

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206976Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: ADEQUATE

**NDA
206976
Review #2**

Drug Name/Dosage Form	Licart(Diclofenac Epolamine) Topical System, 1.3% (b) (4)
Strength	1.3% (product contains 182 mg/system)
Route of Administration	Topical
Rx/OTC Dispensed	Rx
Applicant	IBSA Institut Biochimique SA
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Resubmission	25-JUN-2018	ONDP (API, DB, DP), OPF
IR Response	30-JUL-2018	ONDP (DP)
IR Response	29-AUG-2018	ONDP (DP), OPF
IR Response	14-SEP-2018	ONDP (DB)
IR Response	25-SEP-2018	ONDP (DB)
IR Response	01-OCT-2018	OPF
IR Response	02-NOV-2018	ONDP (OB)

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Paresma Patel	OPQ/ONDP/DNDPAPI/BII
Drug Product	Paresma Patel	OPQ/ONDP/DBRUP/BII
Process	James Norman	OPQ/OPF/DPAII/BV
Microbiology	N/A this cycle	
Facility	Cassandra Abellard	OPQ/OPF/DIA/BII
Biopharmaceutics	Suneet Shukla	OPQ/ONDP/DB/BII
Regulatory Business Process Manager	Steven Kinsley	OPQ/OPRO/RBPMI/BI
Application Technical Lead	Caroline Strasinger	OPQ/ONDP/DBRUP/BV

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

DMFs:

DMF #	Holder	Item Referenced	Status	Date Review Completed	Comments
		(b) (4)	ADEQUATE	17-JUL-2018	
			ADEQUATE	06-AUG-2018	
			ADEQUATE	17-JUL-2018	

2. CONSULTS

DISCIPLINE	STATUS	RECOMMEN DATION	DATE	REVIEWER
Biostatistics	Complete	Adequate	9-JUL-2018	Chao Wang
CDRH	N/A*	No longer required		
Other – Adhesion	Complete	Adequate	3-OCT-2018	Caroline Strasinger

Executive Summary

I. Recommendations and Conclusion on Approvability

Based on the recommendations from ONDP (inclusive of drug substance, drug product, and biopharmaceutics), OPF (inclusive of process, facilities, and microbiology), the Office of Pharmaceutical Quality recommends **approval for NDA 206976**. A shelf-life of 24 months is granted to this product. Additionally, from a quality perspective, the formulation and product design of the system used in clinical study CRO-PK-317 demonstrates adequate *in vivo* adhesion.

II. Summary of Quality Assessments

A. Product Overview

The proposed Licart (diclofenac epolamine) topical system, 1.3% is (b) (4) to Flector® Patch which was approved in 2007 by the FDA for the treatment of pain associated with minor sports injuries. According to the applicant, the difference between the two topical systems is that Licart contains heparin (as an excipient) which allows for release of the API over 24 hours versus Flector Patch (containing no heparin) which releases the API over 12 hours, although the strength of both is expressed as the same, 1.3%. Each Licart topical system contains 182 mg of diclofenac epolamine (b) (4)

(b) (4) The systems are contained in a re-sealable envelope (b) (4)

(b) (4) with each envelope containing (b) (4) 5 topical systems. The envelopes are packed into a carton box. A shelf-life of 24 months is granted to this product.

Proposed Indication(s) including Intended Patient Population	Topical treatment of acute pain due to minor strains, sprains, and contusions
Duration of Treatment	Shortest duration consistent with individual patient treatment goals
Maximum Daily Dose	One LICART system applied to the most painful area once daily (1.3% for 24 hours of wear)
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance:

(b) (4)

(b) (4)

(b) (4) Diclofenac epolamine is a salt. DMF (b) (4) was referenced for the drug substance and found adequate by Erika E. Englund, Ph.D. on 12/9/2016. In the 2018 NDA resubmission, updated drug substance specifications were included and the test for (b) (4) was also removed based on a risk assessment in accordance with ICH Q3D. Paresma Patel reviewed the new information and the drug substance and all associated DMFs remain adequate for use in the drug product and for reference under NDA 206976.

Drug Product:

LICART is a topical system (b) (4) is a non-woven polyester felt, followed by a (b) (4) adhesive (b) (4) containing the API, heparin and a multitude of other excipients, and (b) (4) a removable polypropylene release liner. Each Licart topical system contains 182 mg of diclofenac epolamine (b) (4) (b) (4) (b) (4) (b) (4) The size of a single system is (b) (4) approximately 140 cm². (b) (4) (b) (4) (b) (4)

The drug product is manufactured by Teikoku Seiyaku Co. LTD in Japan. The manufacturing process is (b) (4) (b) (4)

#1 for additional detail. As part of the 2018 resubmission, the applicant withdrew the (b) (4) manufacturing site and is now only proposing Teikoku as the commercial manufacturer which is consistent with where the clinical trial batches were manufactured. Additionally, in 2017 Teikoku manufactured (b) (4) new batches to support the resubmission and for use in the Complete Response Letter (CRL) #1 requested in vivo adhesion study. The intended commercial manufacturing process at Teikoku has been validated. The overall process control strategy has been deemed adequate by the process reviewer and concerns with heparin uniformity throughout the system has been addressed in the resubmission. The applicant provided adequate data to demonstrate comparability of the clinical drug product batches from 2013 and the proposed commercial drug product (2017 registration and stability batches). The release and stability specification have been deemed adequate by the Drug Product and Biopharmaceutics Reviewers. With the resubmission the applicant developed a new in vitro release method. Stability data for the Teikoku batches are adequate to support an expiry of 24 months when stored

in the original envelope at 20-25°C (68-77°F) with excursions of 15-30°C (59-86°F) permitted. Refer to [DP Review #2](#) for additional information.

In the [Review #1](#) (18-FEB-2016) thirteen quality related deficiencies were noted from Drug Product, Process, and Biopharmaceutics disciplines. The review #2 for all disciplines focused on the responses to the 13 CMC deficiencies and the new batch information provided. Note, that the removal of the (b) (4) site addressed several of the previous deficiencies associated with the new manufacturing site and bridging of the two sites. The remaining deficiencies were addressed adequately in the resubmission and are briefly summarized below. Refer to each discipline's specific review for more detail.

(b) (4)

Special Product Quality Labeling Recommendations

- Diclofenac epolamine is a salt and as such label and labeling should carry a salt equivalency statement, despite the original Flector not carrying the statement. The OPQ nomenclature group was consulted and the following statement is recommended for the back panel of the label as well as to include comparable language in the PI as appropriate.

“Each LICART topical system contains 182 mg of diclofenac epolamine. Each gram of adhesive contains 13 mg of diclofenac epolamine (equivalent to 9.4 mg diclofenac).”

- The term (b) (4) is not a preferred term for this dosage form as noted in USP <1151> Dosage Forms. All instances of (b) (4) in the Label and Labeling should be replaced with LICART, topical system, or system as appropriate.
- The in vivo adhesion review notes perfect adhesion in the controlled wear trial with calf application. The proposed labeling indicates taping or overlay may be used as needed (consistent with Flector Label). Given the evidence of perfect adhesion, OND may need to consider the appropriateness of inclusion of taping instructions as well as if results of the adhesion study should be included in Section 14.



Caroline
Strasinger

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NDA 206976
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LABELING

I. Package Insert

The relevant sections of the PI were updated with the strength of the drug product (1.3%) following an information request to the applicant. Revised PI labeling, carton labeling, and container labels were submitted on 05-Nov-2018 (SD 57). The recommended edits to the CMC sections of the PI are shown in red below.

(b) (4)

Reviewer's Assessment of Package Insert: *Adequate.*

The CMC sections: Highlights—Dosage Forms and Strength, Section 3, Section 11, and Section 16 of the prescribing information meet all regulatory requirements. The suggested edits are provided in red for each section above.

The strength of the drug product will be consistent with the listed drug and based on the salt form diclofenac epolamine. A salt equivalency statement was added to Section 11 of the drug product based on a recommendation from the Product Quality Labeling team.

The recommendations will be sent to the applicant for acceptance.

II. Labels:

The following IRs were sent to the Applicant on 30-Oct-2018 and Responses Received on 05-Nov-2018 (SD57):

- **CMC Comment:** Include a salt equivalency statement on the back panel of your container label and carton labeling, preferably above the inactive ingredients list. For example: "Each LICART topical system contains 182 mg of diclofenac epolamine. Each gram of adhesive contains 13 mg of diclofenac epolamine (equivalent to 9.4 mg diclofenac)."

Applicant Response: The applicant provides a salt equivalency statement on the carton and container labels.

Evaluation: *Adequate.*

- **CMC Comment:** We note that the draft labeling submitted on 25-June-2018 does not include the strength as part of the embossed text, and the submission on 16-Feb-2017 does include the strength (1.3%) in the embossed text. We recommend

that the proposed embossed text include the strength and be consistent with the carton labeling and container label (i.e. LICART (diclofenac epolamine) topical system 1.3%). Provide clarification and updated embossing text in your submission.

Applicant Response: The applicant requested clarification regarding the presentation of the strength based on a prior communication from the Agency. The applicant revised the embossed text to include the strength (1.3%).

Evaluation: *Adequate.*

- **CMC/DMEPA Comment:** To comply with 21 CFR 201.10 (d)(1), include the strength of the product on the principal display panel of the container label and carton labeling. For example, revise to read: Licart (diclofenac epolamine) topical system 1.3%

Applicant Response: The applicant included the strength on the container label and carton labeling. The applicant also provided updated PI labeling that includes the strength.

Evaluation: *Adequate.*

- **CMC/DMEPA Comment:** To comply with 21 CFR 201.10(i)(I) and 21 CFR 201.17, ensure the lot and expiration date are included on the container label and carton labeling. Additionally, to minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use to express the expiration date. We recommend using a format like either:
DDMMYYYYY (e.g., 31JAN2013)
MMYYYYY (e.g., JAN2013)
YYYY-MMM-DD (e.g., 2013-JAN-31)
YYYY-MM-DD (e.g., 2013-01-31)

Applicant Response: The applicant included the lot and expiration date and format on the container label and carton labeling.

Evaluation: *Adequate.*

- **CMC/DMEPA Comment:** For consistency, we recommend replacing the dash symbol located in the storage statement with the word “to”. For example, revise to, “Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].”

Applicant Response: The applicant included revised the storage statement to include the reference to USP Controlled Room Temperature and the format was revised.

Evaluation: *Adequate.*

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(b) (4)

Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2)))	X	X
Dosage strength	X	X
Net contents	X	X
“Rx only” displayed prominently on the main panel	X	X
NDC number (21 CFR 201.2)	X	X
Lot number and expiration date (21 CFR 201.17)	X	X
Storage conditions	X	X
Bar code (21CFR 201.25)	X	X
Name of manufacturer/distributor	X	X
And others, if space is available		

Reviewer’s Assessment of Labels: Adequate.

The carton labeling and container labels comply with the regulatory requirements from the perspective of CMC. During the review cycle the applicant was asked to include the strength of the drug product (1.3%) on all labels, labeling, and embossed text.

The applicant was also asked to include a salt equivalency statement on the back panel of the container label and carton labeling.

Overall Assessment and Recommendation: Adequate, upon acceptance of the recommendations provided above. The PI labeling, carton labeling, and container label meet regulatory requirements.

