CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-612 / S-003

Trade Name: Lidoderm

Generic Name: (lidocaine)

Sponsor: Teikoku Pharma USA, Inc.

Approval Date: July 2, 2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-612 / S-003

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-612 / S-003

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-612/S-003

Teikoku Pharma USA, Inc.
745-D Camden Ave.
Campbell, CA 95008-4146

Attention: Larry Caldwell, Ph.D.
Vice President, Scientific Affairs

Dear Dr. Caldwell:

Please refer to your supplemental new drug application dated February 15, 2001, received February 15, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lidoderm (lidocaine) Adhesive Patch 5%.

We acknowledge receipt of your submissions dated September 14, 2001, and March 26 and June 27, 2002.

Your submission of March 26, 2002, constituted a complete response to our March 15, 2002, action letter.

This supplemental new drug application, provides for an upper limit for the adhesive strength and a change in acceptance criterion for drug release *in vitro*.

We have completed the review of this supplemental application, as amended, and it is approved effective on the date of this letter.

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

If you have any questions, call Kimberly Compton, Regulatory Project Manager, at (301) 827-7432.

Sincerely,

Dale Koble, Ph.D.
Chemistry Team Leader
Division of Anesthetic, Critical Care, and
Addiction Drug Products
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Dale Koble
7/2/02 05:32:44 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-612 / S-003

NOT APPROVABLE LETTER(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-612\S-003

Teikoku Pharma USA, Inc.
745-D Camden Ave.
Campbell, CA 95008-4146

Attention: Larry Caldwell, Ph.D.
Vice President, Scientific Affairs

Dear Dr. Caldwell:

Please refer to your supplemental new drug application dated, February 15, 2001, received February 15, 2001, submitted under section 505(b) pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Lidoderm (lidocaine) Adhesive Patch 5%.

We acknowledge receipt of your submission dated September 14, 2001.

Your submission of September 14, 2001 constituted a complete response to our August 15, 2001, action letter.

This supplemental application proposes ——— in the adhesive strength upper limit specification and broadening the existing drug release specifications.

We have completed our review and find the information presented is inadequate, and the supplemental application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

[ ]

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action, FDA may proceed to withdraw the supplemental application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This products may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this changes prior to approval of this supplemental application.

Sincerely,

{See appended electronic signature page}

Cynthia McCormick, M.D.
Director
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Bob Rappaport
3/15/02 06:16:04 PM
for CG McCormick, MD

2. The following comments pertain to the proposed change in the acceptance criteria for drug release.

[redacted]

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with this division to discuss what further steps need to be taken before the application may be approved.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change prior to approval of this supplemental application.

If you have any questions, call Laura Governale, Pharm.D., Regulatory Project Manager, at (301) 827-7410.

Sincerely,

{See appended electronic signature page}

Cynthia McCormick, M.D.
Director
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Cynthia McCormick
8/15/01 06:38:55 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-612 / S-003

MEDICAL REVIEW

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857 Tel:(301)827-7410

Medical Officer's Review and Evaluation of Clinical Data

NDA #:	**20-612 (SCS-003 AB AC)**
Drug Name (generic):	**Lidoderm Patch (lidocaine)**
Sponsor:	**Teikoku Pharma USA, Inc.**
Indication:	**Treatment of pain in post-herpetic neuralgia (shingles)**
Type of Submission:	**Response to Agency Comments Dated August 16, 2001**
Date of Submission:	**14SEP01**
Date of Receipt:	**17SEP01**
Date of Review:	**08JAN01**
Project Manager:	**Kim Compton**
Reviewer:	**Gerald J. Dal Pan, MD, MHS**

1 Background

Lidoderm patch is a skin patch containing lidocaine, designed for topical treatment of pain due to post-herpetic neuralgia. In a recent review of a periodic safety data, it was noticed that there were a number of consumer complaints related to the patch not sticking to the skin. The Division sent a letter to the Sponsor asking for details of the manufacturing and specifications regarding adhesion, as well as adverse event and consumer complaints regarding lack of adhesion.

2 Clinical Review of Consumer Complaints and of Adverse Events

The Sponsor notes that since the product was launched in September 1999, about 17 million patches have been distributed in the USA, corresponding to approximately 6 million prescriptions that have been written for the product.

