika E. Englund, Ph.D.
	Type IV			Adequate	01/08/2016	Adequate. Reviewed by Erika E. Englund, Ph.D.
	Type III			Deficient	3/21/2016	**Deficient.** Reviewed by Erika E. Englund, Ph.D.
	Type III			Adequate	3/16/2016	Adequate. Reviewed by Erika E. Englund, Ph.D.
	Type III			Adequate	1/20/2016	Adequate. Reviewed by Erika E. Englund, Ph.D.

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

2. CONSULTS: N/A

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation and Conclusion on Approvability

Based on the recommendations from drug product, biopharmaceutics, process, and the office of compliance, we recommend a complete response from a Chemistry, Manufacturing, and Control (CMC) perspective. The drug substance and microbiology group have recommended approval but insufficient quality information was provided for the other disciplines.

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

N/A

II. A. Description of Drug Substance and Drug Product

The drug substance, Lidocaine is manufactured by (b) (4) and is referenced in DMF# (b) (4) (adequate, last reviewed 2/26/2016). Lidocaine is a white or almost white crystalline powder that is insoluble in water. Lidocaine is packaged in (b) (4) Lidocaine has a (b) (4) month retest period when stored at (b) (4) C.

The drug product, Ztildo (lidocaine patch) is manufactured by Oishi Koseido Co., Ltd. Ztildo contains 36 mg of lidocaine drug substance compounded in an anhydrous adhesive patch intended for cutaneous route of administration. The drug product comprises of an adhesive material containing lidocaine that is applied to a nonwoven cloth and covered with a polyethylene terephthalate release liner. The release liner is removed prior to application to the skin. The size of the patch is 10 cm x 14 cm. An expiry cannot be granted at this time due to insufficient quality information.

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

ZTlido is a single use cutaneous product indicated for the treatment of pain associated with postherpetic neuralgia. The drug product will be applied to intact

skin to cover the area of pain. ZTlido consists of 36 mg of lidocaine drug substance compounded in an anhydrous adhesive patch. The applicant is proposing that the patches, which are 10 x 14 cm, can be cut to smaller sizes prior to removal of the release liner. They are also proposing that up to 3 patches may be applied for up to 12 hours in a 24 hour period (12 hours on and 12 hours off).

C. Basis for Approvability or Not-Approval Recommendation

The sponsor has not provided adequate information in the manufacturing and controls in the areas of drug product, process, and biopharmaceutics. The office of compliance has given an overall recommendation of withhold for the Oishi Koseido Co., Ltd drug product site (FEI: 3010166685) and the drug substance manufacturing site (b) (4) . The application is currently recommended as a complete response until the sponsor provides sufficient quality information for the following CMC deficiencies.

CMC Deficiencies:

Drug Substance:

1. DMF (b) (4), which was referenced for the (b) (4), was found inadequate to support this NDA.

   To address the DMF deficiencies, a letter was sent to the holder of DMF (b) (4).

2. DMF (b) (4), which was referenced for the (b) (4), was found inadequate to support this NDA. This DMF describes multiple products. Provide the product name which this NDA is referencing for the container closure system.

   To address the DMF deficiencies, a letter was sent to the holder of DMF (b) (4).

Drug Product:

3. In conjunction with your new comparative bioavailability study discussed in the Clinical Pharmacology section above, provide residual drug data for your product and the comparator at the completion of the delivery period. Residual drug data should be determined based on analysis of used drug product and not a theoretical calculation. The amount of drug left on the skin surface should be assessed and any drug that may have been transferred to packaging or other components during storage or use should be accounted for in an attempt to perform a mass balance. Your control should include an analysis of a sufficient number of unused products from the same lot as those used in the trial to provide an estimate of drug load and not simply an expression of label claim.

(b) (4)

Application Technical Lead Signature:

Ciby J. Abraham, Ph.D.
Quality Assessment Lead (Acting)
ONDP/DIV II/Branch IV

Ciby J. Abraham -A

Digitally signed by Ciby J. Abraham -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000827346, cn=Ciby J. Abraham -A
Date: 2016.05.05 20:16:44 -04'00'

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I concur with Dr. Englund's assessment that the information provided on the drug product is inadequate for approval.