Primary Labeling Reviewer Name and Date:

Paresma Patel, Ph.D.
November 06, 2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Donna Christner, Ph.D.
November 06, 2018



Paresma
Patel

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BIOPHARMACEUTICS**Product Background:****NDA:** NDA-206976-ORIG-RESUB-46**Drug Product Name / Strength:** Diclofenac epolamine topical system (Licart™)/1.3% (b) (4)
Topical (b) (4) /182 mg (b) (4)**Route of Administration:** Topical**Applicant Name:** Institut Biochimique SA (IBSA)***Review Summary:***

The current submission is a resubmission to the original NDA 206976 for Diclofenac epolamine topical system (Licart™)/1.3% (b) (4) Topical (b) (4) /182 mg (b) (4) from Institut Biochimique SA (IBSA). The drug product is a topical dosage form (b) (4) containing the active pharmaceutical ingredient diclofenac epolamine (182 mg (b) (4), (b) (4) on a non-woven felt backing and covered with a polypropylene film release-liner which is removed prior to application of the (b) (4) to the skin. This drug product is (b) (4) to the Flector Patch previously approved in January 2007 for the treatment of pain associated with minor sport injuries (NDA 21234), (b) (4)

The application received a ‘Complete Response’ decision during last cycle. The Biopharmaceutics review (see Biopharmaceutics review in panorama by Drs. Min Li and Sandra Sharp) had two issues as below:

- (1) The weight-of-evidence approach (risk-based approach) to support the manufacturing site change from Teikoku (b) (4) was considered inadequate due to the issues with the drug product formulation, process, and in process controls.
- (2) The in vitro release method was considered inadequate as the method did not demonstrate a discriminating ability of the method towards meaningful changes of the critical material attributes or process parameters.

To address the issue under bullet point 1 above, the Applicant withdrew (b) (4) as a new manufacturer thereby eliminating the need for manufacturing site bridging. Further, no major changes were introduced into the manufacturing process of Diclofenac epolamine topical system from the time the clinical batches were produced in 2013. Therefore, a comparative drug release testing is not necessary between the batches manufactured in 2013 for clinical purposes that expired in March 2016, and current validation batches manufactured in November 2017.

The Applicant also developed and validated a new drug release method with discriminatory ability relating to critical quality attributes. The new method was used for release of the validation batches manufactured at the Teikoku site.

The Biopharmaceutics review is focused on evaluating the in vitro drug release method and in vitro drug release acceptance criteria as part of the drug product specifications.

- 1. In vitro drug release method and acceptance criteria:** The following table summarizes in vitro release method and acceptance criteria. These acceptance criteria were agreed upon with the Applicant (refer to submission dated 11/02/2018; [Application 206976 - Sequence 0055 - 0055 \(56\) 11/02/2018 TRIAGE-1 /Electronic Submission/Gateway](#)).

Apparatus	Speed (rpm)	Medium/Temperature	Volume (mL)	Sampling points/Detection method	Dissolution acceptance criteria
Paddle overdisk, disk assembly (b) (4) (u) (4)	50	Phosphate buffer pH6.0/ 32.0 C ± 0.5 C	500	30-240-600 minutes* *For comparative testing, additional sampling points could be employed; i.e. 60, 120, 360, 480, 600 min. HPLC detection using UV Detector λ= 254 nm	30 min: (b) (4) % 240 min: (b) (4) % 600 min: Not less than (b) (4) % and complies with USP <724>, L1, L2 and L3 specifications

The in vitro release method was found acceptable based on its ability to discern in vitro drug release rate variations in drug product batches.

2. Bridging of formulations:

- i. *Phase 3 pivotal batches to validation batches:* Based on the Applicant's and FDA/OPQ reviewer's analyses, the changes implemented are considered minor requiring compliance with the recommended in vitro drug release acceptance criteria. Therefore, no bridging of formulation is required.

Recommendation: From Biopharmaceutics perspective, NDA 206976 for Diclofenac epolamine topical system is **recommended for approval**.

List Submissions being reviewed (table):

06/25/2018	Application 206976 - Sequence 0044 - 0044 (46) 06/25/2018 ORIG-1 /Resubmission/Class 2
03/04/2015	Application 206976 - Sequence 0000 - 0000 (1) 03/04/2015 ORIG-1 /Multiple Categories/Subcategories
09/14/2018	Application 206976 - Sequence 0050 - 0050 (52) 09/14/2018 ORIG-1 /Quality/Response To Information Request
09/25/2018	Application 206976 - Sequence 0052 - 0052 (53) 09/25/2018 ORIG-1 /Quality/Response To Information Request
11/02/2018	Application 206976 - Sequence 0055 - 0055 (56) 11/02/2018 TRIAGE-1 /Electronic Submission/Gateway

Highlight Key Outstanding Issues from Last Cycle: The application received a ‘Complete Response’ decision during last cycle with two issues as below

- (1) The weight-of-evidence approach (risk-based approach) to support the manufacturing site change from Teikoku (b) (4) was considered inadequate due to the issues with the drug product formulation, process, and in process controls.
- (2) The in vitro release method was considered inadequate as the method did not demonstrate a discriminating ability of the method towards meaningful changes of the critical material attributes or process parameters.

Concise Description Outstanding Issues Remaining: None

Comments for the Applicant: None

BCS Designation:

Reviewer’s Assessment: The BCS classification of the API in this topical product is not relevant for regulatory decision-making of this NDA, because BCS classification system is mainly designed for oral drug products.

Solubility: The solubility of the active ingredient DHEP was tested at (b) (4) different pH values from (b) (4) at 32°C solution temperature. (b) (4)

Results are provided in Table 1 (from 3.2.P.5.3).

Table 1: DHEP Solubility at Different pH

(b) (4)

Reviewer's Assessment: Adequate

Solubility: (b) (4) A medium of pH 6.0 was selected for in vitro drug release study based on the appropriateness of the in vitro release profiles (see selection of in vitro release medium in in vitro release method development below).

Permeability: No data provided

In vitro drug release: See 'In vitro drug release method and Acceptance Criteria' below.

In Vitro Drug Release Method development and Acceptance Criteria

The drug release method was developed using Apparatus 5 (paddle over disk) as below.

Selection Dissolution Medium: pH

(b) (4)

(b) (4) The DHEP in vitro release profile for drug product batch 160727 (Teikoku manufacturer) in phosphate buffer media with various pH are provided in Figure 1 (from 3.2.P.5.3). The profile obtained at pH 6.0 was considered the most appropriate.

(b) (4)

Selection Dissolution Medium: Volume

Dissolution medium (Phosphate buffer pH 6.0) was used to compare the in vitro release obtained with two vessel volumes 500 mL (b) (4). Since, no meaningful difference was observed in the two conditions, a volume of 500 mL was selected. It should be noted that the sink conditions were achieved in 500 ml volume also (see below- sink conditions).

Selection of Apparatus

Apparatus 5 (paddle over disk) was selected as recommended by the USP General Chapter <724> Drug Release. Temperature of the medium in the vessel is $32 \pm 0.5^{\circ}\text{C}$. The agitation speed is 50 RPM, which is the lowest speed applicable with Apparatus 5. Stainless steel disk assembly (b) (4)

Sample Size Assessment

The sample is obtained from a portion of the (b) (4) and the disk assembly as referenced in USP <724> was used. A (b) (4)

(b) (4)

Figure 2a-b

(b) (4)

Verification of Sink Conditions in Selected Medium Volume

DHEP solubility was tested in the presence of drug product excipients at DHEP saturation, and it was verified that the volume of medium selected for the in vitro release method was more than three times the saturation volume. (b) (4)

(b) (4)

The theoretical content of DHEP in the portion of (b) (4) used for the test (b) (4) (b) (4) contains 182 mg of DHEP and has surface 140 cm², (b) (4)

(b) (4) It can be concluded that the sink conditions are achieved during in vitro release studies.

Stability of DHEP in Medium

To evaluate the stability of DHEP in the medium, three samples were prepared: DHEP working standard (WS) in medium; DHEP and placebo in medium; (b) (4) sample in medium. The samples were analyzed immediately after their preparation (T0), and after 24, 48 and 72 hours to demonstrate their stability. The recovery results were within the range 98.0-102.0% and showed that DHEP is stable in the medium for 72 hours.

Potential DHEP Adsorption in Filters and Compatibility with Glass and Plastic Materials

The recovery of DHEP was assessed with the types of materials used in the analytical method to verify potential adsorption. (b) (4)

(b) (4)

A 1.4 cm x 1.4 cm portion of (b) (4) and a reconstituted sample of DHEP and placebo were subjected to the drug release test conditions for three hours. Samples were filtered with the two types of filters and analyzed. The results were compared to each other by calculating the recovery of DHEP referred to the centrifuged solutions. Recovery results in Table 3 showed no adsorption effect, and (b) (4) filter was selected.

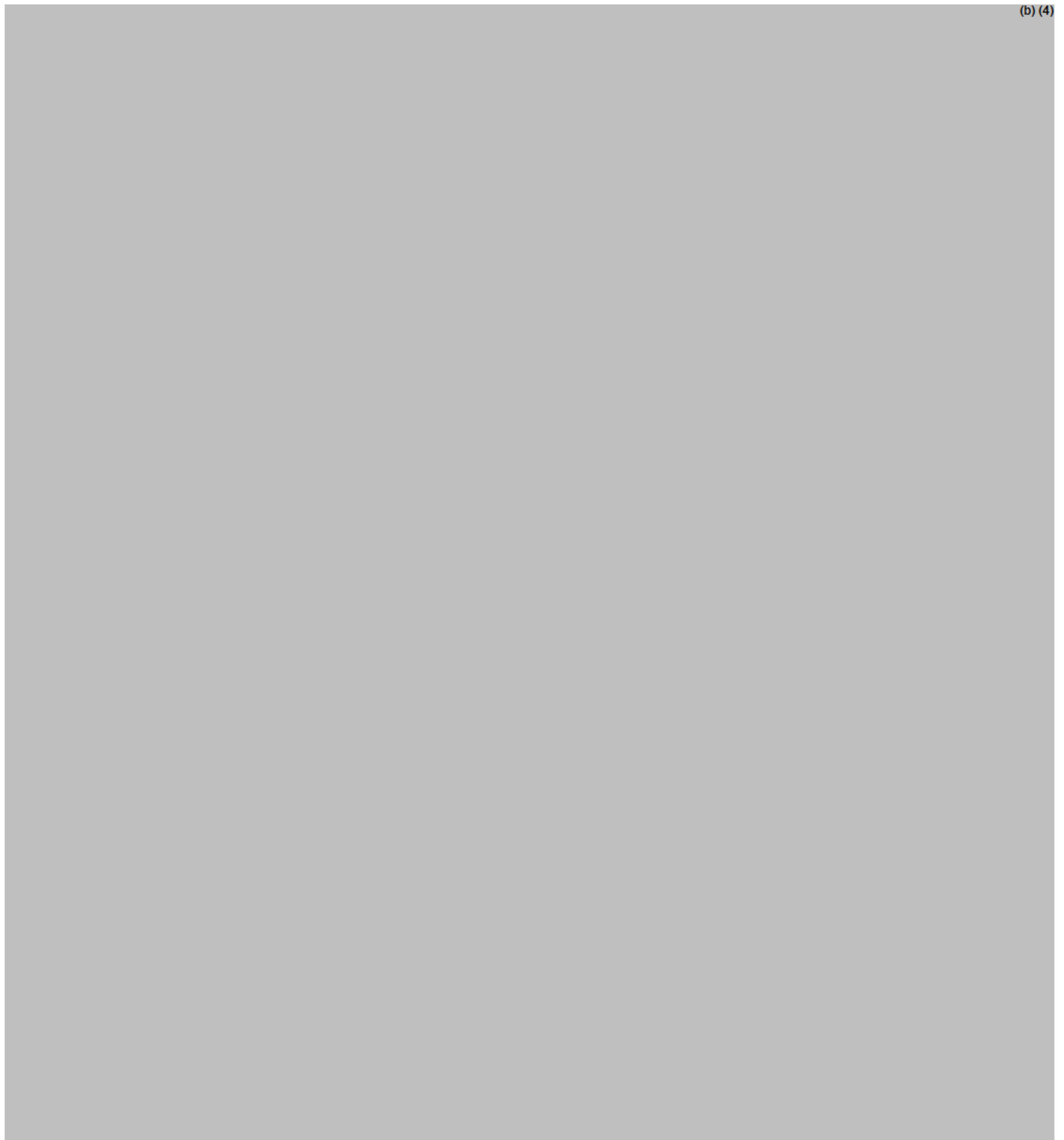
Table 3: DHEP Recovery %

Sample	Recovery with (b) (4) (b) (4) Filter	Recovery with (b) (4) (b) (4) Filter
Batch 160726	104.62%	100.32%
DHEP and placebo	102.25%	100.40%

(b) (4)

The results showed no adsorption occurred.

