

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206976Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



NDA 206976

REFUSAL TO FILE

Institut Biochimique SA (IBSA)
4249 Via Encanto
Thousand Oaks, CA 91320

Attention: Clarence E. Jones, Ph.D.
IBSA U.S. Agent

Dear Dr. Jones:

Please refer to your New Drug Application (NDA) dated and received March 4, 2015, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Diclofenac Epolamine 1.3% / (b) (4) Topical (b) (4)

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the following reasons:

1. The document titled Integrated Summary of Safety and Efficacy in Module 5.3.5.3 is not acceptable as an Integrated Summary of Safety (ISS). Your description of the safety data is limited to one paragraph on page 7 of the document that fails to provide an analysis of how the data support the safety of the product. Neither Modules 2.5 (Clinical Overview) nor 2.7 (Clinical Summary) include any analyses of the pooled safety data. You must provide an analysis of the pooled safety data for all the Phase 2 and 3 studies that used the to-be-marketed formulation, which must include the overall exposure to the study drug including a breakdown by age, race, and gender, tables of common treatment emergent adverse events and serious adverse events, an analysis of dropouts due to adverse events, as well as textual description and analyses of the data. The analyses must support a discussion of why the data support the overall safety of the product.

In addition, for this topical product, perform an SMQ for severe cutaneous adverse reactions on the pooled adverse event data and include the results in your ISS.

2. You have not provided an integrated safety dataset of all Phase 2 and 3 trials. Phase 1 trials may be pooled separately.
 - A. Include the following fields/variables in the integrated dataset:
 - 1) A unique patient identifier
 - 2) Study/protocol number
 - 3) Patient's treatment assignment
 - 4) Demographic characteristics, including gender, chronological age (not date of birth), and race

- 5) Dosing at time of adverse event
 - 6) Dosing prior to event (if different)
 - 7) Duration of event (or start and stop dates)
 - 8) Days on study drug at time of event
 - 9) Outcome of event (e.g., ongoing, resolved, led to discontinuation)
 - 10) Flag indicating whether or not the event occurred within 30 days of discontinuation of active treatment (either due to premature study drug discontinuation or protocol-specified end of active treatment due to end of study or crossover to placebo).
 - 11) Marker for serious adverse events
 - 12) Verbatim term
- B. The adverse event dataset must include the following MedDRA variables: lower level term (LLT), preferred term (PT), high level term (HLT), high level group term (HLGT), and system organ class (SOC) variables. This dataset must also include the verbatim term taken from the case report form.
- C. In the adverse event data set, provide a variable that gives the numeric MedDRA code for each lower level term.
- D. Provide a detailed description for how verbatim terms were coded to lower level terms according to the ICH MedDRA Term Selection: Points to Consider document. For example, were symptoms coded to syndromes or were individual symptoms coded separately.
- E. For the concomitant medication dataset, you must use the standard nomenclature and spellings from the WHO Drug dictionary and include the numeric code in addition to the ATC code/decode.
- F. For the laboratory data, be sure to provide normal ranges, reference ranges, and units as well as a variable that indicates whether the lab result was from the local lab or central lab. Also, the variable for the laboratory result must be in numeric format.
- G. Perform adverse event rate analyses at all levels of MedDRA hierarchy (except for LLT) and also broken down by serious versus non-serious.
- H. Across all datasets, the same coding must be used for common variables, e.g. "PBO" for the placebo group. Datasets must not incorporate different designations for the same variable, e.g. "PBO" in one dataset, and "0 mg" or "Placebo," in another datasets. If the coding cannot be reconciled, another column using a common terminology for that variable must be included in the datasets.

All datasets must contain the following variables/fields (in the same format and coding):

- 1) Each subject must have one unique ID across the entire NDA
- 2) Study number

- 3) Treatment assignment
 - 4) Demographic characteristics (age, race, gender, etc.)
- I. A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities must be provided. A listing must be provided of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the “investigations” SOC or in an SOC pertaining to the specific abnormality. For example, all AEs coded as “hyperglycemia” (SOC metabolic) and “low blood glucose” (SOC investigations) should be tabulated. The NDA analyses of the frequency of abnormalities across treatment groups is not sufficient without ready identification of the specific patients with such abnormalities. Analyses of laboratory values must include assessments of changes from baseline to worst value, not simply the last value.
3. All clinical trials were conducted outside of the US. You must provide a justification as to how the results of these trials can apply to the US population. Include in your justification factors such as demographics, diagnostic criteria used in the studies, and standard of care for the injuries studied.
 4. The NDA did not contain the following items. Include them in any resubmission.
 - A. Summary of biopharmaceutics and clinical pharmacology in Module 2 supporting the new formulation.
 - B. Electronic datasets containing PK data from studies CRO-PK-02-92, and CRO-PK-98-13.
 5. You have not submitted leachable data for your final drug product. We communicated to you at the pre-IND and at the pre-NDA meetings that the NDA submission must include a full leachable profile for your product, including identification of and justification for the safety of those compounds that may transfer from the patch to the skin. We acknowledge that you are intending to use the extraction study to justify the lack of leachables assessment, however, you have not provided adequate support for your assertion that a safety evaluation based exclusively on results from an extraction study can adequately predict what any leachables that could be released from the product under conditions of use. Therefore, we cannot conduct an adequate toxicological risk assessment to support your drug product formulation.

Conduct a leachable study for your product that evaluates leachable levels at appropriate timepoints within the shelf-life of your product to allow for trend analysis and quantitate all leachables at the end of shelf-life. The analysis for potential leachables should be guided by the results of your extraction studies. Provide justification for your testing conditions. Provide a safety assessment for all leachables that exceeds a total daily intake threshold of 5 mcg/day.