Donna F. Christner, Ph.D.
Branch Chief (Acting)

30-Mar-2016

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature:

The required content was not included on the pouch and carton. A comment will be sent to the applicant to include the inactive ingredients on the carton and the pouch. A full review of the labeling information will be conducted during the next review cycle.

An additional comment will be sent to the applicant to include an image of the strength and product name on the patch.

Secondary Review Comments and Concurrence:

I concur with Dr. Englund's conclusion that the labeling will be reviewed in the next review cycle and comments sent at that time.

Donna F. Christner, Ph.D.
Branch Chief (Acting)

30-Mar-2016

ASSESSMENT OF THE PROCESS

2.3.P DRUG PRODUCT

2.3.P.2.3 Manufacturing Process Development

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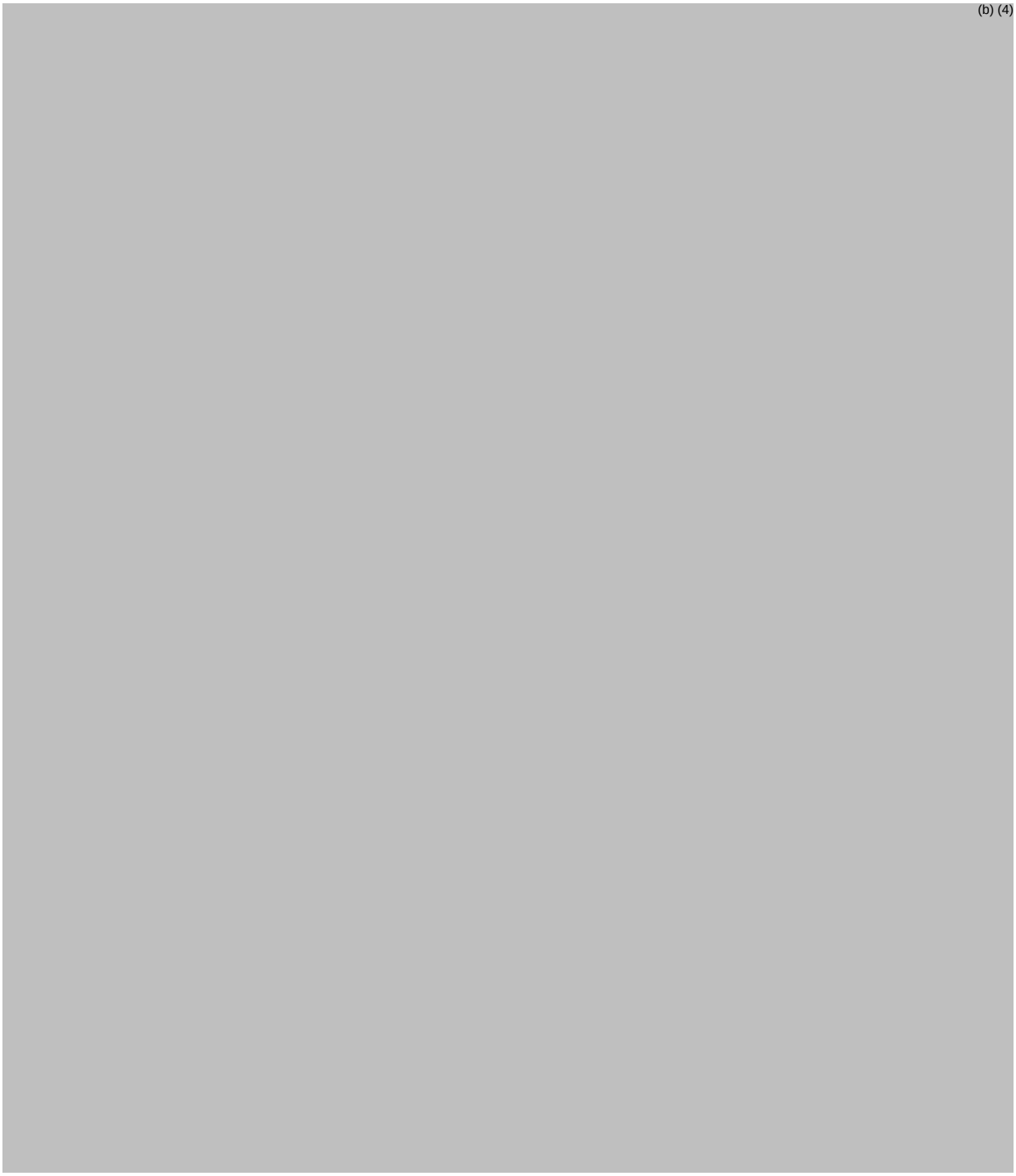
(b) (4)



