# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 206610Orig1s000

# SUMMARY REVIEW

**Food and Drug Administration**
**CENTER FOR DRUG EVALUATION AND RESEARCH**
**Division of Anesthesiology, Addiction Medicine, and Pain Medicine**
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

# Summary Review for Regulatory Action

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|---|---|
| **Date** | January 15, 2021 |
| **From** | Rigoberto Roca, MD |
| **NDA/Supplement No.** | 206610 |
| **Applicant Name** | Mylan Laboratories, Ltd. |
| **Date of Original Submission** | May 05, 2014<br>Complete Response letter issued February 27, 2015 |
| **Date of First Complete Response Submission** | September 10, 2015<br>Complete Response letter issued March 10, 2016 |
| **Date of Second Complete Response Submission** | August 04, 2016<br>Complete Response letter issued February 01, 2017 |
| **Date of Third Complete Response Submission** | June 07, 2017<br>Complete Response letter issued December 06, 2017 |
| **Date of Fourth Complete Response Submission** | December 06, 2018<br>Complete Response letter issued June 06, 2019 |
| **Date of Fifth Complete Response Submission** | July 10, 2019 |
| **PDUFA Goal Date** | January 10, 2020 |
| **Proprietary Name / Established (USAN) Name** | Acetaminophen for injection |
| **Dosage Forms / Strength** | Lyophilized powder for injection, 1 g/vial |
| **Proposed Indications** | 1. Management of mild to moderate pain<br>2. Management of moderate to severe pain with adjunctive opioid analgesics<br>3. Reduction of fever |
| **Action** | Approval |

| **Material Reviewed/Consulted**<br>OND Action Package, including reviews by: | |
|---|---|
| OPQ | Christina Cappaci Daniel, PhD; Anika Lalmansingh, PhD; Valerie Amspacher, PhD |
| Project Management Staff | Swati Patwardhan; Matthew Sullivan, MS |

OND = Office of New Drugs

OPQ = Office of Pharmaceutical Quality

# 1. Introduction

The Applicant, Mylan Laboratories, Ltd., has submitted a complete response to the Complete Response letter issued on April 21, 2015. This is the sixth review cycle for this application, from the time the first Complete Response Letter was issued on February 27, 2015.

This is a 505(b)(2) application relying on Ofirmev (NDA 22450). Ofirmev is a sterile, clear, colorless, preservative-free, isotonic formulation of acetaminophen. Each 100 mL glass vial contains 1000 mg acetaminophen (10 mg/mL). The product that is the subject of this NDA is a lyophilized powder rather than a solution and is intended to have greater stability and a longer shelf-life than the referenced product. The nature of this formulation change precludes submission of a 505(j) application.

# 2. Background

The assessment and conclusions by the review team are discussed further in Section 8 (Safety) of this review.

# 3. Chemistry, Manufacturing, and Controls (CMC)

There was no new information submitted during this review cycle related to product quality.

*Outstanding or Unresolved Issues*

I concur with the conclusions reached by the product quality reviewers during the previous review cycles that there are no manufacturing issues that would preclude approval of this application.

# 4. Nonclinical Pharmacology/Toxicology

There had not been any nonclinical issues identified during the first three review cycles that would have precluded approval. The Applicant did not submit any new nonclinical data submitted during this review cycle.

However, the changes to the package insert that had been recommended during the first two cycles had not been communicated to the Applicant yet, so the review team focused on whether the recommendations were unchanged and the conversion sections of the insert to be in compliance with the Pregnancy and Lactation Labeling Rule (PLLR).

*Outstanding or Unresolved Issues*

There were no outstanding or unresolved pharmacology/toxicology issues that precluded approval during the first review cycle, and there are none during this review cycle.

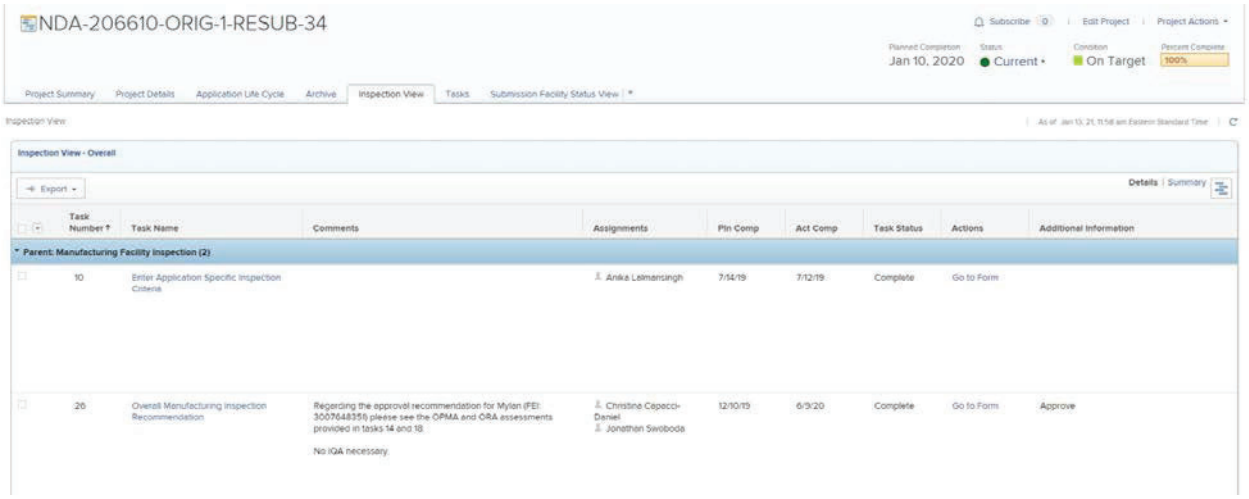
# 5. Clinical Pharmacology

There were no outstanding or unresolved clinical pharmacology issues that precluded approval during the previous review cycles, and there are none during this review cycle.