While not issues related to our refusal to file this application, you should address the following issues if the application is resubmitted.

1. For each of the three pivotal Phase 3 studies, provide the following:
 - A. List of study sites with address and principle investigator's name
 - B. Number of study subjects screened
 - C. Number of study subjects enrolled
 - D. Number of study subjects completing study
 - E. Number of major protocol violations

- 2.
- 3.
- 4.
- 5.
- 6.
- 7.



Please note that this filing review represents a preliminary review of the application and is not indicative of deficiencies that would be identified if we performed a complete review.

We will refund 75% of the total user fee submitted with the application.

Within 30 days of the date of this letter, you may request in writing a Type A meeting about our refusal to file the application. A meeting package should be submitted with this Type A meeting request. To file this application over FDA's protest, you must avail yourself of this meeting.

If, after the meeting, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested the meeting. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee.

If you have any questions, call Matthew Sullivan, Supervisory Regulatory Health Project Manager, at (301) 796-1245.

Sincerely,

{See appended electronic signature page}

Sharon Hertz, M.D.
Director
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

SHARON H HERTZ
04/29/2015



PIND 111538

MEETING MINUTES

Clarence E. Jones, Ph.D.
U.S. Agent, representing
Institut Biochimique SA (IBSA)
4249 Via Encanto
Thousand Oaks, CA 91320

Dear Dr. Jones:

Please refer to your Pre-Investigational New Drug (PIND) file concerning [REDACTED] (b) (4)
(diclofenac epolamine, [REDACTED] (b) (4))

We also refer to the meeting between representatives from IBSA and the FDA on November 15, 2012. The purpose of the meeting was to discuss the development program for [REDACTED] (b) (4) [REDACTED] (b) (4) now at pre-NDA stage of development.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1183.

Sincerely,

{See appended electronic signature page}

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA
Meeting Date and Time: November 15, 2012, 3:00 to 4:00 PM (EST)
Meeting Location: 10903 New Hampshire Avenue
 White Oak Building 22, Conference Room 1315
 Silver Spring, Maryland 20903
Application Number: PIND 111538
Product Name: (b) (4) (diclofenac epolamine) (b) (4)
Indication: Treatment (b) (4)
Sponsor/Applicant Name: Institut Biochimique SA (IBSA)

Expected Meeting Attendees:

| FDA Attendees | Title |
|--------------------------|---|
| Bob A. Rappaport, MD | Director, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) |
| Sharon H. Hertz, MD | Deputy Director, DAAAP |
| Christina Fang, MD | Medical Officer, DAAAP |
| Dan Mellon, PhD | Nonclinical Supervisor, DAAAP |
| Huiqing Hao, PhD | Nonclinical Reviewer, DAAAP |
| Dominic Chiapperino, PhD | Senior Regulatory Health Project Manager, DAAAP |
| Yun Xu, PhD | Team Leader, Division of Clinical Pharmacology II (DCP-II) |
| Srikanth Nallani, PhD | Clinical Pharmacology Reviewer, DCP-II |
| Dionne Price, PhD | Statistics Team Leader, Division of Biometrics II (DB-II) |
| David Petullo, PhD | Statistics Reviewer, DB-II |
| Danae Christodoulou, PhD | CMC Lead, Office of New Drug Quality Assessment (ONDQA) |
| Terrance Ocheltree, PhD | Director, Division 1, ONDQA |
| Caroline Strasinger, PhD | Chemist, ONDQA |
| Tapash Ghosh, PhD | Biopharmaceutics Reviewer, ONDQA |
| Kavita A. Vyas, PhD | Senior Review Chemist, ONDQA |
| IBSA Attendees | Title |
| Giuseppe Mautone, MSc | Director, IBSA R&D |
| Stefano Rovati, MSc | Senior Manager, IBSA R&D |
| Pascale Passera, MSc | Manager, IBSA Regulatory |
| Alberto Bernareggi, PhD | Director, IBSA Pharmaceutical R&D |
| Clarence Jones, PhD | IBSA U.S. Agent |
| Christopher Jones, PhD | Manager, Clinical/Regulatory, IBSA U.S. |

1.0 BACKGROUND

IBSA has requested a Pre-NDA meeting to discuss (b)(4) a proposed reformulation of the approved Flector Patch.

IBSA has submitted a meeting briefing package, dated August 6, 2012, and received August 8, 2012, to describe the planned contents of their eventual NDA submission for (b)(4) and confirm that the planned submission will adequately address FDA recommendations and requirements, which were discussed previously at a pre-IND meeting held May 10, 2011.

Below in italic font are IBSA's questions, with pertinent background information from their meeting briefing package, and DAAAP's responses and additional comments, in bold font.

FDA provided "Preliminary Comments" to IBSA on November 14, 2012, containing responses to IBSA's questions from their meeting briefing package. These questions, in italic font, and FDA responses, in bold font, are presented below. Discussion during the meeting is summarized below, presented in normal font.

2.0 DISCUSSION

2.1. Nonclinical Questions

Background for Question 1

FDA previously advised: "A nonclinical repeat-dose dermal toxicology study should be completed prior to clinical studies to support a novel dermal application of a previously approved parenteral drug product. Given your reported human experience with this drug product (1200 individuals), the acute indication (<7 days) of (b)(4), the predicted lack of absorption of heparin from the patch (b)(4) as your approved Flector patch product, we will waive the nonclinical dermal toxicology requirement for this product. However, if review of the existing human data raises unexpected safety concerns or you consider a more prolonged clinical indication, additional nonclinical studies may be necessary."