The Sponsor further notes that there have been 86 complaints, and one adverse event, in which the product was "not sticking". The Sponsor notes that this corresponds to a frequency of about 0.0005%. In all cases in which the product was returned, it was sent for quality control (QC) testing. There were no cases in which the product failed the test for minimum adhesive strength. The Sponsor assumes "that the complaint results from oily skin, either form the use of a 'beauty' soap containing oil, or from naturally oily skin."

Review of the complaints of the product "not sticking" sheds little light on the problem. In general, the complaint is that the product does not stick or that it falls off. No specific adverse consequences of the patch falling off were reported. In some cases, the concomitant use of lotions and/or creams was use of denied. In most other cases, there was no information about the concomitant use of lotions and/or creams.

The Sponsor has also included three adverse event reports related to the product "sticking too much". In two cases, the patients were described as having "sensitive" or "thin"skin, and each of these two patients experienced a local reaction after the patch was removed. In one case, there was pain, irritation, and inflammation. In the other case, the "skin became irritated and torn up…to the point of bleeding." This patient, a 90-year woman who was hospitalized because of cardiac problems including ventricular tachycardia, COPD and atrial fibrillation, died on the sixth day of hsopitalization. For progression of the cardiac disease. It is not clear when the patch was removed relative the date of death. In the third case, the patient had trouble getting the patch to stick on the first four occasion, and tried using various tapes. On the fifth occasion, she used tape again, but also had trouble removing the patch because "it was sticking too well." There was some itching as well as "red scratches" at the site of patch application.

3 Comments

Review of the complaints of the product "not sticking" sheds little light on the problem. In general, the complaint is that the product does not stick or that it falls off. No specific adverse consequences of the patch falling off were reported. Regarding the patch "sticking too well", there are only three cases of this event and the actual reason for the patch appearing to stick too well is not clear.

RECOMMENDATIONS: -

No clinical action indicated at this time.

Gerald J. Dal Pan, MD, MHS Date Medical Officer	Bob Rappaport, MD Date Deputy Director, DACCADP

CC: NDA #20-612

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/s/

Gerald DalPan
1/13/02 02:04:54 PM
MEDICAL OFFICER

You've already initialed for entry into DFS.

Bob Rappaport
1/18/02 01:14:42 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-612 / S-003

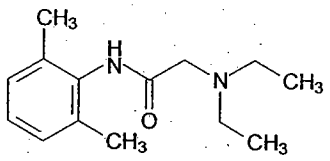
CHEMISTRY REVIEW(S)

Chemistry Review #1

1. Division HFD-170 Division of Anesthetic, Critical Care, and Addiction Drug Product	**2. NDA** 20-612 Approval Date: March 19, 1999
3. Name and Address of Applicant Teikoku Pharma USA, Inc. 745-D Camden Avenue Campell, CA 95008 Phone: (408) 871-7331 Fax: (408) 374-0181	**4. Supplement** Number: SCS-003 Doc. Date: February 15, 2001 Rev. Date: February 15, 2001
5. Name of Drug Lidoderm	**6. Nonproprietary Name** Lidocaine
7. Supplement Provides for: Proposing an upper limit for the adhesive strength and broaden the specification for in vitro drug release from	**8. Amendment(s)** None
9. Pharmacological Category Anesthetic (topical)	**10. How Dispensed** Prescription
11. Related Documents None	
12. Dosage Form Transdermal	**13. Potency(ies)** 5% w/w

14. Chemical Name and Structure

- Lidocaine
- Acetamide, 2-(diethylamino)-*N*-(2,6-dimethylphenyl)-
- $C_{14}H_{22}N_2O$
- 234.34
- 37-58-6



15. Comments

Biopharmaceutics reviewer found the proposed limit for in vitro drug release is not acceptable. Comments in the attachment should be included in the letter.

16. Conclusions and Recommendations

The applicant should submit more information. This supplemental application is not approvable from chemistry standpoint view. The project manger should draft a not approvable letter.

17. Name (and signature)

Naiqi Ya, Ph.D., Reviewer Date:

Dale Koble, Ph.D, Team Leader Date:

CC: NDA 20-612
HFD-170/Division File
HFD-170/NYa
HFD-170/DKoble
HFD-170/KCompton

File: C:\Yafiles\Review\supplement\20612s03rv1.doc

SUPPORTING DOCUMENTS:

Type/Number	Subject	Holder	Status	Review Date	Letter Date

RELATED DOCUMENTS (if applicable):

None.