(b) (4)

**Discriminating Ability**

The discriminating ability of the above in vitro release method was demonstrated by comparing in vitro release profiles of formulations that were intentionally manufactured with meaningful changes for the most relevant critical manufacturing variables (Table 4).

Table 4: Discriminatory Ability Study Plan

(b) (4)



f2-similarity factor was calculated, with all time points being included in the calculus that met the guidance criteria, but an in vitro release profile that did not have an acceptable release value (b) (4) % was not used for comparison.

Reviewer's Assessment: Adequate

(b) (4)
(b) (4) the release profile appears adequate using Apparatus 5. Therefore, the selection of Apparatus 5 appears adequate for the in vitro release studies.

The Applicant demonstrated the discriminating ability of the method (b) (4)
(b) (4)

Assessment of in vitro release acceptance Criteria

The time points used for setting the in vitro release acceptance criteria were selected based on above discriminating study results that were critical to similarity test failure. Mean DHEP release values were determined based on above in vitro release method from (b) (4) industrial batches of different ages, manufactured by Teikoku according to the same process, site and quality standards used to prepare the clinical batches. The Applicant selected earliest time point of 30 minutes to define initial (b) (4) behavior and the final time point of (b) (4) minutes where release of active is essentially complete, the intermediate sampling points from 60 minutes to 600 minutes were compared to identify the time point that showed most powerful discriminatory ability (i.e. maximum absolute difference in drug release between pre-change and post-change that caused

similarity test failure). The mean values for the difference between the standard and modified batches that failed the similarity tests is shown below (Table 6).

Table 6: DHEP Release and Absolute Difference in Discriminating Study

Batch	Changes to Formulation/Process	DHEP % (Abs. Diff. vs STD %)					
		60 min	120 min	240 min	360 min	480 min	600 min
17047MP2		(b) (4)					
17051MP2							
17052MP2							
17049MP2							
170627-dried							
17064MP2B							
17064MP2A							
Mean of Abs Diff. vs STD %		12	13	17	14	10	10

Samples obtained from modified drug product at 240 minutes exhibited the greatest mean difference in DHEP release in comparison to the standard and was chosen as the intermediate time point for routine drug product release testing. Subsequently, drug product release specifications were developed for the 30 min, 240 min and (b) (4) minutes' time points as summarized below.

(b) (4) industrial batches of different ages (from < 6-month to ~30-month), manufactured by Teikoku according to the same manufacturing process as Clinical batches, were tested in replicates of 12, and the results along with a statistical summary are provided in Table 7.

Table 7: Data and Statistical Analysis of (b) (4) Batches

Batch (Age)	Disk #	DHEP %		
		30 min	240 min	(b) (4) min
150624 (30 months)	1	(b) (4)		
	2			
	3			
	4			
	5			
	6			
	7			
	8			
	9			
	10			
	11			
	12			
150625 (30 months)	1			
	2			
	3			
	4			

Batch (Age)	Disk #	DHEP %		
		30 min	240 min	(b) (4) min
	5			
	6			
	7			
	8			
	9			
	10			
	11			
	12			
	1			
	2			
	3			
	4			
160726 (17 months)	5			
	6			
	7			
	8			
	9			
	10			
	11			
	12			
	1			
	2			
	3			
	4			
160727 (18 months)	5			
	6			
	7			
	8			
	9			
	10			
	11			
	12			
	1			
	2			
	3			
	4			
170627 (5 months)	5			
	6			
	7			
	8			
	9			
	10			
	11			
	12			
	1			
	2			
	3			
	4			
170628 (6 months)	5			
	6			
	3			
	4			
	5			
	6			

Batch (Age)	Disk #	DHEP %		
		30 min	240 min	(b) (4) min (b) (4)
	7			
	8			
	9			
	10			
	11			
	12			
171107 (5 months)	1			
	2			
	3			
	4			
	5			
	6			
	7			
	8			
	9			
	10			
	11			
	12			
171108 (2 months)	1			
	2			
	3			
	4			
	5			
	6			
	7			
	8			
	9			
	10			
	11			
	12			
Mean		30.66	69.79	(b) (4)
Min		19.92	55.14	
Max		43.65	89.61	
SD		4.80	8.44	
CV		10.99	9.41	

The Applicant determined the proposed original acceptance criteria as follows: (1) for the initial and intermediate time points, the specifications were $\pm$ (b) (4) % around the corresponding mean release value, and (2) for the terminal time point, release must be greater than (b) (4) % (Table 8).

Table 8: Proposed Specifications – Drug Release DHEP %

	Time Points (min)		
	30	240	(b) (4)
DHEP Release	(b) (4) %	(b) (4) %	(b) (4) %
Justification	Early time point.	Intermediate time point chosen to define the in vitro release rate profile.	(b) (4)

To confirm that routine in vitro release testing with three-time points could preserve the discriminating essence of the procedure as shown with multiple-time-point f2 testing, the Applicant compared data obtained from the modified batches are presented in Table 9.

Table 9: Proposed Specifications – Drug Release DHEP %

Batch	Changes to Formulation/Process	F2*	DHEP % Mean 12 Units			OOS†
			30 min (b) (4) %	240 min (b) (4) %	(b) (4) min (b) (4) %	
17047MP2	(b) (4)	-	(b) (4)			(b) (4)
17051MP2		44.1				
17052MP2		44.4				
17053MP2		68.3				
17054MP2		67.9				
17049MP2		44.6				
17050MP2		65.5				
170627-Deyhydrated		41.2				
17065MP2		72.5				
17068MP2		58.3				
17064MP2B		N/C‡				
17064MP2A		N/C				
17045MP2		N/C				
17044MP2		57.4				

* F2 calculated on 12 units; † Out of proposed drug release specifications (also in red). ‡ Not calculable.

(b) (4)

Reviewer's Assessment: Adequate

It should be noted that the above in vitro release studies for determination of the acceptance criteria were not performed on the pivotal clinical batches since the clinical batches expired in 2016 and the proposed in vitro release method was developed later. Instead, the Applicant used (b) (4) industrial batches of different ages (from < 6-month to ~30-month), manufactured at the same site (Teikoku, where the clinical batches were manufactured) according to the same manufacturing process as Clinical batches. The reviewer confirmed with the Process and the Drug Product reviewers in the CMC team that there is no or minimal change in the

manufacturing process between the clinical and the industrial batches. However, as stated above, the industrial batches are up to 30 months old. The Agency's policy is to set the acceptance criteria based on the pivotal batches. However, in the absence of pivotal batches, data from the fresh validation batches and not the stability/ industrial batches should be used to determine the in vitro release acceptance criteria.

The following IR was sent to the applicant on 8/27/2018 clarifying above issues.

We are in the process of reviewing your NDA and have identified some issues and the lack of some relevant information/data as follows. Before we can continue with the review of the biopharmaceutics related data and adequacy of the dissolution acceptance criteria, we request that you consider the following recommendation:

1. We acknowledge your batch release data submitted on 7/30/2018. However, it is not clear when the analysis for DHEP Drug Release was done on the three validation batches. Provide the complete dissolution data [individual (n=12), mean, range, %RSD at each time point, and mean profiles] for these batches. Report the dissolution data as the cumulative percentage of drug dissolved with time (the percentage is based on the product's label claim). Provide detailed information for the tested batches of drug product using your proposed dissolution method (i.e., Batch/Lot No., manufacturing date, manufacturing site, testing date, batch size, dissolution testing protocol effective date, etc.). Further, provide a complete dissolution profile data including 30, 60, 120, 240, 360, 480, 600 and (b) (4) minute time points, if available.
2. You used in vitro dissolution data from (b) (4) industrial batches to propose the dissolution acceptance criteria. Note that, the Agency's policy is to set the acceptance criteria based on the pivotal clinical batches. However, given the nature of your development program and in the absence of pivotal batches, data from the fresh validation batches and not the stability/industrial batches will be used to establish the dissolution acceptance criteria. We remind you that a $\pm 10\%$ variation is allowed in the dissolution release values obtained in this case, from the fresh validation batches. A higher value (such as (b) (4) as proposed by you) may be allowed only if supported by clinical justification or a valid IVIVC which is not provided in this submission. Considering this, revise your proposed dissolution acceptance criteria based on the dissolution values obtained from fresh validation batches and submit the data for Agency's review.

In addition, please be advised, that all validation batches are expected to meet the revised dissolution acceptance criteria in your stability program through your proposed expiry period. Discuss any corrective actions to avert any dissolution failures and provide a new batch to demonstrate correction of the issue, if needed.

The applicant responded on 09/14/2018 (see detailed response [Application 206976 - Sequence 0050 - 0050 \(52\) 09/14/2018 ORIG-1 /Quality/Response To Information Request](#)) and additionally responded on 09/25/2018 ([Application 206976 - Sequence 0052 - 0052 \(53\) 09/25/2018 ORIG-1 /Quality/Response To Information Request](#)).

In response to IR1 comments, the Applicant stated that the age of the process validation batches at the time of DHEP in vitro release test were 6 months (Table below).

Table: Age of PV Batches at DHEP Drug Release Testing by QC

Batch	Manufacturing Date	DHEP Drug Release Testing Date	Batch Age at Testing Date
171107	11/07/2017	05/07/2018	6 months
171108	11/08/2017	05/02/2018	6 months
171109	11/09/2017	05/03/2018	6 months

The Applicant further stated that in vitro release test for the PV batches (#171107 and #171108) were also part of the method development program where these batches were also tested according to the final regulatory method at the age of five and two months as below:

Table 1.11.1.1.2: DHEP Release % of Label Claim - Batch 171107 – Age 5-Month (R&D)

Time Points	Disk 1	Disk 2	Disk 3	Disk 4	Disk 5	Disk 6	Disk 7	Disk 8	Disk 9	Disk 10	Disk 11	Disk 12	Mean	CV
30	(b) (4)												25	7.3
60	(b) (4)												35	7.0
120	(b) (4)												46	6.1
240	(b) (4)												60	5.8
360	(b) (4)												71	5.7
480	(b) (4)												78	5.3
600	(b) (4)												84	5.2
(b) (4)	(b) (4)												100	7.1

Table 1.11.1.1.3: DHEP Release % of Label Claim - Batch 171108 – Age 2-Month (R&D)

Time Points	Disk 1	Disk 2	Disk 3	Disk 4	Disk 5	Disk 6	Disk 7	Disk 8	Disk 9	Disk 10	Disk 11	Disk 12	Mean	CV
30	(b) (4)												24	6.2
60	(b) (4)												35	6.1
120	(b) (4)												48	5.1
240	(b) (4)												64	4.6
360	(b) (4)												75	4.0
480	(b) (4)												83	4.0
600	(b) (4)												90	3.9
(b) (4)	(b) (4)												101	2.9

The Applicant stated that the comparison of the two curves showed that f_2 -similarity factor value was 74 and no relevant differences were observed between two and five month aged samples.

The reviewer also calculated the f_2 -similarity factor between above two profiles (see below) and observed a value of 72 indicating a similarity between profiles and suggesting that the dissolution profile from batches ranging from 0-5 months will be the same.