IBSA Response: As indicated in the 5/10/2011 meeting with DAAAP, IBSA has performed two preclinical toxicity studies with the (b)(4), (1) a 4-week repeated dose dermal toxicity study in rabbits, and (2) a guinea pig contact hypersensitivity maximization test, the results of which are provided in Attachment 1 and Attachment 2, respectively.

Question 1: Since the requirement for nonclinical dermal toxicology studies has been waived, should the above studies even be included in the NDA for review?

FDA Response to Question 1:

Yes. As per 21 CFR §314.50 your NDA "...is required to contain reports of all investigations of the drug product sponsored by the applicant, and all other information

about the drug pertinent to an evaluation of the application that is received or otherwise obtained by the applicant from any source.” We consider the completed 4-week repeat-dose local dermal toxicity study in rabbits and the guinea pig delayed-contact hypersensitivity study to be pertinent.

Discussion:

No further discussion of Question 1 was necessary.

Background for Question 2.

FDA previously advised: “Your NDA submission must contain a full leachable profile for the final drug product formulation including identification of and justification for the safety of the potential materials (b) (4) that may transfer from the patch into the skin. You must provide a toxicological evaluation of those substances identified as leachables to determine the safe level of exposure via the transdermal route of administration. The approach for toxicological evaluation of the safety of leachables must be based on good scientific principles and take into account the potential that these impurities may either be known or suspected highly reactive and/or genotoxic compounds.”

IBSA Response: *As per this request, IBSA contracted with (b) (4) to perform an extraction study on the packaging materials which are (b) (4) the (b) (4) and Flector® Patch; i.e. (1) the nonwoven felt backing to which the drug product (b) (4) is applied, (2) the release liner affixed to the drug product after application to the nonwoven felt backing which is removed prior to patient usage, and (3) the pouch in which the patches are stored (5 patches/pouch) (Attachment 3). IBSA also contracted with (b) (4) (b) (4) to perform an extraction study with the finished product (b) (4)*

(b) (4) (Attachment 4). The purpose of the two studies is to ascertain if there are any potentially toxicological elements in the Flector or (b) (4) consistent with the concerns in Item 2 above, (b) (4)

Although both studies are near-completion, final reports will not be available for another month or so, but will certainly be available for inclusion in an NDA for this product.

Question 2: *Are the protocols provided in Attachment 3 and Attachment 4 adequate to generate an acceptable extractable/leachable profile on the (b) (4) ?*

FDA Response to Question 2:

While your approach may satisfy the relevant CMC requirements to support filing of an NDA, we do not agree that the two protocols submitted, (b) (4)

(b) (4) will adequately address the safety of potential leachables from your final drug product.

For Study Plan BT0270.01, provide justification for the selection of extraction solvents and conditions chosen. The study should delineate the worst-case scenario for exposure to

identified extractables taking into consideration the maximum daily exposure to the drug product. A toxicological risk assessment can be made on the extractable data, however, we recognize that these conditions may not reflect exposures during clinical use. The extraction studies can be used to guide your assessment of the potential leachables from drug product held on stability for the requested shelf-life. Monitor and report potential leachables during your stability studies and provide sufficient results at planned timepoints, e.g. every-three-month intervals, to assess leachable trends. An assessment of leachables from the long-term stability samples guided by the results of the extraction studies will be used for toxicological risk assessment. In general, leachables with chemical structures either known or predicted to be genotoxic or carcinogenic must be reduced to NMT 1.5 mcg/day or otherwise justified via toxicology data. Leachables that do not have genotoxicity or carcinogenicity safety concerns must be qualified if they exceed 5 mcg/day, as proposed.

For Study Plan BU0061.02, the protocol does not appear to provide clear delineation of the conditions of the extraction procedures, such as justification for the choice of solvent(s) used, duration(s) of extractions, temperature(s) of extraction procedures. The general design comments and toxicological risk assessment provided above for Study Plan BT0270.01 also apply to this study protocol.

Discussion:

IBSA acknowledged that the two study protocols addressing leachables were not provided in the meeting briefing package but will be included in the NDA. IBSA asked if it would be acceptable to assess the leachable profile at release and at the end of shelf-life. The Division stated that multiple time points are preferred for leachable testing to assess whether leachable compounds increase or tend to plateau over the shelf-life. It is helpful to have sufficient data to determine the level at which leachable impurities appear to plateau for future extrapolation of expiry. If the leachable profile is only generated at release and at end of shelf-life, it is possible that the quantity of leachable compounds at the end of shelf-life will exceed the specification's threshold, and IBSA runs the risk that it will not have sufficient data to estimate the trend in the leachable profile from only two time points.

(b) (4)

Background for Question 3.

FDA previously advised: "In Module 2 of your NDA (2.6.6.8 Toxicology Written Summary/Other Toxicity), you must include a table listing the drug substance and drug product impurity specifications, the maximum daily exposure to these impurities based on the maximum daily dose of the product and how these levels compare to ICH Q3A(R2) and Q3B(R2) qualification thresholds and determination if the impurity contains a structural alert for mutagenicity. Any proposed specification that exceeds the qualification thresholds should be adequately justified for safety from a toxicological perspective."