CONSULTS:

None.

REMARKS:

None.

CONCLUSIONS & RECOMMENDATIONS:

The applicant should submit more information. This supplemental application is not approvable from chemistry standpoint view.

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Chemistry Review 1

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/s/

Naiqi Ya
8/15/01 10:34:01 AM
CHEMIST

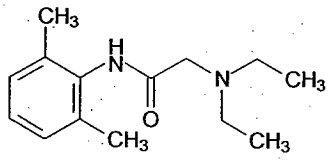
Dale Koble
8/15/01 10:42:46 AM
CHEMIST

Chemistry Review #2

1. Division HFD-170 Division of Anesthetic, Critical Care, and Addiction Drug Product	**2. NDA** 20-612 Approval Date: March 19, 1999
3. Name and Address of Applicant Teikoku Pharma USA, Inc. 745-D Camden Avenue Campell, CA 95008 Phone: (408) 871-7331 Fax: (408) 374-0181	**4. Supplement** Number: SCS-003 Doc. Date: Sept. 14, 2001 Rev. Date: Sept. 17, 2001
5. Name of Drug Lidoderm	**6. Nonproprietary Name** Lidocaine
7. Supplement Provides for: Proposing an upper limit for the adhesive strenath and broaden the specification for in vitro drug release from	**8. Amendment(s)** None.
9. Pharmacological Category Anesthetic (topical)	**10. How Dispensed** Prescription
11. Related Documents None	
12. Dosage Form Transdermal	**13. Potency(ies)** 5% w/w

14. Chemical Name and Structure

- Lidocaine
- Acetamide, 2-(diethylamino)-*N*-(2,6-dimethylphenyl)-
- $C_{14}H_{22}N_2O$
- 234.34
- 37-58-6



15. Comments

The applicant's proposed acceptance criterion for in vitro release is reviewed the biopharmaceutics reviewer.

16. Conclusions and Recommendations

The applicant's responses are inadequate for the proposed acceptance criterion for maximum adhesive strength. This supplemental application is not approvable from chemistry standpoint. The project manger should draft a not approvable letter, include the attached draft comment and any comments from the biopharmaceutics reviewer.

17. Name (and signature)

Naiqi Ya, Ph.D., Reviewer Date:

Dale Koble, Ph.D, Team Leader Date:

CC: NDA 20-612
HFD-170/Division File
HFD-170/NYa
HFD-170/DKoble
HFD-170/KCompton

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Chemistry Review 2

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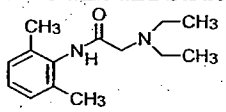
/s/

Naiqi Ya
3/15/02 10:07:18 AM
CHEMIST

Dale Koble
3/15/02 10:57:29 AM
CHEMIST

Chemistry Review Review #3	1. Division HFD-170	2. NDA Number 20-612
3. Name and Address of Applicant Teikoku Pharma USA, Inc. 745-D Camden Avenue Campbell, CA 95008		4. Supplement Number Date SCS-003 15-FEB-01
5. Name of Drug LIDODERM®	6. Nonproprietary Name Lidocaine Patch	
7. Supplement Provides for: An upper limit for the adhesive strength and a change in acceptance criterion for drug release *in vitro*		8. Amendment(s) 26-MAR-02/BC
9. Pharmacological Category Anesthetic (topical)	10. How Dispensed Rx	11. Related Documents
12. Dosage Form Patch	13. Potency(ies): Lidocaine, 5% w/w	

14. Chemical Name and Structure see USAN



$C_{14}H_{22}N_2O$
M.W. 234.34
Acetamide, 2-(diethylamino)-N-(2,6-dimethylphenyl)-

LIDOCAINE CAS-137-58-6

15. Comments: In response to the recommendation that the proposed acceptance criterion for maximum adhesive strength is inadequately justified and in need of revision based on historical batch data, the sponsor has submitted additional data to support a revised acceptance criterion.