# 6. Other Relevant Regulatory Issues

During the last review cycle, a facilities inspection identified deficiencies that precluded approval. As noted by Dr. Amspacher in the OPQ review:

> The previous recommendation of complete response was due to an inspection (May 2019) resulting in a change in facility status to Potential Official Action Indicated. The facility issues have been resolved and the Office of Pharmaceutical Manufacturing Assessment (OPMA) (formerly OPF) now recommend approval. See screenshot from Panorama at the bottom of this page.




### Financial Disclosure

The Applicant's submission did not include form FDA 3455, "Certification: Financial Interests and Arrangements of Clinical Investigators". There were no clinical studies conducted including *bioequivalence studies. A* biowaiver was requested and was granted.

# 7. Labeling

The Office of Prescription Drug Products (OPDP), and the Division of Medication Error Prevention and Analysis (DMEPA) provided recommendations for modifications to the package insert, container labels, and carton labeling during the previous review cycles. As mentioned above, the review team also reviewed the package insert to assess what modifications were

needed in order for it to be in compliance with the Pregnancy and Lactation Labeling Rule. This included a consultation with the Division of Pediatric and Maternal Health.

# 8. Decision/Action

Regulatory Action

Approval.

While the Applicant had adequately addressed prior deficiencies, the manufacturing facility was found to have sufficient deficiencies to result in a withhold recommendation at the end of the last review cycle. These deficiencies have been addressed and the recommendation from the OPQ team is that the application can be approved.

In addition, the Applicant responded to the outstanding deficiencies regarding patent certification and recertification.

Recommendation for Postmarketing Risk Management Activities

None.

Recommendation for other Postmarketing Study Requirements

None.

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RIGOBERTO A ROCA
01/15/2021 05:37:56 PM

June 6, 2019

# Summary Review for Regulatory Action

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|---|---|
| **Date** | (electronic stamp) |
| **From** | Sharon Hertz, MD – Division Director |
| **Subject** | Division Director Summary Review |
| **NDA** | 206610 |
| **Applicant Name** | Mylan Laboratories, Ltd |
| **Date of Submission** | December 6, 2018 |
| **PDUFA Goal Date** | June 6, 2019 |
| **Proprietary Name / Established (USAN) Name** | Acetaminophen for injection |
| **Dosage Forms / Strength** | Lyophilized powder for injection, 1 g/vial |
| **Proposed Indication(s)** | 1. Management of mild to moderate pain<br>2. Management of moderate to severe pain with adjunctive opioid analgesics<br>3. Reduction of fever |
| **Action** | Complete Response |

| **Material Reviewed/Consulted**<br>OND Action Package, including: | **Names of discipline reviewers** |
|---|---|
| Pharmacology Toxicology Review | Carlic Huynh, PhD, Newton Woo, PhD, R. Daniel Mellon, PhD |
| CMC Review | Jason God, PhD, Denise Miller, Valerie Amspacher, PhD, Julia Pinto, PhD |

## 1. Introduction

This is the fifth review cycle for NDA 206610, acetaminophen injection, that received Complete Response actions for the first four review cycles, the most recent being on December 6, 2017. This is a 505(b)(2) application relying on the listed drug Ofirmev (NDA 22450). Ofirmev is a sterile, clear, colorless, preservative-free, isotonic formulation of acetaminophen. Each 100 mL glass vial contains 1000 mg acetaminophen (10 mg/mL). The product that is the subject of this NDA is a lyophilized powder rather than a solution and is intended to have greater stability and a longer shelf-life than the referenced product. The nature of this formulation change precludes submission of a 505(j) application.

## 2. Background

In support of this fifth review cycle the applicant has addressed the deficiencies from the Complete Response letter dated February 1, 2017 by changing (b) (4) . A

new leachables study conducted with the (b) (4). In addition, the Applicant conducted a study to evaluate the physio-chemical compatibility of the (b) (4) with the acetaminophen (b) (4). In previous review cycles, issues with the acetaminophen (b) (4) reacting with the (b) (4) were identified.

## 1. CMC/Device

The CMC review was conducted by Valerie Amspacher, PhD, with secondary concurrence from Julia Pinto, PhD. The microbiology review as conducted by Jason God, PhD with secondary concurrence from Denise Miller. The following conclusion has been excerpted from the OPQ review.