ASSESSMENT OF THE BIOPHARMACUETICS

28. Are the in-vitro dissolution test and acceptance criteria adequate for assuring quality control and consistent bioavailability of the drug product?

Applicant's Response:

A release test was developed in accordance with USP <724> and involved the following:
• Medium selection;
• Selection of parameters (medium volume, rotation speed, and sampling time points); and
• Confirmation of method discrimination.
The commercial release method is summarized in the Table below. Apparatus 5 was selected as it is commonly used for patches, and demonstrated adequacy in the release testing of lidocaine patch 1.8%.

Drug Product Drug Release Method Parameters

Apparatus	5
Medium	Water
Volume	500 mL
Temperature	32 ± 0.5°C
Rotation speed	50 rpm
Sampling time points (commercial release):	(b) (4) minutes
Replacement volume	4 mL

Medium Selection

(b) (4)

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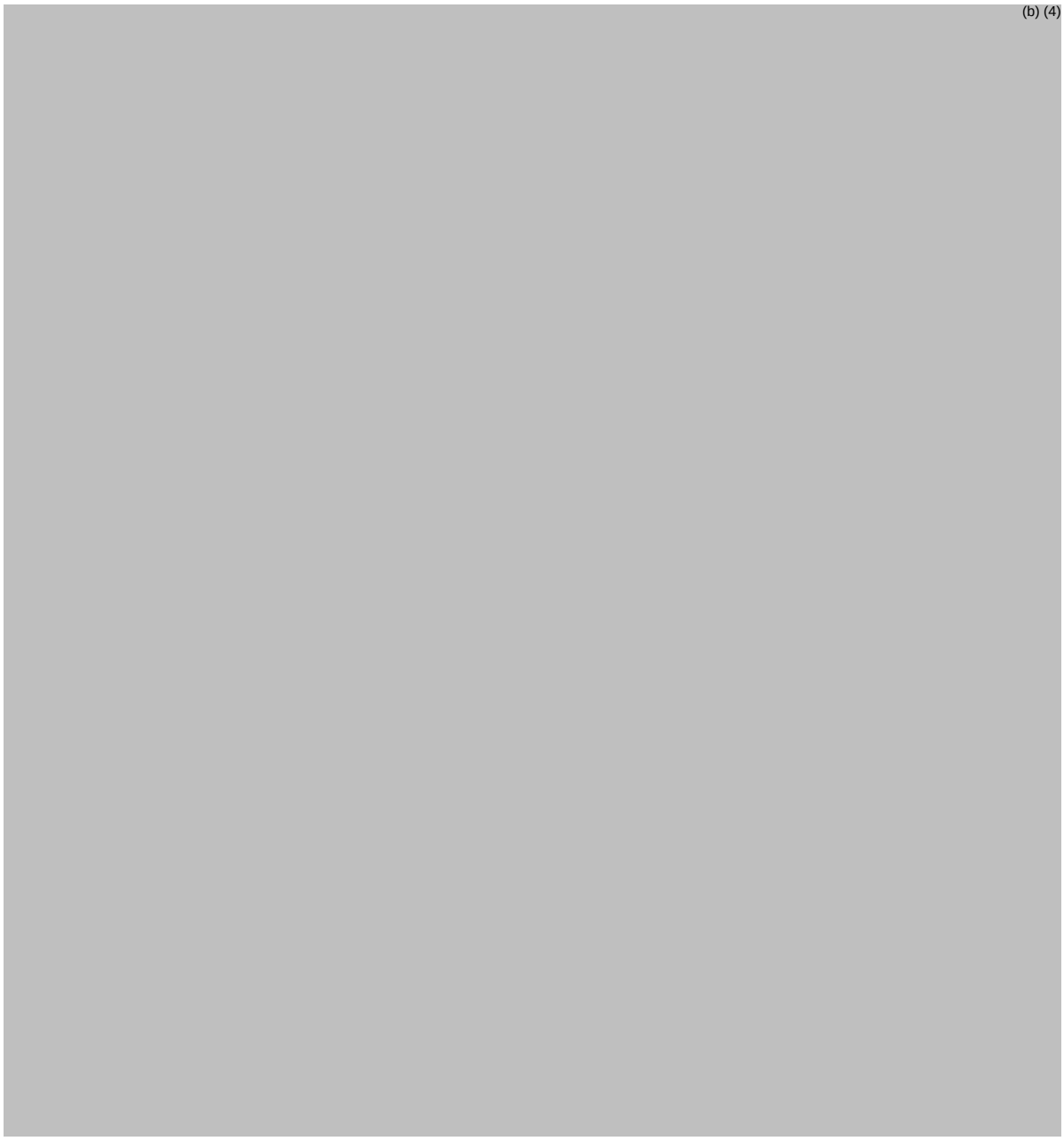
(b) (4)