[redacted]

17. Name Signature	Date
Allan Fenselau, Review Chemist	
Concurrence Signature	Date
Dale Koble, Chemistry Team Leader	

cc: NDA 20-612
HFD-170/Division File
HFD-170/CSO/K.Compton
HFD-170/CHEM/A.Fenselau
HFD-170/CHEM/TeamLdr/D.Koble
HFD-170/Div.Dir./C.McCormick
HFD-820/DNDCII/E.Duffy

Doc ID: n20612s.003

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Chemistry Review 3

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/s/

Allan Fenselau
6/27/02 07:14:40 AM
CHEMIST

Dale Koble
6/28/02 12:42:14 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-612 / S-003

CLINICAL PHARMACOLOGY/ BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20-612 SUBMISSION DATE: 09/14/01

LIDOCAINE USP (LIDODERM®) 5%
ADHESIVE PATCH

TEIKOKU PHARMA USA, INC
745-D CAMDEN AVENUE
CAMPBELL, CA95008-41146 REVIEWER: David G. Udo, Ph.D.

SUBMISSION TYPE: SUPPLEMENT (S-003 AC)

I. SYNOPSIS/BACKGROUND

Supplement S-003 AC was submitted to NDA 20-612 for lidocaine USP (Lidoderm®) 5% adhesive patch by the sponsor on September 14, 2001. Lidocaine USP adhesive patch is approved for application to the skin for the treatment of pain in post-herpetic neuralgia (shingles). In Supplement SCS-003 submitted on February 15, 2001, the sponsor proposed to change the approved lower limit of *in vitro* drug release specification from [redacted] a letter dated August 2001, the Agency conveyed the discipline Comments for the Supplement review (Attachment I) to the sponsor. Comment 2.d pertains to the biopharmaceutics of the drug product. This supplement is submitted to address the issues raised in the Agency's Comments.

II. REVIEW OF SPONSOR'S RESPONSE

Comment 2.d: Provide appropriate data that the [redacted] drug product with the [redacted] *in vitro* release will have equal *in vivo* effectiveness as the originally approved product.

Sponsors's Response: The sponsor states (i) that the dissolution test used in the initially submitted Supplement (SCS-003) is designed to confirm that the drug product releases a large percentage [redacted] of its lidocaine content [redacted] into a stirred solution within 30 min of test initiation, (ii) that during the recommended 12 h duration of application of the patch, the *in vivo* release of lidocaine is 3-5% (i.e., [redacted] and (iii) that the method is not used for assessing correlation of *in vitro* release of lidocaine from the patch and its *in vivo* performance.

The dissolution method used by the sponsor entitled, "Transdermal Delivery Systems – General Drug Release Standards", using Apparatus 5 (USP 23 [pages 1796-1797) was submitted in an amendment to the NDA on August 30, 1997. The drug release specification of 40% in 30 min was based on a mean release of 51.1%, 52.6% and 51.8% (n=6) for drug product Lots 76062, 76063 and 76064, respectively, at the beginning

(Month 0) of a 9-month stability testing period. Testing was performed at the 10, 20, 30, 60, 120 and 180 min time-points. The mean percentage release at the 180 time-point was 99.1%, 99.1% and 97.2% for the Lots 76062, 76063 and 76064, respectively. The dissolution method and the specification were considered acceptable from a biopharmaceutic perspective (see Attachment II [page 11]).

The sponsor then explains the differences in *in vitro* release of lidocaine from the [redacted] patches as follows:

1. The backing material of the [redacted] patch is relatively loose over its entire surface. This allows the dissolution medium to flow through the fabric freely contacting both the back and the adhesive surfaces of the patch.

2. For the [redacted] patch, the [redacted] process compresses and fuses a certain percentage of the fibers in the backing material. In this case the flow of the dissolution medium on the back of the patch is not as free as in the [redacted] patch.

3. The differences in the texture of backing material of the [redacted] patches described in items 1 and 2 above result in a lower rate of *in vitro* release of lidocaine from the [redacted] patch as compared to the [redacted] patch.

4. The lower rate of *in vitro* drug release for the [redacted] product was observed only after it had gone into commercial production and has been consistent over the last two years of production.

5. The quality control data accumulated over the last two years of production warrant the requested change in the lower limit of *in vitro* release specification of the patch from [redacted]

The sponsor states that upon application of the patch to the skin, lidocaine release from the patch occurs only from the adhesive surface that is in contact with the skin and is primarily a function of the skin itself rather than a property of the dosage form. The sponsor, subsequently, feels that the [redacted] in the *in vitro* lidocaine release of the [redacted] patches may not result in a significant difference between the two patches in the amount of lidocaine released into the skin in clinical practice.