**Drug Product and Microbiology reviews were completed in this review cycle. All recommend approval. Also, see screenshot of facility approval at the end of this executive summary.**
**The sponsor changed (b) (4) This is a significant change because the drug product is a (b) (4) lyophilized powder for intravenous use.**
**The sponsor performed adequate leachables/drug loss studies (b) (4) .**
**They also performed adequate microbiology studies showing validation of the drug product (b) (4) lyophilization process.**
**Validation of the (b) (4) of the components of the container closure system was also shown to be adequate.**

However, as reported in an addendum to the OPQ review:

> OPF has issued a withhold for the Mylan Laboratories Ltd. (FEI 3007648351) manufacturing facility for this application. In an email dated 20 May 2019 facilities reviewer Christina Capacci-Daniel states, "During a recent inspection of the Mylan Laboratories Ltd. (FEI 3007648351) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved."

I concur with the conclusions reached by the OPQ review team that this application may not be approved until the manufacturing facility deficiencies have been satisfactorily corrected..

## 2. Nonclinical Pharmacology/Toxicology

The nonclinical review was conducted by Carlic Huynh, PhD, with secondary concurrence from Newton Woo, PhD, and R. Daniel Mellon, PhD. The following was excerpted from the pharmacology/toxicology review.

> This is the fifth cycle review of NDA 206610. The NDA has repeatedly received a complete response action due to an outstanding nonclinical deficiency that stems from inadequate extractables/leachables data to establish safety for (b) (4) of the drug product. To address this deficiency, the Applicant has elected to change (b) (4) There were no leachable compounds coming from (b) (4) used that were above the qualification threshold of (b) (4) mcg/day. The leachables study report was reviewed by the Chemistry, Manufacture, d Controls review team and was deemed acceptable. After review of the data in this fifth cycle submission, the proposed product is recommended for approval from the Pharmacology Toxicology perspective.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

## 3. Regulatory

The following deficiencies were communicated to the Applicant in an, information request on May 14, 2019. Responses have not been received.

a. Provide updated letters from Mallinckrodt that clearly indicate a specific date upon which your application can be approved.

b. Provide appropriate patent certification, recertification or statement to U.S. patent 9,399,012 which is listed in the Orange Book with new use codes since your January 24, 2017, paragraph IV certification for NDA 022450 for Ofirmev (acetaminophen).

c. Provide an appropriate patent certification or recertification for the new condition of use (new dosing instructions for neonates and infants) proposed in your draft labeling.

## 4. Decision/Action/Risk Benefit Assessment

- Regulatory Action – Complete Response

- Risk Benefit Assessment
  While the Applicant has adequately addressed prior deficiencies by (b) (4) resolving the concern about extractable and leachable material in the final drug product, the manufacturing facility was found to have sufficient deficiencies to result in

a withhold recommendation. In addition, the Applicant must respond to the outstanding deficiencies regarding patent certification, recertification or statement to US patent 9,399,012; appropriate patent certification or recertification for the new condition of use for neonatal and infant dosing instructions proposed in draft labeling; and updated letters from Mallinckrodt stating a specific date upon which this application can be approved.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

None

- Recommendation for other Postmarketing Requirements and Commitments

None

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SHARON H HERTZ
06/06/2019 04:12:55 PM

December 7, 2017

# Summary Review for Regulatory Action

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|---|---|
| **Date** | (electronic stamp) |
| **From** | Ellen Fields, MD, MPH |
| **Subject** | Deputy Division Director Summary Review |
| **NDA** | 206610 Complete Response/Fourth Cycle |
| **Applicant Name** | Mylan Laboratories, Ltd |
| **Date of Submission** | June 7, 2016 |
| **PDUFA Goal Date** | December 7, 2017 |
| **Proprietary Name / Established (USAN) Name** | Acetaminophen for injection |
| **Dosage Forms / Strength** | Lyophilized powder for injection, 1 g/vial |
| **Proposed Indication(s)** | 1. Management of mild to moderate pain<br>2. Management of moderate to severe pain with adjunctive opioid analgesics<br>3. Reduction of fever |
| **Action** | Complete Response |

| **Material Reviewed/Consulted** OND Action Package, including: | **Names of discipline reviewers** |
|---|---|
| Pharmacology Toxicology Review | Carlic Huynh, PhD, Newton Woo, PhD, R. Daniel Mellon, PhD |
| CMC Review | Ciby J. Abraham, PhD, Julia Pinto, PhD |

## 1. Introduction

This is the fourth review cycle for NDA 206610, acetaminophen injection, that received Complete Response actions for the first three review cycles, the most recent being on February 1, 2017. This is a 505(b)(2) application relying on the listed drug Ofirmev (NDA 22450). Ofirmev is a sterile, clear, colorless, preservative-free, isotonic formulation of acetaminophen. Each 100 mL glass vial contains 1000 mg acetaminophen (10 mg/mL). The product that is the subject of this NDA is a lyophilized powder rather than a solution, and is intended to have greater stability and a longer shelf-life than the referenced product. The nature of this formulation change precludes submission of a 505(j) application.

## 2. Background

The following deficiencies were noted in the Complete Response letter dated 2/1/17. They are similar to the deficiencies conveyed to the Applicant in prior cycles.