IBSA Response: *Module 2.6.6.8 is included in Attachment 5 along with the drug substance and drug product specifications (including impurities) for the (b)(4) as taken from Flector Patch NDA 21-234, Amendment 17. None of the impurities contain a structural alert for mutagenicity.*

Question 3: Is the information provided in Attachment 5 sufficient to address FDA requirements?

FDA Response to Question 3:

The proposed drug substance and drug product acceptance criteria for impurities in the specifications in Attachment 5 of the briefing document are below the safety qualification thresholds of ICH Q3A(R2) and Q3B(R2) and do not appear to raise any concerns at this time. The adequacy of the final drug substance and drug product stability specifications will be determined at the time of NDA review.

Discussion:

No further discussion of Question 3 was necessary.

Background for Question 4.

FDA previously advised: "Your NDA submission should include a detailed discussion of the nonclinical information in the published literature and should specifically address how the information within the published domain impacts the safety assessment of your drug product. This discussion should be included in Module 2 of the submission. Copies of all referenced citations should be included in the NDA submission in Module 4. Journal articles that are not in English must be translated into English."

IBSA Response: *A PubMed search, completed in May, 2012 using the Key Words Diclofenac Topical-Toxicity (Animals) and no time limitation, yielded 18 citations (Attachment 6), only one of which was considered to be of potential relevance to the subject of (b)(4) - associated toxicity (Attachment 6a), and even then somewhat limited because the dosage form was substantially different (3% gel) and the murine model of photocarcinogenesis in which it was evaluated was quite extreme. It is expected, moreover, that the nonclinical pharmacology/toxicology profile for the (b)(4) will be (b)(4) from that reported in the Flector NDA and subsequent IND Annual Reports (Attachment 6b), as the (b)(4) between the two formulations is the presence of a (b)(4) t of heparin (b)(4) which does not appear, based on available data, to even leave the*

patch, (b) (4) the release of the active diclofenac (see Attachment 9). Consistent with this thesis, outcome for both the (b) (4) 4-week repeated dose dermal toxicity study in rabbits and guinea pig contact hypersensitivity maximization test was similar to that observed for the same studies reported in the Flector Patch NDA. Please also note that the non-clinical toxicological profile for the (b) (4) would be expected to be substantially more favorable than that reported in the physician insert for Voltaren (1% diclofenac sodium gel) (Attachment 6c), as blood levels achieved by the latter in a human PK study with 4 x 4 g/day dosing (160 mg) are more than 7-fold greater than those attained at steady state when human subjects are exposed to the (b) (4) (see Attachment 10).

Question 4: If the information presented in IBSA Response is incorporated into a Module 2 narrative in the (b) (4) NDA, would that be adequate to address this issue?

FDA Response to Question 4:

Your proposal to address the new nonclinical information in the published literature subsequent to the date of approval of the original Flector Patch is acceptable.

Discussion:

No further discussion of Question 4 was necessary.

Background for Question 5.

FDA previously advised: “The nonclinical information in your proposed drug product label must include relevant exposure margins with adequate justification for how these margins were obtained. If you intend to rely upon the Agency’s previous finding of safety for an approved product, the exposure margins provided in the referenced label must be updated to reflect exposures from your product. If the referenced studies employ a different route of administration or lack adequate information to allow scientifically justified extrapolation to your product, you may need to conduct additional pharmacokinetic studies in animals in order to adequately bridge your product to the referenced product label. Should there be evidence that heparin is absorbed from the patch, the potential impact of this exposure will have to be considered with respect to potential reproductive and developmental toxicology labeling.”

IBSA Response: The concentration of diclofenac epolamine in the (b) (4) is (b) (4) (b) (4) to its predecessor Flector, the latter having been shown to be significantly (but only relatively modestly) more effective than a placebo patch in reducing pain in patients with mild to moderate sports injuries (~15% greater than placebo) when applied for two 12-hour periods/day. Since only ~5% of the diclofenac leaves the Flector patch over a 12-hour application period (Attachment 7), it is highly unlikely that the active content could be reduced further without compromising clinical activity. The enhanced effectiveness of the (b) (4) (b) (4) in comparison to Flector, as observed in several pivotal Phase 3 studies conducted to date (Attachment 8), is believed to be due to increased movement of diclofenac out of the patch and through the skin of the patient (Attachment 9), resulting in a slightly higher local deposition of active, but not enough to significantly alter its plasma pharmacokinetic profile (Attachment 10). Most importantly, in the numerous clinical trials performed to date, both patch formulations have been well-tolerated with minimal side effects.

Question 5a: Does this response adequately address FDA concerns?

FDA Response to Question 5a:

No. The exposure ratios in Flector patch drug product label were based on the data demonstrating that ~5% of the diclofenac was no longer present in the patch following removal after 12 hours and, therefore, is presumed to have been delivered to the body. Provide comparable data for the (b) (4) in your NDA and adjust the exposure margins in the labeling accordingly.

Discussion:

No further discussion of Question 5a was necessary.

Question 5b: Additionally, does FDA agree that the information provided in Attachment 9 convincingly supports the IBSA position that role of heparin in its formulation is that of an excipient not an active?

FDA Response to Question 5b:

Based on the information provided to date, it appears as though there are adequate data to support your conclusion that the heparin in the patch is not an active ingredient. However, to confirm that heparin is not released from the patch, provide residual heparin data for the (b) (4) following maximum clinical use.

Discussion:

No further discussion of Question 5b was necessary.

Additional Nonclinical Comments

FDA previously advised that any impurity or degradation product that exceeds ICH thresholds must be adequately qualified for safety as per ICHQ3A(R2) and ICHQ3B(R2).