III. RECOMMENDATION

Supplement S-003 AC submitted to NDA 20-612 for lidocaine USP (Lidoderm®) 5% adhesive patch by the sponsor on September 14, 2001 has been reviewed by the Division of Pharmaceutical Evaluation II of the Office of Clinical Pharmacology and Biopharmaceutics. It is noted that the change in the lower limit of *in vitro* drug release specification from [redacted] Data currently available show no correlation between *in vitro* and *in vivo* release of lidocaine from the patch, subsequently, the effect of this change on its *in vivo* release of lidocaine is not known. In the *in vitro* release test, both the back and the adhesive surfaces of the patch are exposed to the dissolution medium. However, in clinical practice, only the adhesive surface of patch is applied to the skin. The lidocaine content of the patch should, therefore, permeate the skin mainly by passive diffusion. Accordingly, the amount of lidocaine that enters the skin from the patch should be controlled mainly by the condition of the skin and not by the texture changes in the material of the back of the patch that [redacted] the lower limit of *in vitro* drug release specification of the [redacted]

Like the [redacted] lidocaine patch, the [redacted] lidocaine patch contains [redacted] of lidocaine of which only a small percentage, [redacted] is released for the intended therapeutic effect. Furthermore, there is no change in the drug formulation.

It is reasonable to expect that the [redacted] in the lower limit of the *in vitro* release specification of the [redacted] patch (as compared to the [redacted] patch) would not result in its release of sub-therapeutic levels of lidocaine into the skin when it is used in clinical practice.

Please convey this Recommendation, as appropriate, to the sponsor.

David G. Udo, Ph.D.
Division of Pharmaceutical Evaluation II

Concurrence: Suresh Doddapaneni, Ph.D. _____

cc: NDA 20-612, HFD-170, HFD-170 (Compton, Rappaport, Dalpan, Koble and Ya), HFD-870 (Doddapaneni and Udo), CDR (Attn: Zom Zadeng).

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/s/

David Udo
3/14/02 05:00:46 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
3/15/02 06:50:35 AM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20-612 (S-003) SUBMISSION DATE: 02/15/01

LIDOCAINE USP (LIDODERM®) 5%
ADHESIVE PATCH

TEIKOKU PHARMA USA, INC
745-D CAMDEN AVENUE
CAMPBELL, CA95008-41146 REVIEWER: David G. Udo, Ph.D.

SUBMISSION TYPE: SUPPLEMENT (S-003)

I. SYNOPSIS/BACKGROUND

Supplement S-003 was submitted to NDA 20-612 for lidocaine USP (Lidoderm®) 5% adhesive patch by the sponsor on February 15, 2001. Lidocaine USP adhesive patch is approved for application to the skin for the treatment of pain in post-herpelic neuralgia (shingles). In this supplement, the sponsor proposes (i) to [redacted] the upper limit specification of patch adhesive strength and (ii) to broaden the existing drug release specification [redacted]. The sponsor then submits data from multiple drug product lots/batches to support the proposed changes.

II. REVIEW OF SPONSOR'S RESPONSE

(a) [redacted] the Upper Limit Specification of Patch Adhesive Strength: The request to [redacted] the upper limit specification of patch adhesive strength is being reviewed by the HFD-170 chemistry review team.

(b) Broadening the Existing Drug Release Specification [redacted] The approved lidocaine USP adhesive patch consists of non-[redacted] specification is presented in Table 1.

The sponsor then evaluates the drug release of 35 commercial lots and three validation lots of lidocaine USP patch consisting of [redacted] (Table 2) and finds (i) that [redacted] (ii) that some of the commercial lots of the newly proposed [redacted] lidocaine USP patch fail to

[redacted]

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Clin Pharmacology and Biopharmaceutics

specification of [redacted] r *in vitro* testing of drug release of commercial lots of the [redacted] lidocaine USP adhesive patch.