You have not provided an adequate assessment of the presence of possible extractables from the [redacted] in the final drug product formulation. We are unable to complete our review of the data submitted to date without responses to the following information request:

1. Your limit of detection (LOD) and limit of quantitation (LOQ) from your extractable study report and leachable study report are not consistent. Specifically, you appear to be able to detect lower levels of compounds in your extraction study than you were able to detect in the leachable study.

2. Based on the data provided, there is not an adequate extractables/leachables correlation. Specifically, based on your assessment [redacted]; however, your extraction study results only predict [redacted] mcg/day. This suggests that either the extraction conditions were not adequate or [redacted]

3. There are still two unknowns listed in your extraction study and four unknowns in the leachable study that exceed the qualification threshold of [redacted] mcg/day.

Information needed to address these deficiencies:

1. Explain the apparent discrepancy in the LOD and LOQ in your extraction studies and leachable studies and provide the basis for these limits in both the extractable study and the leachable study in light of the Analytic Evaluation Threshold (AET). For a [redacted] mL total daily dose, we calculate an AET of [redacted] ppm will be necessary to be able to detect a compound that would result in exposure of [redacted] mcg/day or greater. If you believe that this AET is not feasible, justify your analytical capability. If your assay cannot meet our calculated AET, the toxicological risk assessment will be based on the limit of quantitation (LOQ). Revise your toxicological risk assessment accordingly.

2. Provide an analysis of the extractables/leachables correlation and justify the conditions of your assays. In the absence of an adequate justification for your extractable leachable stud conditions, it is not clear if the extractable/leachable data accurate reflect the levels of potential [redacted] contaminants in the final drug product.

3. In order to complete a toxicological risk assessment, identify all unknowns greater than [redacted] mcg/day from both the extractable and leachable studies and update the toxicological risk assessment accordingly.

Alternatively, analyze the final lyophilized drug product to determine if the compounds identified in the extraction study of the (b) (4) are present in the final product using an analytical method able to detect (b) (4) mcg/day.

# 1. CMC/Device

The CMC review was conducted by Ciby Abraham, PhD, with secondary concurrence from Julia Pinto, PhD.

The only purpose of the CMC review of this resubmission was to update the facilities recommendation for this application. Dr. Abraham notes in his review that Facilities have given an overall recommendation of approval, and therefore CMC recommends approval of this application.

# 2. Nonclinical Pharmacology/Toxicology

The nonclinical review was conducted by Carlic Huynh, PhD, with secondary concurrence from Newton Woo, PhD, and R. Daniel Mellon, PhD.

As noted in the first three review cycles, there were no nonclinical safety concerns with the formulation, drug substance specifications, and drug product specifications. As stated in the nonclinical review, the history of the application from the nonclinical perspective is the following:

> The original application received a Complete Response letter in part because review of an extraction study of (b) (4) indicated a (b) (4) was lost in the extraction study. The Division was concerned that there were components from (b) (4) present in the final drug product formulation and asked the Applicant to simply analyze the final drug product to determine if extracted materials from (b) (4) were in the final drug product. The Applicant elected to pursue alternative approaches to justify the safety of the materials that may be leaching (b) (4) in their subsequent submissions; however, several of the chemicals were not able to be identified or the limits of detection and quantification are not adequate to meet the recommended safety concern threshold (SCT) of (b) (4) mcg/day for a nongenotoxic material. In the subsequent complete response letters the Division requested additional analytical data for the alternative approach the Applicant was taking to address this issue and noted that if the analytical evaluation threshold (AET) necessary to ensure detection of any chemical above the SCT could not be met the Division would have to do the toxicology assessment on the Limit of Quantitation (LOQ). In the third Complete Response letter dated February 1, 2017, we noted that, the Applicant did not provide an adequate assessment of the presence of possible compounds from the (b) (4) in the final drug product formulation. To address this deficiency the Applicant was again asked to characterize and quantitate any unidentified foreign material from (b) (4) that may be present in the final drug

product as well as provide a toxicological risk assessment for any compound above the requested Safety Concern/Qualification Threshold (QT) of (b) (4) mcg/day.

The review goes on to say:

> In this current submission, the Applicant attempted to address the deficiencies identified in the Complete Response Letter by analyzing the drug product (b) (4) and provided the limit of detection (LOD) and limit of quantitation (LOQ) for each compound present only in the (b) (4) (b) (4) and based on the maximum daily intake of a potential leachable appropriately on the LOQ.
>
> After review of the data in this fourth cycle submission, the Applicant did not adequately address the deficiencies. The Applicant did not provide an adequate toxicological risk assessment of the potential leachables associated with the (b) (4) Interestingly, several compounds appear to be newly generated compounds that reacted with (b) (4) and several of the identified compounds were not adequately justified for safety as the NOAELs could not be independently verified in many instances and therefore a Permissible Daily Exposure (PDE) could not be established

The nonclinical review team again recommends a CR action for this NDA, and that the following should be communicated to the Applicant in the CR letter.

**Deficiency**

> You have not provided an adequate assessment of the presence of possible extractable and leachable compounds from the (b) (4) in the final drug product formulation. Further, you have not provided adequate safety justification for several leachable/extractable compounds that includes (b) (4) because the referenced studies cannot be independently evaluated or for the presumed drug product-related impurities (b) (4) . QSAR evaluations for general toxicity are not acceptable.