Adequate qualification must include:

- a. Minimal genetic toxicology screen (two *in vitro* genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay**
- b. Repeat dose toxicology of appropriate duration to support the proposed indication**

In response, you have stated that this will be addressed in the NDA, and that you are currently awaiting the results of the two studies described in the background for Question 2 above.

We note that the ICH Q3A(R2) and Q3B(R2) guidances do not apply to extractables and leachables. However, as long as your drug substance and drug product stability specifications are below the ICH qualification thresholds and do not contain any structural alerts for genotoxicity or carcinogenicity, the specifications will likely be acceptable from a toxicology perspective. We do note that, for a patch product where a significant amount of the drug likely remains in the patch following normal use, if you can provide data to show

that no drug product degradant is released from the patch completely, the maximum daily dose can be based on the actual levels released. In the absence of adequate data that demonstrate drug product degradants are not completely released from the patch, we will assume 100% release from the patch in order to conduct a toxicology risk assessment.

Discussion:

Refer to the discussion summary for Question 2.

2.2. Clinical Questions

Background for Question 6.

FDA previously advised: “The information about study design that you have provided is insufficient to determine if the studies that have been performed could be considered adequate and well-controlled and capable of supporting a finding of efficacy and filing of your NDA. We recommend that you submit the protocols for these studies for review. If the design of these studies is appropriate, the multiple-dose efficacy data briefly summarized in your submission may be adequate support for a finding of efficacy for your NDA submission; however, this is a review issue and is also dependent on study conduct, demographic characteristics of the study population, dropout rates, proportion taking rescue and time to rescue, and the prespecified statistical analysis plan. In addition, information about single-dose effects (pain intensity reduction, pain relief, onset, and duration of the initial dose) is required along with data on onset of action of the patch following the initial application, the proportion of patients who request rescue medication or additional doses (patches), and the time it takes for patients to request rescue or remediation.”

IBSA Response: As requested in the May 10, 2011 meeting with DAAAP, IBSA provided protocols for four ^{(b) (4)} clinical studies in a June 9, 2011 submission. In a subsequent letter dated February 23, 2012, DAAAP requested the following additional information from each study:

- a. The pain intensity difference (PID) from baseline to all scheduled time points using the group mean of pain intensity scores from patient diaries.*
- b. The time to the first dose of rescue medication after the initial patch application and after each daily patch application.*
- c. The proportion of patients taking rescue during the multiple-dose treatment period.*
- d. One graph, from each study, plotting pain intensity over time and including all the treatment groups.*

On April 5, 2012, the information requested above was submitted through ESG in eCTD 0000, and is provided for convenience in Attachment 8.

Question 6: In their preliminary review of the clinical protocols requested and the follow-up analyses summarized in Attachment 8, do the DAAAP medical reviewers agree that sufficient clinical data are available on the ^{(b) (4)} to support an NDA filing?

FDA Response to Question 6:

Yes, the clinical data proposed appear sufficient to support filing the NDA.

Discussion:

No further discussion of Question 6 was necessary.

Background for Question 7.

FDA previously advised: "You must conduct dermatological safety studies with the final to-be-marketed drug product. Doses to be tested in the cumulative irritation study should be similar to what is planned for efficacy studies and proposed labeling. The contact sensitization study must have at least 200 evaluable subjects and may be combined with cumulative irritation in a single study, with the induction phase (if of sufficient length) serving to detect cumulative irritation. You must study phototoxicity and photosensitization if your drug product absorbs anywhere in the UV/visible light spectrum. The phototoxicity and photosensitization studies may be waived if there is no absorption of the drug product in the UV/visible light spectrum. If you are planning to request a waiver, an absorption spectrum analysis of the drug product should be submitted to the Agency for review. You may refer to the Draft Guidance on Lidocaine for additional information on the conduct of dermatologic safety studies."

IBSA Response: Previous studies presented in the Flector Patch NDA indicated that this product is neither phototoxic (Attachment 11) nor photosensitizing (Attachment 12), despite diclofenac being a known photosensitizing/phototoxic agent (Attachments 13), perhaps due to the active in the Flector Patch being protected from UV radiation following patient application and the low levels in skin following patch removal. IBSA has recently shown that the heparin component of the (b) (4) does not absorb in the UV/visible spectrum (Attachment 14), a finding consistent with the absence of any references suggesting otherwise in a PubMed search (Attachment 13). It should also be noted that phototoxic/photosensitization reactions have not been reported in the many minor sports injury patients who have been treated with either the Flector or (b) (4), nor during post-approval pharmacovigilance monitoring except for a single case in 2001 (Attachment 13a), the latter report lacking sufficient detail and follow-up to allow for a definitive assessment of either diagnosis or causality. Although a 50 subject contact sensitization study has been performed (Attachment 15), IBSA intends to conduct a second 200 patient study as requested above, the protocol synopsis for which is provided in Attachment 16.

Question 7: IBSA would appreciate FDA comments on the appropriateness of the proposed design for the second study, with specific questions identified in Attachment 16a.

FDA Response to Question 7:

Regarding the potential phototoxicity associated with (b) (4) you may request a waiver of phototoxicity and photoallergy studies if all components of the drug product (b) (4)

Regarding your specific questions in Attachment 16a concerning the proposed 200-patient irritation/sensitization study, we have the following responses to Question 7-1 through 7-4:

Question 7-1:

During the induction phase of the proposed RIPT study, applications of a one-fourth section of the test, reference and vehicle patches will be simultaneously made to each subject every day, with skin irritation assessment performed daily at the time of patch removal. Does FDA consider it acceptable to not use partial patches in the induction phase of the study given that the evaluation of patch adhesion is not an objective of the study since it has already been assessed in the PK/PD studies as well as the 50-volunteer RIPT study previously conducted?