DISSOLUTION PROFILE COMPARISONS: Similarity (f_2) and Difference (f_1)			
SAMPLE #	SAMPLE TIME	MEAN (refer)	MEAN (test)
1	30	25	24
2	60	35	35
3	120	46	48
4	240	60	64
5	360	71	75
6	480	78	83
7	600	84	90
8	(b) (4)		
9			
10			

SIMILARITY (f_2): 71.84

$$f_2 = 50 \log_{10} [100 / (1 + 1/n * \sum_{i=1}^n (R_i - T_i)^2)^{0.5}]$$

DIFFERENCE (f_1): 4.61

$$f_{1(R)} = [100 * (\sum_{i=1}^n |R_i - T_i|) / \sum_{i=1}^n R_i]$$

The Applicant also stated that DHEP drug release testing of commercial batches will typically be conducted between the second and third month of age. Considering this, the in vitro release testing studies submitted in the current submission from process validation batches, which were six months old, will be considered sufficient for determining the in vitro drug release acceptance criteria.

In response to IR2, the Applicant stated that the (b) (4) used in pivotal clinical studies were 5-32 months old and these (b) (4) elicited essentially the same clinical outcome as their younger counterparts, with the magnitude of the effect and statistical significance relative to placebo being indistinguishable.

According to the Applicant, the degree of separation between active and placebo for pain reduction is maintained across the entire (b) (4) age-range (Figures below).

(b) (4)

Based on this information, the Applicant proposed two different in vitro release acceptance criteria with $\pm 10\%$ limits at batch release and $-10\%/+15\%$ for stability samples. The Applicant

justified that a higher value at the upper end for stability studies will not be expected to affect product performance following topical application and will allow for variability.

The Applicant proposed the following in vitro release acceptance criteria (submitted on 9/25/18) for batch release and stability testing.

Test	Acceptance Criteria	Method (3.2.P.5.2)	Release (R)/ Stability (S)
DHEP Drug Release	At 30 min (b) (4) % (Batch Release) and At 240 min (b) (4) % (Batch Release) and (b) (4) % (Stability) At (b) (4) min NLT (b) (4) % and Complies to USP <724>	HPLC 3.2.P.5.2.9	R/S

The acceptance criteria were based on the in vitro release data from validation batches (complete in vitro dissolution data provided on page 3-4, response to IR received on 9/14/2018)

Batch #	Statistic (Sample Number)	30 minutes	240 minutes	(b) (4)
171107 - QC	Mean (n=12)	31	69	
171108 - QC	Mean (n=12)	31	69	
171109 - QC	Mean (n=12)	33	66	
	Grand Mean (n=3)	31.7 ± 1.2	68.0 ± 1.7	

Reviewer's comments: The reviewer consulted with the clinical team about Applicant's retrospective analysis to demonstrate that 5-24 months old (b) (4) used in pivotal studies have similar in vivo performance in reducing pain. The Clinical team (via tcon and emails from Dr. Christina Fang) indicated that the only two clinical studies, Study S-10 (protocol #05DCz/FHp11) and Study S-11 (protocol #06EU/FHp03) provided positive results for efficacy and the batches used in these studies were 12-24 months old. Therefore, in vitro release acceptance criteria can be determined based on the industrial batches which are between 12-24 months old. However, the age of the industrial batches manufactured by the Applicant spanned from 2-30 months. Considering above justification for the clinical performance from the pivotal batches and to account for manufacturing variability, in vitro release data from 12-24 months old industrial batches can be used to determine the in vitro release acceptance criteria.

The reviewer therefore considered the following data from two validation batches #160726 and #160727 (out of total (b) (4) validation batches) which were 17 and 18 months old, respectively for determination of the final in vitro drug release acceptance criteria.

Stability batches											
160726 (17 months)						160727 (18 months)					
	30 min	240 min	(b) (4) min	(b) (4)			30 min	240 min	(b) (4) min	(b) (4)	
1					1						
2					2						
3					3						
4					4						
5					5						
6					6						
7					7						
8					8						
9					9						
10					10						
11					11						
12					12						
	31	65	(b) (4)				31	65	(b) (4)		

Based on above data driven analysis of in vitro drug release data from two 12-24 old industrial batches, the reviewer recommended the following acceptance criteria

30 min: (b) (4) %

240 min: (b) (4) %

600 min: Not less than (b) (4) % (justification discussed below)

Further, (b) (4) minutes-time point (b) (4) is unacceptable since (b) (4) % release is achieved between (b) (4) minutes as observed in the in vitro release profiles from discriminatory studies and process validation batches. Therefore, the reviewer recommends 600 minutes as the last time point where (b) (4) % DHEP drug release should be observed.

Further, two 30-month old industrial batches (#150624 and #150625) will not pass the Applicant's proposed in vitro release acceptance criteria for batch release testing and the remaining seven industrial batches (aged 2-18 month) will pass the reviewer's recommended in vitro release acceptance criteria.

The Applicant responded with the following question (refer to email by Steven Kinsley on Oct 17, 2018).

'FDA states "in vitro release acceptance criteria should be established based on data from the batches which are between 12-24 months old". We agree but also believe that all batches for which 12-24-month data are available should be included in the calculus for release at 30, 240 and 600 minutes, thereby allowing for a more accurate expression of procedural variability in the establishment of these specifications. If we include 12-month data from batches 170627 and 170628 along with 17-18-month data for 160726 and 160727, the acceptance criteria become:

30 min: (b) (4) %

240 minutes: (b) (4) %

600 minutes: not less than (b) (4) %

If the reviewers agree with this proposal, we will update our documentation accordingly and resubmit the corresponding files to our NDA.'

As explained above and discussed with the clinical team, in vitro release acceptance criteria should be determined based on the industrial batches which are between 12-24 months old. Considering this, the Applicant request of the inclusion of additional data from 12 months and 17-18 months is acceptable. Therefore, the reviewer agreed with the Applicant's revised in vitro drug release acceptance criteria.

Taken together, the reviewer recommended the following method and in vitro release acceptance criteria (agreed by the Applicant in response to IR received on 11/02/2018) for both batch release testing and stability testing as below:

Agency's recommended in vitro release method and acceptance criteria

Apparatus	Speed (rpm)	Medium/Temperature	Volume (mL)	Sampling points/Detection method	Dissolution acceptance criteria
Paddle overdisk, disk assembly (b) (4)	50	Phosphate buffer pH 6.0/ 32.0 °C ± 0.5°C	500	30-240-600 minutes* *For comparative testing, additional sampling points could be employed; i.e. 60, 120, 360, 480, 600 min. HPLC detection using UV Detector λ= 254 nm	30 min: (b) (4) % 240 min: (b) (4) % 600 min: Not less than (b) (4) % and complies

					with USP <724>, L1, L2 and L3 specifications
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Clinical relevance of dissolution method & acceptance criteria (e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)

Reviewer's Assessment: The Applicant did not provide clinical/ in vivo data from the industrial batches demonstrating clinical relevance of in vitro drug release acceptance criteria obtained. However, considering the fact that industrial batches were manufactured at the same Teikoku facility as the pivotal batches with no major CMC changes introduced between the manufacture of pivotal and industrial batches (confirmed by the CMC reviewer), in vitro drug release data from industrial batches were considered for establishing the acceptance criteria. Because the in vitro drug release method and the acceptance criteria are based on similar batches (e.g., composition and manufacturing process) compared to pivotal batches which demonstrated to be efficacious and the plasma concentrations are likely to be lower than those after oral administration, they can be considered clinically relevant.

MODIFIED RELEASE ORAL DRUG PRODUCTS –In-Vitro Alcohol Dose Dumping

Reviewer's Assessment: This is a topical dosage form; therefore, the in vitro alcohol dose dumping is not applicable,

In-Vitro Permeation Testing (IVPT) for Transdermal/Topical Products

During Pre-IND meetings, the Agency asked the Applicant to define the role of heparin in order to justify its inclusion in the formulation. The Agency wanted to ensure that heparin, per se, is not released in vivo and the pain reduction is not due to a direct pharmacodynamic action of heparin on the inflammatory response.

The Applicant provided following justification (in the Pharmaceutical Development section [Application 206976 - Sequence 0044 - 3.2.P.2 Pharmaceutical Development](#) (b) (4) Teikoku)) in the submission.

1. The percutaneous absorption of both diclofenac and heparin was assessed following b.i.d. 12 hr applications of the (b) (4) for 6 days to the backs of 12 volunteers at a single center (see Module 2.7.6 CRO-PK-02-92 Synopsis). Although the steady state absorption of diclofenac was similar to another study (Module 2.7.6 CRO-PK-98-13 Synopsis), heparin was not absorbed through the skin of the volunteers at a concentration that would affect the intrinsic or common pathway of blood coagulation.

2. In a single center, double-blind, randomized, parallel group study, 104 asymptomatic subjects with a latent algogenic condition (subcutaneous and/or muscle hyperalgesia with dystrophic changes) were assigned to one of four (b) (4) treatment groups of 26 subjects per group; (b) (4) Flector, Heparin or placebo (Module 2.7.6 07I/FHp04 Synopsis). For 7 consecutive days, a single (b) (4) was applied for 24 hours to the vastus lateralis muscle of the subject's leg with the lowest pain threshold value, with visits scheduled on days 0, 3 and 7, at which time the following measurements were obtained: (a) pain threshold (mA) to electrical stimulation of skin, subcutis, and muscle, (b) pain threshold to mechanical stimulation (pressure), and (c) thickness of subcutis and muscle through ultrasound examination.

The increase in the pain threshold for electrically-stimulated muscle was greater for the (b) (4) treated subjects than those applying either Flector alone or the Heparin patch, reaching significance or near significance after 3 and 7 days of exposure. A similar increase occurred for Flector treated subjects in comparison to the placebo group for the Day 4 - 8 assessments, but there was no evidence that the Heparin Patch was superior to placebo for any variable/time point.

3.

4.

5. In order to evaluate the diclofenac and heparin residual content in (b) (4) after 24 h application, and the effects of exercise, occlusion and heat on diclofenac absorption in healthy volunteers after once-per-day applications of (b) (4) (b) (4) for 4 consecutive days (Module 5.3.3.1 Study Report CRO-PK-12-272), no change in heparin content was noted, while the amount of diclofenac decreased by 3.6% (Attachment 3.2.P.2.8).

Reviewer's Assessment: Adequate

Based on above justification provided by the Applicant, no release or release below LLOQ of heparin is demonstrated in the (b) (4) in in vitro permeation assays using Franz cells permeation studies. In addition, cumulative concentrations of diclofenac in the receiving chamber of the Franz Cell over 24 hours following patch application was observed and was 2.4 fold greater for the (b) (4) (b) (4) in comparison to Flector alone. Furthermore, the Applicant also demonstrated using clinical studies that heparin was not absorbed through the skin. Taken together the in vitro and clinical data, the heparin appears to behave as an excipient which helps in release of diclofenac from the patch. Therefore, heparin release from the patch should not be monitored from Biopharmaceutics perspective (e.g., as part of the in vitro release studies).

Bridging of Formulations

Reviewer's Assessment: The (b) (4) formulation is same as the pivotal clinical batches formulation. Therefore, bridging of formulation is not required.

List of Deficiencies: NONE pending.

Primary Biopharmaceutics Reviewer Name and Date:

Suneet Shukla 08/23/18, 09/27/2018, 10/31/2018, 11/4/2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Sandra Suarez, 11/02/2018; 11/08/18



Suneet
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Sandra
Suarez

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Date: 11/08/2018 10:09:01PM

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CHAPTER IX: Additional Quality Discipline

Quality In Vivo Adhesion Assessment

[IQA Review Guide Reference](#)

NDANo.:	206976
DATE OF RESUBMISSION:	June 25, 2018
DRUG NAME:	Licart (diclofenac epolamine) topical system (b) (4)
INDICATION:	Treatment of acute pain
SPONSOR:	Institut BioChimique SA
REVIEW TYPE:	In vivo adhesion assessment
REVIEW FINISHED:	September 26, 2018
TDWG REVIEWER:	Caroline Strasinger, Ph.D.
CONSULTS:	Office of Biostatistics Statistical Review: Biometrics Division VI September 10, 2018 – 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 CRO-PK-317 demonstrates ADEQUATE in vivo adhesion. Special considerations for labeling should be discussed with the OND review team as the formal adhesion study has demonstrated perfect adhesion without taping.