**Information needed to address this deficiency:**

> Conduct a 14-day repeat-dose intravenous toxicology study testing an extract (b) (4) Include a dosing regimen that mimics the clinical dosing regimen. The

study design must define a NOAEL for the levels of each of these compounds. Calculate the safety margin for human exposure for these NOAELs based on body surface area (mg/m$^2$). The study report must also include quantitative analysis of the above compounds with an identification of the [redacted] (b) (4) compound in the solutions administered to the animals to ensure that the safety of the compounds leached from [redacted] (b) (4) have been adequately qualified for safety in the study.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are outstanding pharm/tox issues that preclude approval, and that the manner in which to resolve them requires that they conduct a 14-day repeat-dose intravenous toxicology study.

## 3. Decision/Action/Risk Benefit Assessment

- Regulatory Action – Complete Response

- Risk Benefit Assessment
  There is insufficient information from the nonclinical perspective to assess the safety of the drug product. The Applicant has not provided an adequate assessment of the presence of possible extractables from the [redacted] (b) (4) in the final drug product formulation.

  Until this deficiency is adequately addressed, the product cannot be approved.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

None

- Recommendation for other Postmarketing Requirements and Commitments

None

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/s/

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ELLEN W FIELDS
12/06/2017

February 3, 2017

# Summary Review for Regulatory Action

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|---|---|
| **Date** | (electronic stamp) |
| **From** | Ellen Fields, MD, MPH |
| **Subject** | Deputy Division Director Summary Review |
| **NDA** | 206610 Complete Response/Third Cycle |
| **Applicant Name** | Mylan Laboratories, Ltd |
| **Date of Submission** | August 4, 2016 |
| **PDUFA Goal Date** | February 3, 2017 |
| **Proprietary Name / Established (USAN) Name** | Acetaminophen for injection |
| **Dosage Forms / Strength** | Lyophilized powder for injection, 1 g/vial |
| **Proposed Indication(s)** | 1. Management of mild to moderate pain<br>2. Management of moderate to severe pain with adjunctive opioid analgesics<br>3. Reduction of fever |
| **Action** | Complete Response |

| **Material Reviewed/Consulted** OND Action Package, including: | **Names of discipline reviewers** |
|---|---|
| Pharmacology Toxicology Review | Carlic Huynh, PhD, Newton Woo, PhD, R. Daniel Mellon, PhD |
| CMC Review | Ciby J. Abraham, PhD, Julia Pinto, PhD |

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE=Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE=Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

## 1. Introduction

This is the third review cycle for NDA 206610, acetaminophen injection, that received Complete Response actions for the first two review cycles, the most recent being on March 10, 2016. This is a 505(b)(2) application relying on the listed drug Ofirmev (NDA 22450). Ofirmev is a sterile, clear, colorless, preservative-free, isotonic formulation of acetaminophen. Each 100 mL glass vial contains 1000 mg acetaminophen (10 mg/mL). The product that is the subject of this NDA is a lyophilized powder rather than a solution, and is intended to have greater stability and a longer shelf-life than the referenced product. The nature of this formulation change precludes submission of a 505(j) application.

# 2. Background

The Applicant, Mylan Laboratories, Ltd, acquired Agila Specialties Private Ltd, the applicant for the original NDA submission. The original NDA, received by the Agency May 5, 2014, was given a Complete Response action. Refer to the letter dated February 27, 2015 for details of the deficiencies, which were all nonclinical and CMC related issues. The Applicant did not respond to these deficiencies adequately in the submission dated February 27, 2015, and the following deficiencies were identified in the complete response letter issued March 10, 2016. These deficiencies are similar to those from the first cycle.

*Nonclincal*

*You have not provided an adequate assessment of the presence of possible extractables from the* (b) (4) *in the final drug product formulation. Based on your extraction study, as much as approximately* (b) (4) *mcg/vial (*(b) (4) *mcg/day) of unknown material could be present* (b) (4)*. This exceeds the threshold of toxicological concern of* (b) (4) *mcg/day and, therefore, requires adequate safety justification based on a toxicological risk assessment for the identified materials.*

*To address this deficiency, provide the following information:*

1. *Finalize and submit the study report for the ongoing scientific study designed to analyze the final drug product for the presence of potential leachables from* (b) (4)

2. *Definitively identify the unknown extractables* (b) (4) *and determine if they are present in the final drug product formulation.*

3. *Quantitate and characterize any unidentified foreign material from* (b) (4) *that is present in the final drug product. The study must be conducted on the final drug product at release.*

4. *Submit a revised toxicological risk assessment for every leachable that is above the Toxicological Threshold of Concern of* (b) (4) *mcg/day. We remind you that GRAS designations are not applicable to intravenous drug products.*

5. *Include copies of all relevant literature cited as part of your toxicological justification. Any publication that is not in English must be translated.*

This memo will focus on the Applicant's responses to these deficiencies.

# 1. CMC/Device

The CMC review was conducted by Ciby Abraham, PhD, with secondary concurrence from Julia Pinto, PhD.