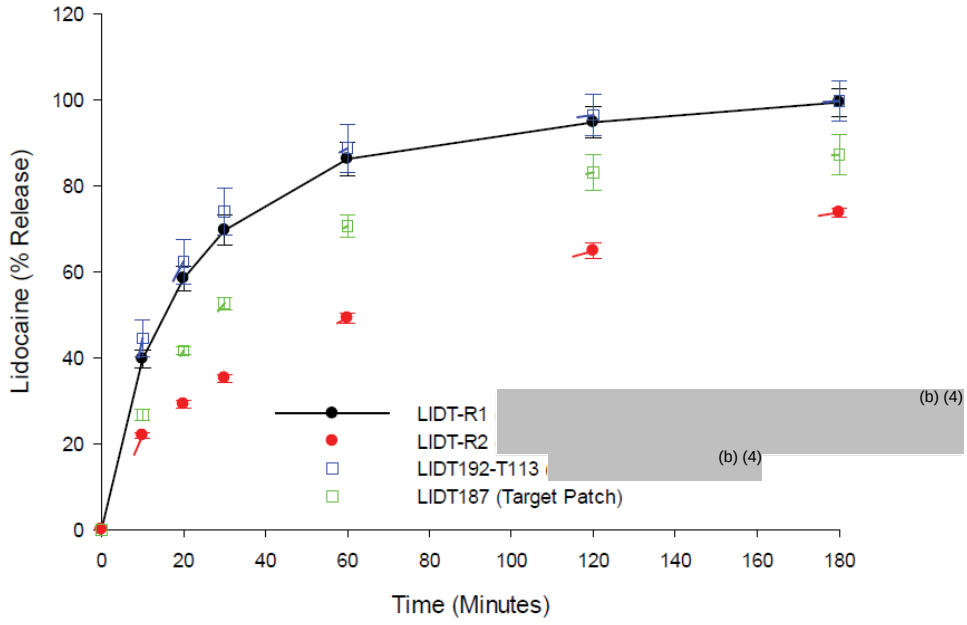
Method Discrimination:
The discriminating power of the release test using the USP media temperature (32ºC) was assessed by performing the method on drug product patches intentionally altered in formulation and process parameters. A summary of the patches used in the study, and the intentional deviation are summarized in Table below:

Development Patches Components and Composition for Release Test Method Discrimination Assessment

System	Component	Composition (%)			
		LIDT187	LIDT-R1	LIDT-R2	LIDT192-T113
(b) (4)	Butylated hydroxytoluene	(b) (4)			
	Dipropylene glycol				
	Isostearic acid				
Active	Lidocaine	1.8	1.8	1.8	1.8
(b) (4)	Mineral oil	(b) (4)			
	Polyisobutylene (high molecular weight)				
	Polyisobutylene (low molecular weight)				
	Silicon dioxide				
	Terpene resin				
	Styrene/isoprene/styrene block copolymer				
	Total	100	100	100	100
	Coating thickness of adhesive (g/m^2)	(b) (4)			