Table 1. Drug Release of [redacted] Lidocaine USP Patch at 25°C and 60% Relative Humidity (RH) for Stability Lots 76062, 76063 and 76064 [redacted] atch/Lot)

Amount of drug release (mg/patch) at 30minutes: (n=6)

Lot		Initial	3M	6M	9M	12M
76062	Max	[redacted]				
	Min					
	Mean	357.7	367.6	348.6	335.6	367.9
	SD	16.17	23.31	9.37	20.39	24.74
	c.v. (%)	4.52	6.34	2.69	6.08	6.72
		18M	24M	30M	36M	39M
	Max	[redacted]				
	Min					
	Mean	381.4	394.5	401.6	378.4	363.0
	SD	14.54	8.83	17.17	31.66	20.38
	c.v. (%)	3.81	2.24	4.28	8.37	5.62
Lot		Initial	3M	6M	9M	12M
76063	Max	[redacted]				
	Min					
	Mean	368.2	364.1	352.8	368.2	382.5
	SD	13.96	8.21	13.00	12.10	8.42
	c.v. (%)	3.79	2.25	3.69	3.29	2.20
		18M	24M	30M	36M	39M
	Max	[redacted]				
	Min					
	Mean	378.1	345.5	384.5	352.4	367.3
	SD	7.25	10.76	12.00	35.40	12.78
	c.v. (%)	1.92	3.12	3.12	10.05	3.48
Lot		Initial	3M	6M	9M	12M
76064	Max	[redacted]				
	Min					
	Mean	362.3	361.4	351.7	361.7	363.0
	SD	9.45	9.14	14.51	11.64	7.24
	c.v. (%)	2.61	2.53	4.13	3.22	1.99
		18M	24M	30M	36M	39M
	Max	[redacted]				
	Min					
	Mean	384.7	363.9	415.6	382.4	366.7
	SD	7.11	5.54	11.25	15.67	22.29
	c.v. (%)	1.85	1.52	2.71	4.10	6.08

Fabric of Lot76062, 76063 and 76064 is [redacted]

↑ : max in this Table, ↓ : min in this Table

Table 2. Drug Release of Thirty-five Commercial Lots and Three Validation Lots of ———, Lidocaine USP Patch (——Batch and 14 Batches/Lot/Day)

Amount of drug release (mg/patch) at 30minutes: (n=14)

Lot No.	5917*1	5918*1	5919*1	5920*2	5921
Max	—	—	—	—	—
Min					
Mean	321.4	333.2	328.9	307.8	297.7
SD	10.34	12.02	12.14	6.10	9.50
c.v. (%)	3.22	3.61	3.69	1.98	3.19
Lot No.	6914	6915	6916	6917	6918
Max	—	—	—	—	—
Min					
Mean	310.0	322.8	313.3	331.5	328.1
SD	11.07	9.25	11.05	12.71	7.57
c.v. (%)	3.57	2.86	3.53	3.84	2.31
Lot No.	7912	7913	7914	7915	7916
Max	—	—	—	—	—
Min					
Mean	331.7	318.3	330.9	323.0	332.8
SD	17.74	16.84	8.37	8.51	15.48
c.v. (%)	5.35	5.29	2.53	2.63	4.65
Lot No.	9911	9913	9914	9915	9916
Max	—	—	—	—	—
Min					
Mean	309.9	312.9	320.6	315.5	313.0
SD	10.34	9.11	16.25	11.90	13.02
c.v. (%)	3.34	2.91	5.07	3.77	4.16
Lot No.	Y903*3	Y904*3	Y905*3	Y906*3	Y908*3
Max	—	—	—	—	—
Min					
Mean	332.7	309.7	315.8	331.6	345.9
SD	10.30	11.58	9.17	15.88	3.88
c.v. (%)	3.10	3.74	2.90	4.79	1.12
Lot No.	Z906*3	Z907*3	Z908*3	Z909*3	Z910*3
Max	—	—	—	—	—
Min					
Mean	318.7	294.4	310.6	299.7	302.7
SD	4.43	6.10	4.55	11.84	14.67
c.v. (%)	1.39	2.07	1.46	3.95	4.85
Lot No.	Z911*3	Z913*3	Z914*3	Z927*3	Z928*3
Max	—	—	—	—	—
Min					
Mean	292.1	297.1	301.2	306.6	312.4
SD	6.57	2.78	4.75	5.60	6.88
c.v. (%)	2.25	0.93	1.58	1.83	2.20
Lot No.	Z929*3	1005*3	1006*3		
Max	—	—	—		
Min					
Mean	311.7	312.0	319.1		
SD	3.82	8.52	5.36		
c.v. (%)	1.22	2.73	1.68		