Dr. Abraham evaluated the analytical methods for the extractables/leachables report to determine whether the level of detection (LOD) and level of quantification (LOQ) are acceptable for the compounds identified in the resubmission. The determination of whether the numerical values are of toxicological concern will be conducted by the nonclinical reviewer.

Dr. Abraham concluded the following as stated in his review:

> The applicant provided their analytical methodology to determine the extractables/leachables in their filter. As shown above, the LOD and LOQ are established for some of the compounds.
>
> The sponsor claims that the unknowns that were detected in the (b) (4) samples exhibited similar UV spectral profile (b) (4) to those already present in the (b) (4) sample indicating that these unknowns may be related to Acetaminophen and/or the product formulation.
>
> The current analytical methods appear to be acceptable. If lower limits of detection and quantitation are needed to fulfill the Pharmacology/Toxicology group's concerns of the extractables/leachables, a change in the method or analytical technology may be warranted. The applicant provided a toxicological risk assessment for the known and unknown compounds. We defer to the Pharmacology/Toxicology group for the analysis.
>
> CMC recommends approval of Acetaminophen for Injection. The facilities for all sites in this submission are acceptable.

I concur with the conclusions reached by the chemistry reviewer that there are no outstanding CMC issues that preclude approval.

# 2. Nonclinical Pharmacology/Toxicology

The nonclinical review was conducted by Carlic Huynh, PhD, with secondary concurrence from Newton Woo, PhD, and R. Daniel Mellon, PhD.

As noted in the first and second review cycles, there were no nonclinical safety concerns with the formulation, drug substance specifications, and drug product specifications. However, it was found that foreign material stemming from the (b) (4) may potentially be present in the final lyophilized drug product. The Applicant was tasked with quantitating and characterizing any unidentified foreign material

from (b) (4) that may be present in the final drug product as well as provide a toxicological risk assessment for any leachable above the Qualification Threshold (QT) of (b) (4) mcg/day.

In the second cycle, the Applicant submitted extraction data and an accompanying toxicological risk assessment, which was found inadequate. In this cycle, leachables data with an accompanying risk assessment were submitted, however this too was determined to be inadequate. The leachables evaluation was conducted on the (b) (4) (b) (4) of the drug product, and not on the reconstituted lypholized drug product. Several discrepancies in the leachables data were identified and could not be resolved in this review cycle.

Dr. Huynh recommends the following nonclinical deficiencies be communicated to the Applicant:

> You have not provided an adequate assessment of the presence of possible extractables from the (b) (4) in the final drug product formulation. We are unable to complete our review of the data submitted to date without responses to the following information request:
>
> a. Your limit of detection (LOD) and limit of quantitation (LOQ) from your extractable study report and leachable study report are not consistent. Specifically, you appear to be able to detect lower levels of compounds in your extraction study than you were able to detect in the leachable study.
>
> b. Based on the data provided, there is not an adequate extractables/leachables correlation. Specifically, based on your assessment (b) (4) however, you extraction study results only predict (b) (4) mcg/day. This suggests that either the extraction conditions were not adequate or (b) (4)
>
> c. There are still two unknowns listed in your extraction study and four unknowns in the leachable study that exceed the qualification threshold of (b) (4) mcg/day.

Information needed to address this deficiency:

1. Explain the apparent discrepancy in the LOD and LOQ in your extraction studies and leachable studies and provide the basis for these limits in both the extractable study and the leachable study in light of the Analytic Evaluation Threshold (AET). For a (b) (4) mL total daily dose, we calculate an AET of (b) (4) ppm will be necessary to be able to detect a compound that would result in exposure of (b) (4) mcg/day or greater. If you believe that this AET is not feasible, justify your an ytical capability. If your assay

cannot meet our calculated AET, the toxicological risk assessment will be based on the limit of quantitation (LOQ). Revise your toxicological risk assessment accordingly.

2. Provide your analysis of the extractables/leachables correlation and justify the conditions of your assays. In the absence of an adequate justification for your extractable leachable study conditions, it is not clear if the extractable/leachable data accurate reflect the levels of potential (b) (4) contaminants in the final drug product.

3. In order to complete a toxicological risk assessment, identify all unknowns greater than (b) (4) mcg/day from both the extractable and leachable studies and update the toxicological sk assessment accordingly.

   Alternatively, analyze the final lyophilized drug product to determine if the compounds identified in the extraction study of (b) (4) are present in the final product using an analytical method able to detect (b) (4) mcg/day

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are outstanding pharm/tox issues that preclude approval.

## 3. Clinical Pharmacology/Biopharmaceutics

No clinical pharmacology data were submitted in support of this application. The Applicant requested and was granted a waiver for clinical bioequivalence studies according to 21 CFR § 320.22 (b)(1) during the first review cycle.

## 4. Clinical Microbiology

N/A

## 5. Clinical/Statistical-Efficacy

No new clinical efficacy studies were submitted in support of this application. The Applicant is relying on the Agency's prior findings of safety and efficacy for the referenced product, Ofirmev. This is acceptable as the proposed product has the same active ingredient, concentration, proposed indication, and proposed dosing instructions.