Summary release data are graphically presented in the Figure below:

Release Test Method (USP <724>) Discrimination Assessment Data (n=6)



Commercial Release Limits:

(b) (4)

(b) (4)

These limits will assure that commercial drug product will have a lot-to-lot release profile consistent with the drug product Registration Lots, and the clinical lot that established bioequivalence with the RLD Lidoderm® Patch 5%, using a method that is demonstrated to be discriminating. Data presented in Figures below also show that the drug product has a very stable release profile over 24 months regardless of the apparatus configuration (USP or JP) used in the test.

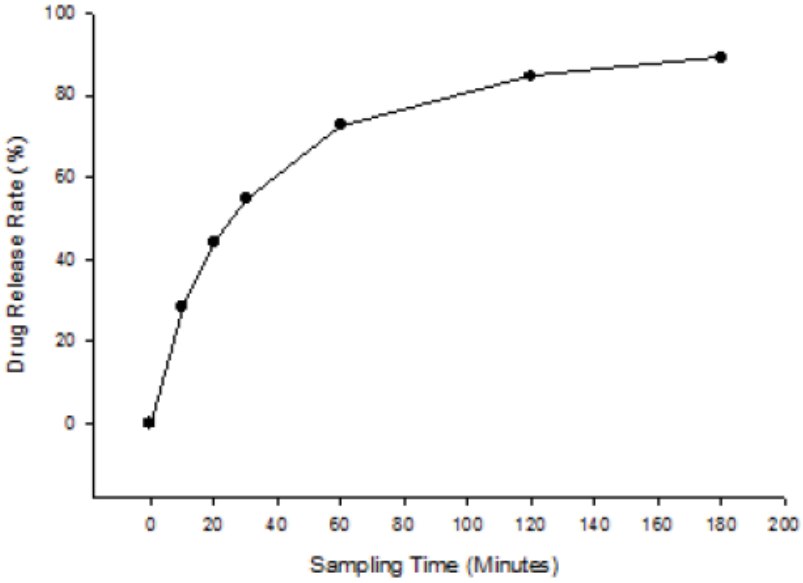
Drug Product Release Limits

Time Points (Minutes)	Limits
(b) (4)	

Summary Drug Product Release and Stability Data (JP: 9 cm disk + 10 mL sample and USP: 4 cm disk + 4 mL sample; Registration Lots)

Summary Drug Product Release and Stability Data (JP: 9 cm disk + 10 mL sample and USP: 4 cm disk + 4 mL sample; Registration Lots) – Expanded View of Plateau Region

In Vitro Drug Release Profile Clinical Lot (LIDT187)



The applicant did not submit method validation and individual data in their initial submission. The applicant was asked to submit the following in the 74-day letter comments. The applicant provided adequate responses on 12/18/2015.
Submit the method validation report for your proposed in vitro drug release method.

Response: It is confirmed that the drug product release method is being performed in accordance with USP <724>. A summary of the selected parameters is presented in Section 3.2.P.2.2 and validation of the method's discriminatory power is presented in Section 3.2.P.5.3. Please refer to the table below for additional details.

Note that the use of water as in vitro drug release medium is discouraged since water has no buffering capacity.

Response: While water may not be preferred for a release method, it is an acceptable media if it provide sufficient performance. Water, in addition to other selected release test parameters, was selected for the following reasons: (b) (4)