FDA Response:

You provided a short protocol synopsis for your Irritation/Sensitization trial, in which you proposed to use a 1/4 section of the (b) (4) Flector Patch (no heparin) and Placebo Patch (heparin and all other excipients) as test materials. We have the following comments regarding the proposed study:

- **It may be acceptable to use a 1/4 section of the patch in topical safety studies intended to assess irritation and sensitization potential as long as alteration of the patch does not alter release of the drug product and steps are taken to secure patches to the application site. Adequate contact of the test product and the skin should be assured.**
- **We recommend that, during the induction phase of the study, in addition to Flector Patch, (b) (4) and Placebo Patch, you use patches containing a positive control [SDS (Sodium Lauryl Sulfate)] and a negative control (Saline).**

Question 7-2:

A total of 220 healthy subjects will be enrolled in the study to ensure that at least 200 will be evaluable for the Per-Protocol (PP) Population (i.e. no formal sample size calculation is planned for the study). Does FDA consider this approach acceptable given the objective of the study is not to establish bioequivalence of the (b) (4) to a reference formulation with regard to skin irritation/sensitization?

FDA Response:

You should enroll a sufficient number of subjects to achieve 200 evaluable subjects.

Question 7-3:

Are the PP populations for the irritation and sensitization analyses correctly defined?

FDA Response:

Yes

Question 7-4:

Are the parameters to be assessed correctly identified? In particular, is the approach described for the identification of any potential sensitized subject correct?

FDA Response:

We agree with your approach to identify potentially sensitized subjects described in your Protocol Synopsis (Attachment 16, page 1499, under heading “Sensitization”).

Discussion:

IBSA asked if it would be acceptable to cross-reference to the Flector NDA to fulfill phototoxicity study requirements since the recommended phototoxicity testing was performed for Flector (b) (4)

The Division stated that this would need further consideration. The addition of heparin may have an unforeseen impact on the formulation overall, despite its own absorbing properties or lack thereof. A post-meeting note from the Division will address this question.

Post-meeting note:

The proposal to cross-reference Flector in place of conducting additional phototoxicity studies is acceptable.

2.3. Regulatory Questions

Background for Question 8.

FDA previously advised: “It is not clear from your meeting package if you intend to rely upon the Agency’s previous finding of safety for one or more approved products. We recommend that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency’s regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry “Applications Covered by Section 505(b)(2).” In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency’s interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408, available at <http://www.fda.gov/ohrms/dockets/dailys/03/oct03/102303/02p-0447-pdn0001-vol1.pdf>.”

IBSA Response: IBSA believes the most appropriate regulatory pathway for a (b) (4) NDA is 505(b)(2). In support of its position, numerous examples of changes to an approved drug “for which 505(b)(2) applications should be submitted” are listed under Item III in the guidance referenced above, one of which is Formulation that states “An application for a proposed drug product that contains a different quality or quantity of an excipient(s) than the listed drug where the studies required for approval are beyond those considered limited confirmatory studies appropriate to a 505(j) application”. Since (b) (4) is (b) (4) in all aspect to Flector (b) (4) except for the presence of heparin whose contribution is that of an excipient (please see Attachment 9), then it would seem that the conditions for submission of a (b) (4) NDA as a 505(b)(2) have been met.

Question 8: Does FDA agree that the (b) (4) NDA should be filed as a 505(b)(2) application?

FDA Response to Question 8:

It is not necessary to list the Flector Patch NDA as a referenced drug to support your NDA since you own the data in that NDA. It is necessary only to cross reference your Flector NDA for any data necessary to support the safety of the proposed (b) (4) NDA. The Flector Patch NDA was approved via the 505(b)(2) pathway based on the reliance on literature references that were neither owned nor for which there was right of reference. Therefore, we agree that an NDA for (b) (4) which relies on cross reference to the Flector Patch NDA must also be submitted as a 505(b)(2) NDA based on reliance on the same literature. We agree also that a 505(j) application is not appropriate for (b) (4) (b) (4) for the reasons you state.

Discussion:

No further discussion of Question 8 was necessary.

Background for Question 9.

FDA previously advised: “If you intend to submit a 505(b)(2) application that relies for approval on FDA’s finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You must establish a “bridge” (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.

IBSA Response: Please see IBSA Response for Question 8 above.

Question 9: Does FDA agree that it is scientifically appropriate for Flector to be the RLD for (b) (4) in a 505(b)(2) application given that it is (b) (4) in (b) (4) to the former except for the presence of heparin, even though clinically superior but with an indistinguishable PK profile, the latter suggesting the systemic safety profile should also be (b) (4)

FDA Response to Question 9:

Refer to our response to Question 8. Your proposal to bridge the data from the Flector Patch to the new (b) (4) formulation appears reasonable. To clarify, the term reference listed drug (RLD) is not applicable for a 505(b)(2) application. The Office of Generic Drugs (OGD) designates an RLD to which all generic drugs must demonstrate bioequivalence in order to be approved as a 505(j). For a 505(b)(2) application, it is necessary only to demonstrate relative bioavailability to one or more listed drugs that were approved as an NDA. Those drugs are referred to as either “referenced” or “listed” drugs. However, as you own the NDA for Flector Patch, rather than referencing an NDA that you do not own or have right of reference for, as is done with a 505(b)(2), in this case, you will cross reference the NDA for Flector Patch that you own. As noted above, the application will be a 505(b)(2) application based on its reliance on literature.