## 6. Safety

No new clinical safety studies were submitted or were required for this Complete Response.

## 7. Advisory Committee Meeting

No advisory committee meeting was held for the 505(b)(2) application as no unusual scientific or regulatory issues requiring discussion in that forum arose.

## 8. Pediatrics

This application does not trigger the requirements of the Pediatric Research Equity Act.

## 9. Other Relevant Regulatory Issues

At the time of the Complete Response action in February, 2015, there were two unexpired patents for NDA 22450, Ofirmev, the listed drug relied upon by this 505(b)(2) NDA. While the Applicant submitted Paragraph 4 certification, the Applicant has been sued for patent infringement by Cadence Pharmaceuticals, the holder of NDA 22450.

In a letter from the Applicant submitted to the NDA dated January 24, 2017, stating that on January 11, 2017, the United States District Court for the District of Delaware entered a Consent Judgment and Order of Permanent Injunction dismissing the '012 Patent Suit.

## 10. Labeling

No labeling was conducted during this review cycle

## 11. Decision/Action/Risk Benefit Assessment

- Regulatory Action – Complete Response

- Risk Benefit Assessment
  There is insufficient information from the nonclinical perspectives to assess the safety of the drug product. The Applicant has not provided an adequate assessment of the presence of possible extractables from the (b) (4) in the final drug product formulation.

  Until this deficiency is adequately addressed, the product may not be approved.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

None at this time

- Recommendation for other Postmarketing Requirements and Commitments

None at this time

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/s/

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ELLEN W FIELDS
02/01/2017

March 10, 2016

# Summary Review for Regulatory Action

| | |
|---|---|
| **Date** | (electronic stamp) |
| **From** | Ellen Fields, MD, MPH |
| **Subject** | Deputy Division Director Summary Review |
| **NDA** | 206610 Complete Response/Second Cycle |
| **Applicant Name** | Mylan Laboratories, Ltd |
| **Date of Submission** | September 10, 2015 |
| **PDUFA Goal Date** | March 10, 2016 |
| **Proprietary Name / Established (USAN) Name** | Acetaminophen |
| **Dosage Forms / Strength** | Lyophilized powder for injection, 1 g/vial |
| **Proposed Indication(s)** | 1. Management of mild to moderate pain<br>2. Management of moderate to severe pain with adjunctive opioid analgesics<br>3. Reduction of fever |
| **Action** | Complete Response |

| **Material Reviewed/Consulted** OND Action Package, including: | **Names of discipline reviewers** |
|---|---|
| Pharmacology Toxicology Review | Carlic Huynh, PhD, Newton Woo, PhD, R. Daniel Mellon, PhD |
| CMC Review | Ciby J. Abraham, PhD, Julia Pinto, PhD |

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

## 1. Introduction

This is the second review cycle for NDA 206610, acetaminophen injection, that received a Complete Response action for the original NDA application. This is a 505(b)(2) application relying on the listed drug Ofirmev (NDA 22450). Ofirmev is a sterile, clear, colorless, preservative-free, isotonic formulation of acetaminophen. Each 100 mL glass vial contains 1000 mg acetaminophen (10 mg/mL). The product that is the subject of this NDA is a lyophilized powder rather than a solution, and is intended to have greater stability and a longer shelf-life than the referenced product. The nature of this formulation change precludes submission of a 505(j) application.

## 2. Background

The Applicant, Mylan Laboratories, Ltd, acquired Agila Specialties Private Ltd, the applicant for the original NDA submission. The original NDA, received by the Agency May 5, 2014, was given a Complete Response action, letter dated February 27, 2015. All deficiencies noted in the letter related to nonclinical and CMC issues as follows:

1. The drug substance impurity [redacted] is reported to be clastogenic and therefore your proposed drug substance specification of NMT [redacted]% is unacceptable.

   To address this deficiency, update the drug substance specification for [redacted]. We recommend that you contact your DMF holder to determine an appropriate specification.

2. The drug substance impurity [redacted] is predicted to be mutagenic via QSAR analysis and therefore, the proposed specification of NMT [redacted]% is unacceptable.

   To address this deficiency, either update your drug substance specification for [redacted] to NMT [redacted] mcg/day (NMT [redacted]%) or conduct an adequate Ames assay to demonstrate that the compound is not mutagenic.

3. You have not provided an adequate characterization of potential leachables from the [redacted]. Based on your extraction study, as much as approximately [redacted] mcg/vial [redacted] mcg/day) of unknown material could be present [redacted] This exceeds the threshold of toxicological concern of [redacted] mcg/day and, therefore, requires adequate safety justification based on a toxicological risk assessment for the identified materials.

   To address this deficiency, identify the extractables from the [redacted] study and determine if they are present in the drug product formulation. Quantitate and characterize any unidentified foreign material from [redacted] that is present in the drug product. Submit an adequate toxicological risk assessment for any leachable that is above the Toxicological Threshold of Concern of [redacted] mcg/day.

:

This memo will focus on the Applicant's responses to these deficiencies.

## 4. CMC/Device

The CMC review was conducted by Ciby Abraham, PhD, with secondary concurrence from Julia Pinto, PhD.