Drug Product Drug Release HPLC Method Summary Validation Data

Validation Parameter	Acceptance Criteria	Results
Range	Acceptance criteria are met for both linearity and precision	10-120% of label claim
Limit of Quantitation	% RSD ≤10% (n = 6)	2.5% of label claim
Specificity	No peak interferes with lidocaine peak	Lidocaine is resolved from any interfering peaks in the chromatogram
Linearity	R^2 ≥0.999	Range = 2.5-120%; R^2 = 0.9999; y-intercept = -312
Accuracy	Average recovery at each concentration = 100 ± 2%	10%: $\bar{x}$ = 99.1% 30%: $\bar{x}$ = 99.7% 50%: $\bar{x}$ = 100.2% 75%: $\bar{x}$ = 99.9% 100%: $\bar{x}$ = 100.4% 120%: $\bar{x}$ = 100.1% Average recovery percentage: 99.9%±0.67% RSD
Repeatability (Precision) 10-120% Label claim	% RSD ≤2.0%	SD: 0.63 RSD: 0.63
Intermediate precision	%RSD ≤1.0%	$\bar{x}$ =100.1±0.56% RSD
System suitability testing	%RSD of the peak area of lidocaine peak ≤1.0% Theoretical plates of lidocaine peak ≥3000 Symmetry factor of lidocaine peak ≤2.0	System repeatability: 0.24% RSD Theoretical plates = 9497 Symmetry factor = 1.1
Sample solution stability	Test sample after 24 hours is NLT 96% of original measured concentration	% Residual after 24 hours: 100.6%
Stability of lidocaine in dissolution medium	Test sample after 24 hours is NLT 96% of original measured concentration	% Residual after 24 hours: 100.2%

NLT: Not less than
RSD: Relative standard deviation
SD: Standard deviation

Reviewer's Assessment:

- The drug product release method was performed in accordance with USP <724>.
- The drug release method validation as submitted by the applicant is acceptable. The applicant submitted acceptable drug release method validation in terms of linearity, range, specificity, accuracy, repeatability, intermediate precision, system suitability, sample solution and stability.
- The drug release method was found to be discriminatory in terms of varying amounts of adhesive used (b) (4)).
- The applicant's proposed specifications are too liberal for the drug product based on the data provided.

Time Points (Minutes)	Limits
(b) (4) inutes	(b) (4)
inutes	
Minutes	%

It is not clear on how many units were tested for the long-term stability data provided in the report. The applicant will be asked to clarify this and provide data for at least 12 units for each of the registration batches used to conduct stability studies.

29. Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?

Applicant's Response: Not applicable.

Reviewer's Assessment: There were no changes to the formulation, manufacturing process, manufacturing sites through the development until the final commercial product.

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACUETICS

Reviewer's Assessment and Signature:

The drug release method as proposed by the firm is incomplete pending the firm's response to the following deficiencies:

- Provide the complete in vitro drug release stability data (individual, mean, standard deviation, and profiles) for at least 12 units of the registration lots.

Haritha Mandula, Ph.D.
Primary Biopharmaceutics Reviewer
OPQ/ONDP/DB
04/04/2016

Secondary Review Comments and Concurrence:

I have reviewed the Biopharmaceutics assessment, and I concur with the deficiencies identified by the reviewer.

Kelly M. Kitchens, Ph.D.
Quality Assessment Lead (Acting)
Division of Biopharmaceutics, Branch II
April 5, 2016

ASSESSMENT OF MICROBIOLOGY

See Panorama – 2/25/16 – Overall recommendation is approval.

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert

1. Container and Carton Labeling

1) Immediate Container Label

(b) (4)

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Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	ZTlido lidocaine (b) (4) 1.8%	Refer to comment in discussion.
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	1.8%	Refer to comment in discussion
Route of administration 21.CFR 201.100(b)(3))	Topical	Adequate
Net contents* (21 CFR 201.51(a))	1 (b) (4)	Adequate
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	The inactive ingredients were not listed.	Inadequate
Lot number per 21 CFR 201.18	Space was provided on the pouch for the lot number.	Adequate
Expiration date per 21 CFR 201.17	Space was provided on the pouch for the expiration date.	Adequate
"Rx only" statement per 21 CFR 201.100(b)(1)	Rx Only included on pouch.	Adequate
Storage (not required)	Storage conditions listed as 25 °C (77 °F) excursions permitted to 15-30 °C (59-86 °F)	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	NDC number listed is 69557-111-01. NDC number listed on professional sample is 69557-111-99.	Adequate
Bar Code per 21 CFR 201.25(c)(2)***	Space was provided on the pouch for the bar code.	Adequate
Name of manufacturer/distributor (21 CFR 201.1)	Scilex was listed as the manufacturer of the product.	Adequate
Others	Professional Sample includes statement that product is not for resale. Other information on pouch was the same.	Adequate

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.