Discussion:

No further discussion of Question 9 was necessary.

Additional Clinical Comment:

You must address (individually) the effect of heat, exercise and overlay on diclofenac bioavailability.

Discussion:

IBSA requested clarification regarding the conditions of use to be studied in the bioavailability study.

The Division clarified that new bioavailability studies are not necessarily required for each of these conditions. In “addressing” each of the three possible effects, IBSA must, at a minimum, discuss these issues in the NDA by providing sufficient information by reference or from new studies, or other rationale, so that labeling can appropriately describe the possible effects these conditions could have on patch performance and safety. If BA studies are conducted, the following advice applies:

- For any of the three effects to be studied, an evaluable group of 12 patients is acceptable.
- For studying the effect of exercise, the same study design as used for Flector Patch is acceptable, i.e., 20 minutes on the treadmill.
- The effect of topical heat (e.g. from a heating pad) should be assessed during typical use (e.g., 20 minutes on, 20 minutes off).
- Regarding overlay, if an occlusive bandage will not be studied nor recommended, use of such overlay should be specifically discouraged in product labeling.
- CMC also indicated that [REDACTED] (b) (4)

2.4. Chemistry, Manufacturing, and Controls (CMC) Questions

Background for Question 10.

FDA previously advised: “We strongly recommend that you perform pivotal clinical trials with your proposed commercial formulation. Any changes to the proposed commercial formulation from developmental formulations require sufficient bridging studies. In addition, we strongly encourage you to make all possible changes to your manufacturing process and design of the patch prior to initiation of pivotal clinical trials; we believe that clinical trials are the best validation of the performance of complex dosage forms.”

IBSA Response: [REDACTED] (b) (4)

(b) (4)

Question 10. After reviewing Attachment 17, does FDA agree that IBSA can continue to use heparin from (b) (4) in the (b) (4) formulation to be sold in the U.S.?

FDA Response to Question 10:

Yes, we agree with your proposal provided that there is adequate information about the source and manufacturing process of the heparin used in the (b) (4) patch. You may provide this information either in the appropriate sections of the NDA or reference an active DMF for the heparin supplier.

Discussion:

IBSA stated that there appears to be a contradiction between the response to Question 10 and the response to Question 13 regarding the requirement to reference or provide a DMF for heparin.

The Division clarified that a DMF would be necessary if sufficient data and information could not be provided directly in the NDA about the source, manufacturing and specifications for the heparin raw material.

Background for Question 11.

FDA previously advised: "It is recommended that you qualify adhesives both prior to and post drug formulation. This insures both optimum product quality attributes in transdermal and topical formulations, and a seamless post-approval change process, in case the raw materials, manufacturing process, or manufacturer of the adhesive(s) is changed. The following tests are not required for release of the drug product but rather to qualify the adhesive component.

(b) (4)

IBSA Response: The (b) (4) components of the (b) (4) formulation (as well as Flector) that are responsible for product adhesivity/stickiness following application to the skin of a patient are (b) (4), each of which is being evaluated for (b) (4)

(b) (4) (see IBSA Response for Question 2). Please note that the adhesive components of the product formulation are (b) (4)

Question 11. Does IBSA's response satisfy the previous FDA recommendations?

FDA Response to Question 11:

The response does not fully address all items raised in this comment. The Adhesive Qualification information in our previous advice is recommended to assist manufacturers in demonstrating scientific understanding of chosen excipients for a particular product. By qualifying adhesives, optimum product quality attributes in formulations can be ensured, and a seamless post-approval change process will be in place should the raw materials, manufacturer or manufacturing process of the adhesive change. Applicable tests are recommended but not required; however, providing such information in an NDA may assist in understanding product and process development.

Discussion:

IBSA asked the Division to clarify what is meant by the term, "adhesive (b) (4)

Conducting these studies prospectively will aid in the change of adhesive excipient suppliers during the product's life cycle.

Background for Question 12.

FDA previously advised: "We recommend that sufficient scientific justification to support the amount of residual drug in a TDDS be included in the 3.2.P.2 section of the common technical document (CTD) format discussion of the product and process development and justification for the final formulation and system design. The level of information in the submission should be sufficient to demonstrate product and process understanding and assure that a scientific and risk based approach has been taken to minimize the amount of residual drug in a system after use. The justification for the percent of residual drug and the overall amount of remaining drug will be assessed during the review. Refer to the "Draft Guidance for Industry – Residual Drug in Transdermal and Related Drug Delivery Systems" for additional information."

IBSA Response: Please see IBSA Response for Question 5.

Question 12: Does the information provided under Question 5 provide adequate justification for the amount of active in the Flector and (b) (4) ?

FDA Response to Question 12:

No, we do not agree. The information provided in the background for Question 5 does not justify the amount of residual drug. The residual drug amount of the (b) (4) product must be assessed after wear. Sufficient scientific justification to support the amount of residual drug should be provided in section 3.2.P.2 of the NDA submission. For more information refer to the Guidance for Industry – Residual Drug in Transdermal and Related Drug Delivery Systems (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM220796.pdf>). The justification for the percent of residual drug and the overall amount of the remaining drug will be assessed during the review.

Additionally, assess the amount of heparin remaining in the system after wear to support the claim that heparin is not an active substance.

Discussion:

No further discussion of Question 12 was necessary.

Background for Question 13.