Background: The purpose of this review is to assess the in vivo adhesion performance of Licart (diclofenac epolamine) topical system (b) (4). A formal adhesion study was not conducted in the original submission dated 04-MAR-2015, though some antidotal adhesion data was collected in multiple PK and efficacy studies performed throughout the life of the product. This data collected (mostly as antidotal adverse event reporting by subjects) did not prove that sufficient study parameters were identified in the protocols to capture the true nature of adhesion of the product thus in the CR letter the applicant was requested to submit the details of an in vivo adhesion study among several other quality, non-clinical, and clinical deficiencies. This review will assess all the adhesion data provided, formal adhesion study and supportive patient data, in order to provide the quality adhesion recommendation to OND.

Test Product:

The test product is the Licart (diclofenac epolamine) topical system, 1.3%. It is (b) (4) in size and shape to the approved product Flector (diclofenac epolamine), 1.3%. However, Licart (b) (4) Flector and includes heparin as an excipient. Additionally, Licart is intended to be worn for up to 24 hours as opposed to 12 hours.



Clinical Study Design: The Applicant collected antidotal data on adhesion throughout the product development life and a formal adhesion study (CRO-PK 17-317); three studies have been highlighted below in the chart.

Study	Type	Subjects	Data Collection Method	General Outcome
05DCZ/FHp11	Efficacy Comparison to Placebo and Flector. Non-crossover design and 14 days of self-treatment with product applied to area of pain.	121, 115, 119 each arm respectively	Patient Diary/Observation	2 subjects reported adhesion issues as an adverse event during the study. Both reports were with the Flector Reference product. Taping of the edges or loose elastic netting was permitted to be used if patient experienced issues with adherence
CRO-PK 12-272	Effect of Exercise, occlusion, and heat	Part 1: 24 subjects with 1 TDS applied to each arm; Part 2: 13 subjects, each condition for 4 consecutive days of application to thigh	Assessment of % at 24 hour (end of wear)	Part 1: ~94% of systems applied (48 TDS total) had 75% or greater of the surface area adhered. Taping corners was permitted. Part 2: All TDS under all four treatment conditions adhered for at least 75% of the

				adhesion area. If detachment occurred the product was replaced with a new product.
CRO-PK 17-317	Adhesion to lower leg	28 subjects with 2 systems applied; one with reinforcement (tape or net) and one without	Multi-time point assessment over 24 hours on 5-point and 100% scale	100% of all systems applied had 75% or greater % adherence. No significant difference noted between products with and without reinforcement.

Because the reporting was antidotal in the first study (subjects were not instructed to note adhesion daily), and reinforcement or replacement of the TDS was permitted in the stressed conditions study, the data is viewed as supportive data only. The remainder of this review will focus on CRO-PK-17-317.

Study CRO-PK-17-317 included 28 subjects with a TDS (manufactured at the (b) (4) site) applied to each lower leg (calf), for a total of 56 systems applied. 28 systems (one per subject) included no reinforcement, and 14 systems included tape reinforcement and 14 systems include a loose elastic mesh reinforcement. Adhesion was assessed at 4, 8, 12, 16, 20, and 24 hours by a trained evaluator utilizing the standard 5 point (0-4) scale and the actual percentage (100% scale). Digital photographs were taken of the systems at each assessment time point. Subjects were confined to the clinical center during the study period, hazardous, strenuous or athletic activities were not permitted.

Reviewer's Assessment: Study CRO-PK-17-317 was suitably conducted for adhesion assessment (i.e. consistently spaced observations throughout wear period, no taping, photographs taken, etc.). Showering was prohibited in the study, however, given the wear time of no more than 24 hours, and the acute topical indication (showers can be taken between applications if necessary) showering is not required. The study also was used to evaluate any differences seen between products reinforced versus products not reinforced. The other two studies noted above are used for supportive information.

Statistical Consult for Adhesion Evaluation: A statistical consult was requested to assess the adhesion data of CRO-PK-317. Information from study was assessed and the conclusion was that the Applicant's data showed the probability of the TDS maintain at least 90% adhesion is 100% with 95% lower confidence limit of 90%.



Biostatistics.pdf

TDWG Analysis:

The applicant reported scores of 0 on the 5 point scale for all systems (reinforced and without reinforcement) and at all time points.

Table 11.4.1.2 Frequency of adhesion scores based on the highest scores for the plaster without reinforcement (PW), for the plaster reinforced using elastic net (PRN) and for the plaster reinforced by corner taping (PRT). PP Set and FAS

Time point	Adhesion score frequency					
	PW Score (N=28) - n (%)		PRN Score (N=14) - n (%)		PRT Score (N=14) - n (%)	
	Score 0	Score 1, 2, 3, 4	Score 0	Score 1, 2, 3, 4	Score 0	Score 1, 2, 3, 4
4 h	28 (100.0)	0 (0.0)	14 (100.0)	0 (0.0)	14 (100.0)	0 (0.0)
8 h	28 (100.0)	0 (0.0)	14 (100.0)	0 (0.0)	14 (100.0)	0 (0.0)
12 h	28 (100.0)	0 (0.0)	14 (100.0)	0 (0.0)	14 (100.0)	0 (0.0)
16 h	28 (100.0)	0 (0.0)	14 (100.0)	0 (0.0)	14 (100.0)	0 (0.0)
20 h	28 (100.0)	0 (0.0)	14 (100.0)	0 (0.0)	14 (100.0)	0 (0.0)
24 h	28 (100.0)	0 (0.0)	14 (100.0)	0 (0.0)	14 (100.0)	0 (0.0)
Overall	168 (100.0)	0 (0.0)	84 (100.0)	0 (0.0)	84 (100.0)	0 (0.0)

Source: Table 14.2.1.3 and Table 14.2.1.7; PW Plaster without reinforcement; PRN: Plaster reinforced using elastic net; PRT: Plaster reinforced by corner taping; Score 0: $\geq 90\%$; score 1: $\geq 75 - < 90\%$; score 2: $\geq 50 - < 75\%$; score 3: $< 50\%$; score 4: 0% (detached)

The Applicant also provided descriptive statistics of the actual adhesion percentage as seen below. A slight decrease in adhesion can be seen over time but does not represent an appreciable loss of adhesion.

Table 11.4.1.3 Descriptive statistics of adhesion percentage data based on the lowest adhesion percentage value for the plaster without reinforcement (PW), for the plaster reinforced with elastic net (PRN) and for the plaster reinforced by corner taping (PRT). PP Set and FAS

Time point	Actual adhesion percentage			
		PW (N=28)	PRN (N=14)	PRT (N=14)
4 h	Mean $\pm$ SD	99.7 $\pm$ 0.5	99.1 $\pm$ 1.0	99.4 $\pm$ 1.1
	Median (Min-Max)	100.0 (99 - 100)	99.0 (97 - 100)	100.0 (96 - 100)
8 h	Mean $\pm$ SD	99.4 $\pm$ 1.0	98.6 $\pm$ 1.0	99.2 $\pm$ 1.2
	Median (Min-Max)	100.0 (95 - 100)	99.0 (97 - 100)	100.0 (96 - 100)
12 h	Mean $\pm$ SD	99.1 $\pm$ 1.1	98.4 $\pm$ 1.1	98.9 $\pm$ 1.3
	Median (Min-Max)	99.0 (95 - 100)	99.0 (96 - 100)	99.0 (96 - 100)
16 h	Mean $\pm$ SD	98.9 $\pm$ 1.3	98.2 $\pm$ 1.0	98.7 $\pm$ 1.2
	Median (Min-Max)	99.0 (95 - 100)	98.5 (96 - 99)	99.0 (96 - 100)
20 h	Mean $\pm$ SD	98.4 $\pm$ 1.8	98.1 $\pm$ 0.9	98.7 $\pm$ 1.2
	Median (Min-Max)	99.0 (94 - 100)	98.0 (96 - 99)	99.0 (96 - 100)
24 h	Mean $\pm$ SD	98.3 $\pm$ 2.0	97.7 $\pm$ 1.8	98.0 $\pm$ 2.6
	Median (Min-Max)	99.0 (93 - 100)	98.0 (92 - 99)	99.0 (90 - 100)
All	Mean $\pm$ SD	99.0 $\pm$ 1.4	98.3 $\pm$ 1.2	98.8 $\pm$ 1.5
	Median (Min-Max)	99.0 (93 - 100)	99.0 (92 - 100)	99.0 (90 - 100)

Source: Table 14.2.1.4 and Table 14.2.1.8; PW Plaster without reinforcement; PRN: Plaster reinforced using elastic net; PRT: Plaster reinforced by corner taping

A selection of photographs was also provided in Meeting Package submission 0041 dated 07/07/2017. The Applicant stated they could provide additional photographs if requested.



Reviewer's Assessment: The unofficial gold standard of 90% of all patients having at least 90% adhesion for the duration of wear was achieved by the product in the formal adhesion study. The data indicates perfect adhesion under all conditions. It is notable subjects were confined to the clinic and prevented from doing strenuous activity. Furthermore, the application site was the calf which is a relative smooth surface that doesn't result in much strain or flexing of the product particularly in a confined clinical environment. The data may very well indicate that taping and reinforcement is not necessary in the labeling, however, given the indication is for acute pain due to strains, sprains and contusions which likely result from strenuous work or athletics it may be necessary to allow for taping or reinforcement in those practical use situations.

In that context it is important to also consider the CRO-PK-12-272 which also demonstrated adequate adhesion but in a less controlled environment (subjects were not confined, free to reinforce when they felt it was appropriate). In that study, although some taping was permitted, some scores of 1 and 2 were reported which may more accurately reflect the real-world adhesion of the product. Still 94% of all systems applied had 75% or greater adhesion and no detachments were observed.

Table 11.5.1.1 Adhesiveness scores – Part 1, N=24

Adhesiveness - score frequency – n (%)		
% Adhered area	Left arm	Right arm
≥ 90%	5 (20.8)	5 (20.8)
≥ 75 - < 90%	18 (75.0)	15 (62.5)
≥ 50 - < 75%	1 (4.2)	4 (16.7)
< 50%	0 (0.0)	0 (0.0)
0% - Detached	0 (0.0)	0 (0.0)

Source: Table 14.3.5.5

Overall Recommendation: From a quality perspective, the formulation and product design of the system used in clinical study CRO-PK-317 demonstrates adequate in vivo adhesion. As such, quality control parameters (such as in vitro adhesion release and stability acceptance criterion) should be based on this product design (including raw material adhesive specifications) and around this clinical batch to ensure adequate product performance batch to batch.

Special considerations for labeling should be discussed with the OND review team as the adhesion study has demonstrated perfect adhesion without taping.

Caroline Strasinger, Ph.D.
OPQ/ONDP
26-SEP-2018



Caroline
Strasinger

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Caroline
Strasinger

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Comments: Thanks Steve.