**For solid oral dosage forms, CDER policy provides for exclusion of "oral" from the container label
**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion:

The PI was not reviewed because this NDA was recommended for a Complete Response. The carton and container labeling from the 03/14/2016 amendment were reviewed. The required content was not included. The inactive ingredients were missing on both the pouch and the carton labeling. The proprietary name, established name and strength were all included on the labeling, but these names will be reviewed during the next review cycle. For example, the use of (b) (4)" as the dosage form will go under review during the next cycle. The following comments will be sent to the applicant:

Include the inactive ingredients on the carton and pouch labels. Refer to 21CFR 201.100(b)(5) and 21CFR201.100(d)(2).

We acknowledge the submitted labeling amendments, and a full review of this information will be conducted during the next review cycle.

A request was sent in the 74 day letter on 09/22/2015 to provide the proposed text which will be on the backing membrane of the drug product. The applicant did not provide an image for how the text on the patch would appear. The applicant responded in the 12/18/2015 amendment that the drug product will be labeled "(b) (4)." The product will be embossed and no inks will be used. However, the size and orientation of this text on the pouch were not provided The following deficiency will be sent:

Provide an image of how the strength and product name will appear on the patch.

2) Carton Labeling

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Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	ZTlido lidocaine (b) (4) 1.8%	Refer to comment in discussion
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))	1.8%	Refer to comment in discussion
Net contents (21 CFR 201.51(a))	30 pouches or (b) (4) pouches (professional sample)	Adequate
Lot number per 21 CFR 201.18	Space was provided on the carton for the lot number	Adequate
Expiration date per 21 CFR 201.17	Space was provided on the carton for the expiration date	Adequate
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(d)(2)]	The inactive ingredients were not listed.	Inadequate
Sterility Information (if applicable)	The product is not sterile.	Adequate
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)	Rx only included on the carton	Adequate
Storage Conditions	Storage conditions listed as 25 °C (77 °F) excursions permitted to 15-30 °C (59-86 °F)	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	NDC number listed is 69557-111-30. NDC number listed on professional sample is (b) (4).	Adequate
Bar Code per 21 CFR 201.25(c)(2)**	Space was provided on the carton for the bar code	Adequate
Name of manufacturer/distributor	Scilex was listed as the manufacturer of the product	Adequate
"See package insert for dosage information" (21 CFR 201.55)	Carton states: "for dosage and full prescribing information, please read accompanying product information"	Adequate
"Keep out of reach of children" (optional for Rx, required for OTC)	Not included	Adequate

Route of Administration (not required for oral, 21 CFR 201.100(d)(1) and (d)(2))	Topical route of administration listed on carton	Adequate

Conclusion:
The PI was not reviewed because this NDA was recommended for a CR. The carton and container labeling that were reviewed were submitted in the 03/14/2016 amendment. CFR 201.55 states: *It is the view of the Food and Drug Administration that when such a situation prevails, compliance with this requirement would be met by a statement such as "See package insert for dosage information".* Because CFR 201.55 does not describe the exact words to be used to reference the dosage information on the package insert, the description of the package insert on the carton is considered adequate. The inactive ingredients were missing on both the pouch and the carton labeling. The proprietary name, established name and strength were all included on the labeling, but these names will be reviewed during the next review cycle. Refer to the deficiencies above which will be sent for both the pouch and carton labeling.

R.3 Environmental Assessment

Reviewer's Assessment:
The environmental assessment was submitted in the 03/24/2016 amendment. Scilex claimed categorical exclusion from preparing an environmental assessment under 21 CFR 25.31(e). They stated that both the drug substance and drug product are manufactured in compliance with local environmental laws.

The reference to CFR 25.31(e) is not appropriate because this is for action on an IND. The following deficiency will be sent:

The reference to CFR 25.31(e) in the Environmental Assessment in 1.12.14 is not

applicable to your NDA because CFR 25.31(e) is for action on an IND. In your resubmission, provide the applicable reference and information for the Environmental Assessment of your NDA.

II. List of Deficiencies To Be Communicated – See Executive Summary

III. Attachments

A. Lifecycle Knowledge Management – N/A