FDA previously advised: “Ensure that the heparin drug substance complies with the updated tests and acceptance criteria as listed in the latest version of the USP monograph. Provide a Letter of Authorization to the Drug Master File describing manufacturing and controls information for heparin.”

IBSA Response: As indicated in IBSA Response – Additional CMC Comments Item 1, the heparin included in the (b) (4) formulation is both EP and USP complaint. Moreover, since the body of evidence suggests that the contribution of heparin to the enhanced clinical effectiveness of the (b) (4) is that of an excipient and not an active (see IBSA Response for Question 5), provision of a letter of authorization to a heparin drug master file would seem inappropriate.

Question 13: Does FDA agree that IBSA does not need a Letter of Authorization from (b) (4) for (b) (4) heparin, if one even exists?

FDA Response to Question 13:

No, we do not agree. Given its nature and history, heparin and its manufacturing process are scrutinized starting from early steps in the manufacturing process. A Letter of Authorization to reference an active DMF for the heparin supplier(s) is necessary to assess the acceptability of heparin, even if it is used as an “excipient,” and not an active.

Discussion:

Refer to the discussion summary after Question 10.

Background for Question 14.

FDA previously advised: “We recommend that you submit a report on the development and validation of in vitro release/dissolution testing with appropriate specifications (preferably multipoint) encompassing the complete dissolution profile with at least 80% release at the final point prior to Phase 3 initiation. If these specifications are anticipated to be used beyond a routine quality control measure, development of an in vitro - in vivo correlation (IVIVC) is encouraged.”

IBSA Response: The method requested has been developed/validated, and demonstrates that more than 80% of the diclofenac in both the Flector Patch and (b) (4) is released within (b) (4) minutes, and the dissolution profiles are the same for each product, the latter indicating that the presence of heparin in a Flector Patch has no effect on product dissolution (Attachment 18). Please note that it would not be expected that the results from this assay would be predictive of clinical performance for several reasons: (1) the release of active from either patch under the conditions of dissolution testing does not mimic actual patch usage (i.e. following application to a patient’s skin vs. placement of patch segments in a dissolution vessel containing a phosphate buffered solution and sampling at various time intervals thereafter), and (2) comparative clinical data on Flector vs. (b) (4) argue that the Flector Patch is more effective than its predecessor in reducing pain for patients with minor soft tissue injuries (see Attachment 8), not equally effective which an equivalent dissolution profile would suggest. Conversely, results from the Franz Cell Assay (Attachment 9) reveal greater movement of diclofenac out of patches containing heparin than those without, a system that more closely imitates in vivo product usage and therefore a more compelling candidate for evaluation of the correlation between in vitro and in vivo Flector (b) (4) performance. Indeed, the data generated to date suggest that this relationship actually exists; i.e. heparin increases the release of active from the patch in the Franz cell and also enhances clinical effectiveness when applied to the skin of patients with minor sports injuries.

Question 14: Is the information in Attachment 18 adequate for the previous FDA recommendation?

FDA Response to Question 13: Your approach appears reasonable; however, the in vitro drug release method will be evaluated during the NDA review cycle.

Discussion:

No further discussion of Question 14 was necessary.

Additional CMC Comments:

1.

(b) (4)



Include the batch numbers and date of manufacture associated with the provided drug product samples. The samples may be sent to the attention of:

**FDA – White Oak
Luz Rivera - CDER/OPS/ONDQA
Bldg. 21, Rm 2605
10903 New Hampshire Avenue
Silver Spring, MD 20993**

2.

(b) (4)

3.

Regarding the Drug Product Release Specifications and Stability Testing:

4.

(b) (4)

5.

6.

7.

8.

9.

(b) (4)

Discussion:

(b) (4)

With respect to manufacturing details and characterization of the state and role of heparin, IBSA may continue discussions with ONDQA if necessary, prior to NDA submission.

(b) (4)

Data should be provided in the NDA to address this point.

Post-meeting Note:

After internal discussion, a biological assay appears unnecessary for heparin at the end of shelf-life, based on the information supplied to date.

(b) (4)

(b) (4)

Additional discussion topics:

IBSA asked the Division to clarify which group reviews pediatric protocols. The Division stated that pediatric protocols should be submitted to the Division via application amendment. Clinical review divisions coordinate with the Pediatric and Maternal Health Team's pediatric group to solicit their recommendations on pediatric study requirements and protocols.

3.0 OTHER ADVICE FOR PRE-NDA STAGE

3.1. PREA Pediatric Study Plan

The Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA) changes the timeline for submission of a PREA Pediatric Study Plan and includes a timeline for the implementation of these changes. You should review this law and assess if your application will be affected by these changes. If you have any questions, please email the Pediatric Team at Pedsdrugs@fda.hhs.gov.

3.2. Prescribing Information

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

3.3. Manufacturing Facilities

To facilitate our inspectional process, the Office of Manufacturing and Product Quality in CDER's Office of Compliance requests that you clearly identify *in a single location*, either on

the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

| Site Name | Site Address | Federal Establishment Indicator (FEI) or Registration Number (CFN) | Drug Master File Number (if applicable) | Manufacturing Step(s) or Type of Testing [Establishment function] |
|-----------|--------------|--|---|---|
| 1. | | | | |
| 2. | | | | |

Corresponding names and titles of onsite contact:

| Site Name | Site Address | Onsite Contact (Person, Title) | Phone and Fax number | Email address |
|-----------|--------------|--------------------------------|----------------------|---------------|
| 1. | | | | |
| 2. | | | | |

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/s/

DOMINIC CHIAPPERINO
12/13/2012