Recommendation: Complete Response

**NDA 206976
Review #1**

Drug Name/Dosage Form	(b) (4) Licart™(Diclofenac Epolamine 1.3% (b) (4) /Topical (b) (4)
Strength	182 mg (b) (4)
Route of Administration	Topical
Rx/OTC Dispensed	Rx
Applicant	Institut Biochimique SA (IBSA)
US agent, if applicable	

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Erika Englund	OPQ/ONDP/DNDPAPI/BII
Drug Product	Erika Englund	OPQ/ONDP/DNDPAPI/BII
Process	James Norman	OPQ/OPF/DPAII/BV
Microbiology	Koushik Paul/Erika Pfeiler	OPQ/OPF/DMA/BI
Facility	Cassandra Abellard/Christina Cappacci-Daniel	OPQ/OPF/DIA/BII
Biopharmaceutics	Min Li/Sandra Suarez	OPQ/ONDP/DB/BII
Regulatory Business Process Manager	Steven Kinsley	OPQ/OPRO/RBPMI/BI
Application Technical Lead	Ciby Abraham	OPQ/ONDP/DNDPAPI/BII
Laboratory (OTR)		
ORA Lead		
Environmental Analysis (EA)		

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

DMF #	Subject	Holder	LOA	Assessment
		(b) (4)	24-FEB-2016	DMF found adequate 12/14/2016 by Erika E. Englund, Ph.D.
			20-MAY-2014	DMF found adequate with IR on 12/23/2016 by Erika E. Englund, Ph.D.
			28-JUL-2016	Adequate information in application

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	Complete	Approval	2/7/17	Katelyn Bittleman
Clinical	N/A			
Other	N/A			

Executive Summary

I. Recommendations and Conclusion on Approvability

Based on the recommendations from drug product, biopharmaceutics, and process, CMC recommends a complete response for NDA 206976. The drug substance, microbiology, and facilities group recommend approval.

II. Summary of Quality Assessments

A. Product Overview

The proposed (b) (4) (name not approved) is (b) (4) to the Flector® Patch which was approved in 2007 by the FDA for the treatment of pain associated with minor sports injuries. According to the applicant, the (b) (4) between the two (b) (4) is that (b) (4) contains heparin which releases the API over 24 hours versus Flector Patch (no Heparin) releases the API over 12 hours. Both products (b) (4) and are designed to deliver the API locally.

The topical (b) (4) consists of a (b) (4) adhesive (b) (4) containing the API which is (b) (4) on a non-woven felt backing and covered with a polypropylene film as a release-liner. The release-liner is removed prior to application of the (b) (4) to the skin. The size of a single (b) (4) is (b) (4) (b) (4) 140 cm². The adhesive layer is applied to the non-woven polyester felt backing (b) (4). The total amount of (b) (4) (b) (4). The (b) (4) are contained in a re-sealable envelope (b) (4). Each envelope can contain up to 5 topical (b) (4). The envelopes are packed into a carton box. An expiry (b) (4)

B. Quality Assessment Overview

The applicant has not provided adequate information in the chemistry, manufacturing and controls in the areas of drug product, process, and biopharmaceutics. The application is currently recommended as a complete response until the applicant provides sufficient quality information for the following CMC deficiencies.

CMC Deficiencies**Drug Product**

1.

(b) (4)

2.

3.

4.

(b) (4)

5.

6.

7.

8.

9.

(b) (4)

Process

1.

(b) (4)

2.

(b) (4)

Biopharm

1. The weight of evidence approach (risk based approach) originally proposed by the Agency to support the manufacturing site change (from Teikoku (b) (4)) is insufficient due to the following deficiencies:

- a. (b) (4)
- b. (b) (4)

Information needed to resolve the clinical hold deficiencies

Given the insufficient data to support a risk based approach as a path forward on the evaluation of the proposed site change and as per SUPAC-MR guidance, in vivo data are needed for bridging the manufacturing site change. Because there is no unexpired drug product manufactured at Teikoku available to perform a head to head comparison of the two sites via a clinical endpoint, a standalone clinical study is recommended to demonstrate the efficacy/safety of batches manufactured at the proposed commercial manufacturing site, (b) (4)

2. A discriminating dissolution method is needed for the drug product. Note that the demonstration of method discriminating ability should compare the in vitro release profiles (provide f2 values for each comparison between pre- and post-change) obtained from the meaningful variations (i.e., ± 10 -20% change to the specification-ranges) of relevant critical manufacturing attributes (i.e., release controlling agents), while other unnecessarily large variations of critical attributes may not be considered appropriate without scientifically sound justification. Alternatively, modify or re-develop an in vitro release method with full validation for quality control purpose. The in vitro release method development should include detailed description of the in vitro release test being proposed and the developmental parameters (i.e., selection of the equipment/apparatus, in vitro release media, agitation/rotation speed, pH, assay, sink conditions, etc.) investigated for the selection of the proposed method as the optimal.
Based on current practice, the acceptance criteria of the in vitro release test are set at multiple time points based on the mean value (i.e., mean value and $\pm 10\%$ range and NLT 80% for the last specification time-point, unless there are in vivo BA/BE and/or IVIVC data supporting wider ranges) of $n=12$ units from batches tested in pivotal clinical studies (e.g., the in vivo BE study used for manufacturing site change). Additional in vitro release data from non-biobatches may be used as supportive documents on case-by-case basis. Note that the proposed in vitro release acceptance criteria with “no less than **% released” at all time points are not appropriate for MR products.

Information needed to resolve the clinical hold deficiencies

Provide additional data demonstrating the discriminating ability of the method towards meaningful changes of the critical material attributes or process parameters. These data are needed to support the adequacy of the method as a QC tool for drug product release and stability testing.

C. Special Product Quality Labeling Recommendations (NDA only) –N/A

D. Final Risk Assessment (see Attachment) – N/A

Application Technical Lead Name and Date:

Ciby J. Abraham, Ph.D.
Acting Quality Assessment Lead
OPQ/ONDP/DIVII/Branch IV

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BIOPHARMACEUTICS**Product Background:****NDA: 206976****Drug Product Name / Strength:** Diclofenac Epolamine/1.3% (b) (4) Topical (b) (4) /182 mg (b) (4) (b) (4) / Licart™**Route of Administration:** Topical**Applicant Name:** Institut Biochimique SA (IBSA)

The drug product is a topical dosage form (b) (4) containing the active pharmaceutical ingredient diclofenac epolamine (182 mg (b) (4)), (b) (4) on a non-woven felt backing and covered with a polypropylene film release-liner which is removed prior to application of the (b) (4) to the skin. The proposed product was developed to achieve a local action (b) (4) to the Flector Patch previously approved in January 2007 by DAAAP for the treatment of pain associated with minor sport injuries (NDA 21234). The inclusion of heparin in the (b) (4) formulation is justified as that the (b) (4) was significantly more effective in reducing pain than its Flector counterpart in two Phase 3 studies enrolling a total of 786 patients, with both formulations also being significantly more effective than placebo. It was claimed that the role of heparin in the increased clinical activity of the (b) (4) in (b) (4) comparison to Flector (b) (4)

The original NDA submission on March 04, 2015 was refused for filing mainly because of clinical concerns. The application was resubmitted on May 27, 2016.

Review Summary/Recommendation: INADEQUATE (Major deficiencies)

The manufacturing site for the commercial product (b) (4) is different from that used for all clinical batches, Teikoku Seiyaku Ltd. (in Japan). In the original re-submission of this NDA dated May 26, 2016, the IVRT study was included to support the proposed manufacturing site change. However, the current thinking of the Agency is that the IVRT using vertical diffusion cells is not appropriate for quality control and supporting quality-related regulatory approval for transdermal patch products, because of the high variability in the IVRT data. As this topical patch formulation is considered as modified release formulation, a Level-3 manufacturing site change requires both in vitro release and in vivo BE documentation (or IVIVC), per SUPAC-MR Guidance. As communicated in the 74-day letter ("Filling Review Issue Identified" dated Aug 8, 2016), based on the regulatory history of this drug product, we recommended a risk assessment approach as the path forward to evaluate the proposed site change, with detailed data and information request included in the IR dated Aug 23, 2016. The risk assessment is mainly

based on 1) the understanding of the product and process and the adequate in process controls and the control strategy to ensure consistent quality of the drug product manufactured at the proposed manufacturing site); and 2) the in vitro release profile comparison between pre-change and post-change drug products with adequate data to show the discriminating ability of the in vitro release method.

However, the weight of evidence approach (risk based approach) originally proposed by the reviewers is insufficient to support the manufacturing site change (from Teikoku (b) (4)) due to the following deficiencies: 1) the data requested indicate that the drug product formulation, process, and in process controls are either different and/or the control strategy are inadequate to ensure similar in vitro/ in vivo performance; and 2) no sufficient data were provided to confirm the discriminating ability of the in vitro release method.

Recommendation

The manufacturing site change is not acceptable from a biopharmaceutics perspective, and ***a complete response is recommended for NDA 206976***. A clinical study designed to demonstrate consistent in vivo performance of drug product manufactured at the proposed commercial site (b) (4)) is recommended. In addition, recommendations for in vitro release method development and acceptance criteria setting are provided for future submission (refer to ***List of deficiencies*** section).

List Submissions being reviewed (table):

Module	Content
1.11.1	Quality information amendment (Dated Sept 12/2016, Jan 4/2017 and Jan 27/2017)
3.2.P.2	Pharmaceutical development
3.2.P.5	Control of drug product
3.2.P.8	Stability

Highlight Key Outstanding Issues from Last Cycle: Manufacturing site change

Concise Description Outstanding Issues Remaining: Manufacturing site change

BCS Designation

Reviewer's Assessment: The BCS classification of the API in this topical product is not relevant for regulatory decision-making of this NDA, because BCS classification system is mainly designed for oral drug products.

Solubility: As reported in the submission (Module 3.2.P.5.3), the solubility of the API in the dissolution medium with the presence of drug product excipients (b) (4)

(b) (4)

Permeability: Not reported

Dissolution: See **Dissolution Method and Acceptance Criteria**

Dissolution Method and Acceptance Criteria

Reviewer's Assessment: INADEQUATE

(b) (4)

appropriate. With such acceptance criteria, it may not be able to discriminate a very fast drug release than expected. A criterion in the middle phase of in vitro release that set within a certain range is recommended.

Since the proposed in vitro release method is considered inadequate (for bridging the manufacturing site change (see *Bridging of Formulations*)) and a BE study may be needed, specific recommendation for the current vitro release acceptance criteria will not be included in the CR letter. Instead, general language for setting MR dissolution specification will be provided as deficiencies.

Clinical relevance of dissolution method & acceptance criteria (e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)

Reviewer's Assessment: N/A

Application of dissolution/IVIVC in QbD

Reviewer's Assessment: N/A

MODIFIED RELEASE ORAL DRUG PRODUCTS –In-Vitro Alcohol Dose Dumping

Reviewer's Assessment: N/A

In-Vitro Soft-food Interaction Study

Reviewer's Assessment: N/A

In-Vitro Release Testing (IVRT) for Semi-Solid Products

Reviewer's Assessment:

An IVRT study was included in the submission for bridging manufacturing site change. However, IVRT studies are considered inappropriate for patch products; therefore, the included IVRT was not reviewed.