*1: Validation Lot, n=84, *2: n=10, *3: n=6

Table 3. Commercial Lots of [redacted] Lidocaine USP Adhesive Patch that Fail to Meet the Drug Release Lower Limit Specification of [redacted] that is Approved for the [redacted] Patch (Given that Drug Release Lower Limit Specification = Mean - 3σ)

Lot No.	5921	9915	Z907	Z909	Z910	Z911
Max	[redacted]					
Min						
Mean	297.7	315.5	294.4	299.7	302.7	292.1
SD	9.50	11.90	6.10	11.83	14.67	6.57
c.v. (%)	3.19	3.77	2.07	3.95	4.85	2.25
Mean -3σ	269.2	279.8	276.1	264.2	258.7	272.4

III. RECOMMENDATION

Supplement S-003 submitted to NDA 20-612 for lidocaine USP (Lidoderm®) 5% adhesive patch by the sponsor on February 15, 2001has been reviewed by the Division of Pharmaceutical Evaluation II of the Office of Clinical Pharmacology and Biopharmaceutics. The efficacy implications of changing the lower limit specification of drug release from [redacted] is not known. Accordingly, the proposed drug release specification [redacted] is not acceptable.

Please convey this Recommendation, as appropriate, to the sponsor.

David G. Udo, Ph.D.
Division of Pharmaceutical Evaluation II

Concurrence: Suresh Doddapaneni, Ph.D. _____

cc: NDA 20-612, HFD-170, HFD-170 (Governale), HFD-870 (Malinowski, Hunt, Doddapaneni and Udo), CDR (Attn: Zom Zadeng).

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/s/

David Udo
8/14/01 03:42:53 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
8/15/01 01:32:00 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-612 / S-003

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-612/S-003

Teikoku Pharma USA, Inc.
745-D Camden Ave.
Campbell, CA 95008-4146

Attention: Larry Caldwell, Ph.D.
Vice President, Scientific Affairs

Dear Dr. Caldwell:

We acknowledge receipt on March 27, 2002, of your March 26, 2002, resubmission to your supplemental new drug application for Lidoderm (lidocaine) patch.

With this amendment, we have received a complete response to our action letter dated March 15, 2002.

If you have any question, me at (301) 827-7432.

Sincerely,

{See appended electronic signature page}

Kimberly Compton
Regulatory Project Manager
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Kimberly Compton
5/10/02 02:54:45 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-612/S-003

Teikoku Pharma U.S.A., Inc.
745-D Camden Avenue
Campbell, CA 95008-4146

Attention: Larry J. Caldwell
Vice President, Scientific Affairs

Dear Mr. Caldwell:

We acknowledge receipt on September 17, 2001, of your September 14, 2001, resubmission to your supplemental new drug application for Lidoderm™ (lidocaine) Adhesive Patch 5%.

This resubmission contains additional information submitted in response to our August 15, 2001, action letter.

With this amendment, we have received a complete response to our August 15, 2001, action letter.

If you have any questions, call me at (301) 827-7410.

Sincerely,

{See appended electronic signature page}

Laura Governale, Pharm.D.
Regulatory Project Manager
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Laura Governale
9/18/01 02:56:59 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-612/S-003

PRIOR APPROVAL SUPPLEMENT

Teikoku Pharma USA, Inc.
745-D Camden Avenue
Campbell, CA 95008-4146

Attention: Larry J. Caldwell, Ph.D.
Vice President, Scientific affairs

Dear Dr. Caldwell:

We have received your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Lidoderm™ (lidocaine USP) Adhesive Patch
NDA Number:	20-612
Supplement number:	S-003
Date of supplement:	February 15, 2001
Date of receipt:	February 15, 2001

This supplemental application proposes a change in the adhesive strength upper limit specification and broadening the existing drug release specifications.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on April 16, 2001, in accordance with 21 CFR 314.101(a).

All communications concerning this supplement should be addressed as follows:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthetics, Critical Care and
Addiction Drug Products, HFD-170
Attention: Document Room 9B23
5600 Fishers Lane
Rockville, Maryland 20857

If you have any question, call me at (301) 827-7410.

Sincerely,

Laura Governale, Pharm.D.
Regulatory Project Manager
Division of Anesthetic, Critical Care and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

/s/

Laura Governale
2/21/01 05:13:53 PM