In-Vitro Permeation Testing (IVPT) for Transdermal/Topical Products**Reviewer's Assessment: N/A*****In-Vitro Dissolution Testing for Abuse-deterrent Products*****Reviewer's Assessment: N/A*****In-Vitro BE Evaluation for Pulmonary Products*****Reviewer's Assessment: N/A*****EXTENDED RELEASE DOSAGE FORMS –Extended Release Claim*****Reviewer's Assessment: N/A*****Bridging of Formulations*****Reviewer's Assessment: INADEQUATE**

For this NDA, the manufacturing site for all clinical batches was Teikoku Seiyaku Ltd. (in Japan), while the proposed site for the commercial product is (b) (4). In the original re-submission of this NDA dated May 26, 2016, the IVRT study was included to support the proposed manufacturing site change. However, the current thinking of the Agency is that the IVRT using vertical diffusion cells is not appropriate for quality control and supporting quality-related regulatory approval for transdermal patch products, because of the high variability in the IVRT data. As this topical patch formulation is considered as modified release formulation, a Level-3 manufacturing site change requires both in vitro release and in vivo BE documentation (or IVIVC), per SUPAC-MR Guidance. As communicated in the 74-day letter ("Filling Review Issue Identified" dated Aug 8, 2016), based on the regulatory history of this drug product, we recommended a risk assessment approach as the path forward to evaluate the proposed site change. In the IR dated Aug 23, 2016, detailed data and information request for bridging manufacturing sites were included as follows:

b. The in vitro drug product release profile comparisons between pre-change and post-change drug products (with raw data and appropriate statistical test for similarity, e.g., f2 test).

c. The in vitro release method development report to demonstrate that the current method (USP Apparatus 5) is an optimal test for your product, along with the data to support the discriminating ability of the selected method. The in vitro release test method development should include detailed description of the in vitro release test being proposed and the developmental parameters (i.e., selection of the equipment/apparatus, in vitro release media, agitation/rotation speed, pH,

assay, sink conditions, etc.) investigated for the selection of the current method as the optimal. For the demonstration of the method's discriminating ability, we recommend you compare the dissolution profiles of the reference (target) product with the test products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (i.e., ± 10 -20% change to the specification-ranges of these variables).

The response for this IR was made separately on Sept 12, 2016, Nov 14, 2016, Jan 4, 2017 and completely responded by the Applicant on Jan 27, 2017. Based on the communication with product and process reviewers, the control of product quality is considered inadequate mainly due to the issues associate with analytical method of heparin (CR letter will be issued). From a biopharmaceutics perspective, there are no adequate data and information demonstrating the discriminating ability of the proposed in vitro release method; therefore, this in vitro release method is considered inappropriate for the risk assessment to bridge the manufacturing sites (based on the in vitro release data). Per SUPAC-MR guidance, in vivo data are needed for bridging the manufacturing sites, along with the in vitro release data (see List of Deficiencies). It was informed that there were unexpired product from the Teikoku site that available for manufacturing site bridging and the facility at Teikoku is not available for future manufacturing. In addition, it is well known the pharmacokinetics and pharmacodynamics studies are very challenging for the local acting patch. Therefore, a clinical study to demonstrate the efficacy of the product manufactured from the commercial site is recommended. The final decision on which type of in vivo study is preferred will be made based on the further discussion with the Clinical and Clinical Pharmacology review teams.

Biowaiver Request

Reviewer's Assessment: N/A

R Regional Information

Comparability Protocols

Reviewer's Assessment: N/A

Post-Approval Commitments

Reviewer's Assessment: N/A

Lifecycle Management Considerations**N/A*****List of Deficiencies:***

1. The weight of evidence approach (risk based approach) originally proposed by the Agency to support the manufacturing site change (from Teikoku (b) (4)) is insufficient due to the following deficiencies:

- a. The data submitted indicate that the drug product formulation, process, and in process controls are either different and/or the control strategy are inadequate to ensure similar in vitro/ in vivo performance (refer to the product and process deficiencies).***
- b. There are no sufficient data demonstrating the discriminating ability of the proposed in vitro release method towards critical quality attributes. (b) (4)***

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Overall, this in vitro release method is considered inappropriate for supporting the proposed manufacturing site change using the risk assessment approach.

- 2. Given the insufficient data to support a risk based approach as a path forward on the evaluation of the proposed site change and as per SUPAC-MR guidance, in vivo data are needed for bridging the manufacturing site change. Because there is no unexpired drug product manufactured at Teikoku available to perform a head to head comparison of the two sites via a clinical endpoint, a standalone clinical study is recommended to demonstrate the efficacy/safety of batches manufactured at the proposed commercial manufacturing site, (b) (4)***
- 3. Provide additional data demonstrating the discriminating ability of the method towards meaningful changes of the critical material attributes or process parameters. These data are needed to support the adequacy of the method as a QC tool for drug product release and stability testing. Note that the demonstration of method discriminating ability should compare the in vitro release profiles (provide f2 values for each comparison between pre-***

and post-change) obtained from the meaningful variations (i.e., ± 10 -20% change to the specification-ranges) of relevant critical manufacturing attributes (i.e., release controlling agents), while other unnecessarily large variations of critical attributes may not be considered appropriate without scientifically sound justification. Alternatively, modify or re-develop an in vitro release method with full validation for quality control purpose. The in vitro release method development should include detailed description of the in vitro release test being proposed and the developmental parameters (i.e., selection of the equipment/apparatus, in vitro release media, agitation/rotation speed, pH, assay, sink conditions, etc.) investigated for the selection of the proposed method as the optimal.

- 4. Based on current practice, the acceptance criteria of the in vitro release test are set at multiple time points based on the mean value (i.e., mean value and $\pm 10\%$ range and NLT 80% for the last specification time-point, unless there are in vivo BA/BE and/or IVIVC data supporting wider ranges) of $n=12$ units from batches tested in pivotal clinical studies (e.g., the in vivo BE study used for manufacturing site change). Additional in vitro release data from non-biobatches may be used as supportive documents on case-by-case basis. Note that the proposed in vitro release acceptance criteria with "no less than **% released" at all time points are not appropriate for MR products.*

Primary Biopharmaceutics Reviewer Name and Date:

Min Li, Ph.D. Feb 9, 2017

Biopharmaceutics Reviewer

Division of Biopharmaceutics, Branch III

FDA/CDER/ONDP

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Sandra Suarez Sharp, Ph.D. 2/10/2017

Acting Biopharmaceutics Lead

Division of Biopharmaceutics, Branch III

FDA/CDER/ONDP



Sandra
Suarez

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MICROBIOLOGY

Product Background: Treatment of minor sport injuries.

NDA: 206976

Drug Product Name / Strength: Diclofenac Epolamine 1.3%/(b) (4) Topical (b) (4) 182 mg (b) (4)

Route of Administration: Topical (b) (4)

Applicant Name: Institut Biochimique SA (IBSA)

Manufacturing Site: (b) (4)

Method of Sterilization: This is a nonsterile product.

Review Summary: The submission is **recommended** for approval on the basis of sterility assurance.

List Submissions being reviewed: 03/05/2015, 08/08/2016, 10/14/2016, and 01/11/2017.

Highlight Key Outstanding Issues from Last Cycle: N/A

Supporting/Related Documents: N/A

Concise Description Outstanding Issues Remaining: List of microbial deficiencies and comments are included at the end of this documents (in the list of deficiencies section).

S Drug Substance

Reviewer's Assessment: The drug substance is not the subject of this review.

P.1 Description of the Composition of the Drug Product**Description of the Composition of the Drug Product**

(3.2.P.1 Description and composition of the drug product (b) (4) (b) (4).pdf)

The topical (b) (4) is a (b) (4) adhesive (b) (4). It is (b) (4) on a non-woven felt backing and covered with a polypropylene film as a release-liner. The release-

liner is removed prior to application of the (b) (4) to the skin. The composition of the adhesive (b) (4) is provided below:

Table 3.2.P.1.1: Composition of the Adhesive (b) (4)

Ingredients	Composition (per (b) (4))		Function	Reference to Standard
	Quantity (mg)	Percent (w/w %)		
Active Substance Diclofenac Epolamine (DHEP)*	182	1.3	Active Ingredient	Drug Master File
Excipients				
Heparin Sodium	(b) (4)			USP/EP current ed.
(b) (4) Sorbitol Solution (b) (4)				USP current ed.
(b) (4) butylene Glycol				(b) (4)
Sodium Polyacrylate				
Carboxymethylcellulose Sodium				USP current ed.
Kaolin				USP current ed.
Propylene Glycol				USP current ed.
Gelatin (b) (4)				USP/NF current ed.
Povidone (b) (4)				USP current ed.
(b) (4)				
Titanium Dioxide				USP current ed.
Tartaric Acid				USP/NF current ed.
Dihydroxyaluminum Aminoacetate				USP current ed.
Polysorbate 80				USP/NF current ed.
Edetate Disodium (EDTA)				USP current ed.
Methylparaben (b) (4)				USP/NF current ed.
Propylparaben (b) (4)				USP/NF current ed.
Fragrance (Dalin PH) †				(b) (4)
Purified Water,				USP/NF current ed.

(b) (4)

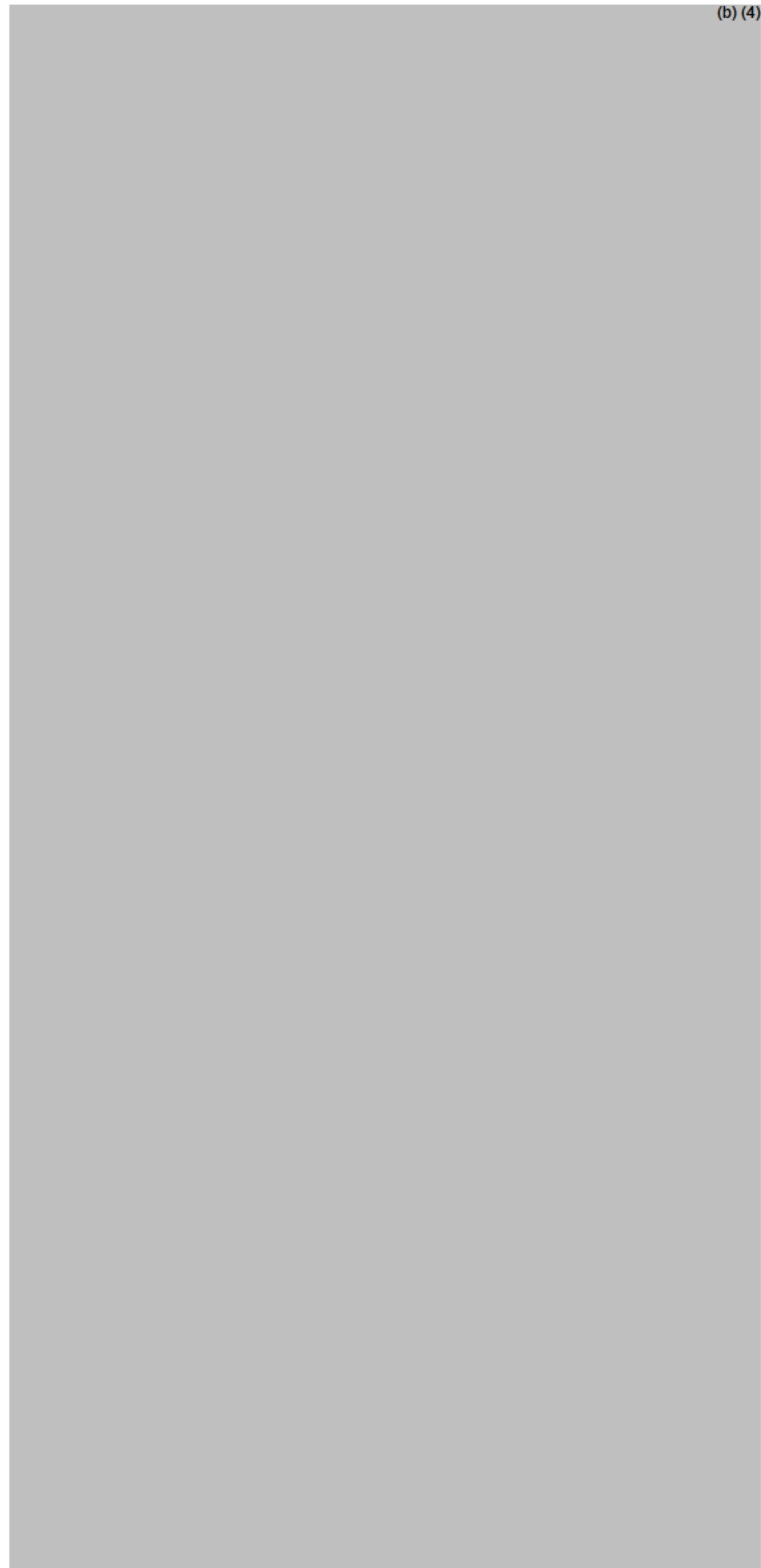
Description of container closure system –

(3.2.P.1 Description and composition of the drug product (b) (4) (b) (4) J.pdf)

The (b) (4) is consist of a re-sealable envelope made from (b) (4). Each envelope contains up to 5 topical (b) (4). The envelopes are packed into a secondary container (carton box) along with the product insert.

The schematic of (b) (4) is provided below:

Figure 3.2.P.1.1: (b) (4) Schematic



Reviewer's Assessment: The applicant provided an adequate description of the drug product composition and the packaging system to support manufacturing process for the drug product.

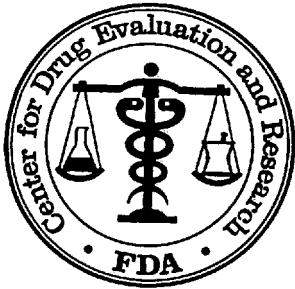
Acceptable

P.2 Pharmaceutical Development

(b) (4)

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NDA 206976



STATISTICAL REVIEW AND EVALUATION

Biometrics Division: VI

NDA No.	206976
SERIAL NO.	
DATE RECEIVED BY THE CENTER	July 09, 2018
DRUG NAME	Licart (diclofenac epolamine)
DOSAGE FORM	TDS
STRENGTH	
INDICATION	
SPONSOR	Instiut BioChimique SA
REVIEW FINISHED	September 11, 2018
STATISTICAL REVIEWER	Chao Wang, Ph.D.
SECONDARY REVIEWER	Meiyu Shen, Ph.D.
PROJECT MANAGER	Steven Kinsley

Chao Wang, Ph.D., Mathematical Statistician, CDER/OTS/OB/DBVI
Meiyu Shen, Ph.D., Lead Mathematical Statistician, CDER/OTS/OB/DBVI

Concur: _____

Yi Tsong, Ph.D., Division Director, CDER/OTS/OB/DBVI
CC List:

Meiyu Shen, Ph.D., CDER/OTS/OB/DBVI/
Yi Tsong, Ph.D., CDER/OTS/OB/DBVI
Lillian Patrician, CDER/OTS/OB
Steven Kinsley, CDER/OPQ/ONDP/DLCAPI/LCBIII

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1 EXECUTIVE SUMMARY

The statistical reviewer evaluated the sponsor's in vivo adhesion reported in Section 5.3.3.1 of the clinical study CRO-PK17-317-2017.

A total of 28 subjects were enrolled and only scores of 0 were recorded at all time points. The estimated probability of a subject having at least 90% adhesion at all time points is 100%, with a 95% lower confidence limit of 90%.

2 INTRODUCTION

On July 9, 2018, FDA Office of Pharmaceutical Quality, Office of New Drug Products requested the Division of Biometrics VI, Office of Biostatistics to evaluate the sponsor's in vivo adhesion reported in Section 5.3.3.1 of the clinical study CRO-PK17-317-2017.

3 STATISTICAL REVIEWER'S COMMENTS

A total of 28 subjects were enrolled and only scores of 0 were recorded at all time points. Thus, the estimated probability of a subject having at least 90% adhesion at all time points is 100%. Because the estimate is 100%, a traditional 95% lower confidence limit given by the normal approximation is not possible. It has also been shown that the confidence limit derived from the normal approximation has poor coverage probability.

We calculate the 95% lower confidence limit by the Modified Jeffreys interval (Brown, Cai et al. 2001), where the formula of the lower $(1 - \alpha)$ -confidence limit of estimated probability 1 with sample size n is given by $(\alpha)^{\frac{1}{n}}$. The formula yields the 95% lower confidence limit as 90%.

4 CONCLUSION AND RECOMMENDATION

The sponsor's data showed that the probability of the TDS maintains at least 90% adhesion is 100%, with 95% lower confidence limit of 90%.

5 REFERENCE

Brown, L. D., T. T. Cai and A. DasGupta (2001). "Interval estimation for a binomial proportion." Statistical science: 101-117.

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/s/

CHAO WANG
09/11/2018

MEIYU SHEN
09/19/2018

YI TSONG
09/19/2018

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
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Date: February 2, 2017

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RPM: Steven Kinsley
steven.kinsley@fda.hhs.gov

Through: Vesa Vuniqui, Acting Branch Chief, POND/DMQ/OC/CDRH

From: Katelyn R. Bittleman, CSO, POND/DMQ/OC/CDRH

Applicant: IBSA Institut Biochimique SA
Via del Piano
CH-6915 Pambio-Noranco, Switzerland
FEI: 3002864272

Application # NDA 206976

Consult # ICC1600471

Product Name: (b) (4)

Pre-Approval Inspection: No

Documentation Review: No Additional Information Required

Final Recommendation: **APPROVAL**

The Office of Compliance at CDRH received a consult request from CDER to evaluate the applicant's compliance with applicable Quality System Requirements for the approvability of NDA 206976.

PRODUCT DESCRIPTION

The (b) (4) (also (b) (4) is (b) (4) to the Flector® Patch previously approved in 2007 by DAAAP for the treatment of pain associated with minor sports injuries, (b) (4)

(b) (4) with the active ingredient (diclofenac epolamine) still being present at 182 mg. The most compelling justification for inclusion of heparin in the Flector (b) (4) is that the (b) (4) was significantly more effective in reducing pain than its Flector counterpart in two phase 3 studies enrolling a total of 786 patients, with both formulations also being significantly more effective than placebo.

Figure 3.2.P.1.1: (b) (4) Schematic



Table 2.3.1: Drug Product Main Characteristics

Proprietary Name of Drug Substance	Diclofenac Hydroxy Ethyl Pyrrolidine (DHEP)
Applicant	IBSA Institut Biochimique SA (Switzerland)
Dosage Form	Topical (b) (4)
Strength	182 mg (b) (4)
Route of Administration	Cutaneous
Proposed Indication	Topical treatment of acute pain due to minor strains, sprains, and contusions.
Final Packaging	(b) (4) 5 (b) (4) envelope (marketed packaging)

REGULATORY HISTORY

The following facilities were identified as being subject to applicable Quality System Requirements under 21 CFR part 820:

1. IBSA Institut Biochimique SA
Via del Piano
CH-6915 Pambio-Noranco, Switzerland
FEI: 3002864272

Responsibility – This is the applicant firm. This site is responsible for the drug product stability testing and QA release of the packaged finished combination product. They are subject to 21 CFR 4 regulations.

Inspectional History – An analysis of the firm’s inspection history over the past 2 years showed that an inspection conducted on July 4-8, 2016. The inspection covered drug GMP requirements and was classified NAI.

Inspection Recommendation:

An inspection is not required because:

- A recent inspection of the firm was acceptable.
- The firm is not responsible for major activities related to the manufacturing and development of the device constituent part;
- NOTE: The firm is responsible for activities related to the manufacturing and development of the final combination product, therefore the next inspection at the firm should cover compliance with applicable Quality System (QS – 21 CFR 820) requirements. (See Inspectional Guidance at the end).

2.

(b) (4)

(b) (4)

DOCUMENTATION REVIEW

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

Management Control, 21 CFR 820.20

IBSA Institut Biochimique SA has the ultimate responsibility to ensure (b) (4), intended as a single-unit combination product, is manufactured in compliance with drug

CGMPs (21 CFR 210/211) and the following provisions from the device Quality System (QS) regulations, as per 21 CFR 4.4(b)(1):

- 21 CFR 820.20 – Management responsibility
- 21 CFR 820.30 – Design controls
- 21 CFR 820.50 – Purchasing controls
- 21 CFR 820.100 – Corrective and preventive actions.

21 CFR 820.50 – Purchasing controls have been extended (b) (4).

Staff to the Head of Quality Assurance is responsible for ensuring:

- That all processes are implemented as provided for in the relevant procedures;
- To report on the performance of the Quality Management System and identify possible areas of improvement;
- Promotion of awareness of regulatory and customer requirements.

Management is responsible for ensuring appropriate communication processes are established and implemented within the organization (by means of SOPs and/or alternative documented written and approved instructions). Communication processes ensure the flow of appropriate information between all levels of the company, and appropriate and timely escalation of certain product quality and pharmaceutical quality system issues. At planned intervals, the QMS is reviewed to assess any deviations between the requirements expected and those assessed.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.20.

Design Control, General, 21 CFR 820.30

The firm provided a summary of each of their design control systems procedures. These procedures were not applied in the development of the (b) (4). The firm states the procedures described will be implemented for the management of the lifecycle of the product after NDA approval.

The topical (b) (4) constituent of the combination product is most similar to devices defined in 21 CFR 880.5240 (medical adhesive tape and adhesive bandage). These devices are considered low risk (Class I; General Controls) and would not be subject to design controls if not part of a combination product. The use of the topical (b) (4) in this combination product does not increase the risk of manufacturing of the (b) (4).

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.30.

Purchasing Controls, 21 CFR 820.50

The firm provided the following diagram describing the qualification procedure of suppliers.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.50.

Corrective and Preventive Action (CAPA), 21 CFR 820.100

The firm states that the QA team is responsible outlining the steps, performing assessments, coordination of events, and conclusion of CAPA procedures and events. CAPAs can be elicited by a product non conformity, deviation from a validated procedure, complaints from the market, trend analysis and monitoring performed in the Annual Quality Review and during the Management Review.

The information provided by the firm has adequately addressed the requirements of 21

CFR 820.100.

Installation, 21 CFR 820.170

Installation is not required for this combination product.

Servicing, 21 CFR 820.200

Servicing is not required for this combination product.

MANUFACTURING

(b) (4)



Acceptance Activities

IBSA Institut Biochimique SA (the applicant firm) has the ultimate responsibility to ensure (b) (4) intended as a single-unit combination product meets specifications. This site is responsible for acceptance activities, drug product stability testing, and QA release of the packaged finished combination product.

DOCUMENTATION REVIEW RECOMMENDATION

The application was searched for documents pertaining to the manufacturing of the combination product. The documentation review of the application for compliance with the applicable Quality system Requirements showed no deficiencies. No additional information is required for the documentation review.

RECOMMENDATION

The application for [REDACTED] (b) (4) – NDA 206976 is approvable from the perspective of the applicable Quality System Requirements.

- (1) The documentation review of the application for compliance with the Quality System Requirements showed no deficiencies.
- (2) There were no facility inspections for compliance with applicable Quality System Requirements needed for approvability determination.

Katelyn R. Bittleman

Prepared: KRBittleman: 2/2/2017
Reviewed: VVuniqui: 2/6/2017

CTS No.: ICC1600471
NDA 206976

Review Cycle Meeting Attendance:
CMC: 2/1/2017

To: ORA

INSPECTIONAL GUIDANCE

Firm to be inspected:

1. IBSA Institut Biochimique SA
Via del Piano
CH-6915 Pambio-Noranco, Switzerland
FEI: 3002864272

CDRH recommends that the next routine inspection of the firm listed above covers compliance with all the requirements of 21 CFR part 4, including the applicable Quality System (21CFR 820) requirements – Management Controls (21 CFR 820.20), Design Controls (21 CFR 820.30), Purchasing Controls (21 CFR 820.50), and CAPA (21 CFR 820.100).

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

Katelyn R. Bittleman

Consumer Safety Officer

Physical Medicine, Orthopedics, Neurology, and Dental Devices Branch

Division of Manufacturing and Quality

Office of Compliance, WO66 RM 3451

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Secondary Contacts (if Primary is unavailable and a timely answer is required)

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

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

/s/

STEVEN A KINSLEY
02/07/2017