The first cycle deficiency from the CMC perspective was combined with the nonclinical deficiency, as stated in #3 in the prior section of this memo.

Dr. Abraham summarized his review findings as follows:

The Applicant has not adequately responded to the CMC CR of February 2015. The sponsor provides a (b) (4)/extractable study that shows a maximum of (b) (4) ug of unidentified material that may be present in the lyophilized acetaminophen. However, they did not quantitate and characterize any unidentified material from (b) (4) that is present in the actual drug product as stated in the February complete response letter to the firm. Therefore, in order to resolve the complete response, the sponsor will need to provide the full characterization of the unidentified material that is present in their product from their (b) (4) process. The study must be conducted on the product itself at release. Evaluation of the compound(s) and specifications will be evaluated by CMC and the pharmacology/toxicology group.

The Office of Compliance has given an overall recommendation of withhold for the drug product manufacturing site Agila Specialties Private Limited (FEI: 3007648351) and for Agila Specialties Private Limited Control Testing Laboratory (FEI: 3003813519).

> Dr. Abraham notes the following deficiency to be conveyed to the Applicant:
>
> Based on the (b) (4) /extractable study, a maximum of (b) (4) ug of unidentified material may be present in (b) (4) the lyophilized acetaminophen drug product. The Sponsor has not identified and quantitated the extractables in the drug product at release.
>
> In order to resolve the deficiency, the Applicant must:
>
> Quantitate and characterize any unidentified foreign material from (b) (4) that is present in the drug product. The study must be conducted on the final drug product at release.

I concur with the conclusions reached by the chemistry reviewer that there are outstanding CMC issues that preclude approval.

## 5. Nonclinical Pharmacology/Toxicology

The nonclinical review was conducted by Carlic Huynh, PhD, with secondary concurrence from Newton Woo, PhD, and R. Daniel Mellon, PhD.

Dr. Huynh summarized the nonclinical findings in his review as follows:

> There were no new toxicology studies submitted or required for this drug product formulation as the reconstituted formulation is virtually identical to the referenced drug product. In the first review cycle, two major deficiencies were identified. Firstly, two drug substance impurities during review of the DMF were identified to contain structural alerts for mutagenicity, specifically (b) (4) and were communicated to the DMF holder. These specifications have been reduced to acceptable levels in the DMF. In the current submission, the drug substance acceptance specifications

have been updated by the Applicant and have been tightened for (b) (4) to reflect the tightened specifications in the DMF and are deemed acceptable.

Secondly, a leachables assessment to evaluate the final drug product for potential compounds that could be present in the drug product due to leaching from (b) (4) was not conducted. In this second cycle submission, the Applicant submitted a toxicological risk assessment for all extractables that exceeded a Threshold of Toxicological Concern (TTC) of (b) (4) mcg/day for genotoxic compounds as well as proposed by the (b) (4) in lieu of conducting the requested analysis for actual leachables in the drug product formulation and basing their risk assessment on the TTC requested by the Agency. It was communicated to the Applicant to conduct a leachables assessment to determine whether any of the identified extractables are present in the final drug product (the lyophilized powder) and to apply a TTC of (b) (4) mcg/day for the subsequent toxicological risk assessment. The Applicant agreed but did not submit the required leachables data and accompanying risk assessment prior to the end of the second review cycle. In addition, based on the data submitted to date, several compounds in the extraction study were not identified and therefore the submitted toxicological risk assessment is incomplete. Therefore from a nonclinical pharmacology toxicology perspective, the recommendation for the second cycle NDA submission is a Complete Response.

From a pharmacology toxicology perspective, the Applicant has not adequately addressed all of the deficiencies from the first review cycle. Specifically, there are inadequate data to support an approval recommendation at this time and therefore, a Complete Response is recommended. There are several extractables that have not been identified. Moreover, it has not been determined if any of the extractables identified in (b) (4) extraction study are actually in the final drug product formulation.

Deficiencies to be communicated to the Applicant:
You have not provided an adequate study to determine if extractables from the (b) (4) are actually present in the final drug product formulation. Based on your extraction study, as much as approximately (b) (4) mcg/vial ((b) (4) mcg/day) of unknown material could be present (b) (4) This exceeds the threshold of toxicological concern of (b) (4) mcg/day and, therefore, requires adequate safety justification based on a toxicological risk assessment for the identified materials.

Information needed to resolve the deficiencies:

1. Finalize and submit the ongoing scientific study designed to analyzed the final drug product for the presence of potential leachables from (b) (4) to determine if there are any extractables in the final drug product that exceed the Toxicological Threshold of Concern of (b) (4) mcg/day.

2. Definitively identify the unknown extractables [redacted] (b) (4) and determine if they are present in the final drug product formulation.

3. Quantitate and characterize any unidentified foreign material from [redacted] (b) (4) that is present in the final drug product.

4. Submit a revised toxicological risk assessment for every leachable that is above the Toxicological Threshold of Concern of [redacted] (b) (4) mcg/day. We remind you that GRAS designations are not applicable to intravenous drug products.

5. Include copies of all relevant literature cited as part of your toxicological justification. Any publication that is not in English must be translated.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are outstanding pharm/tox issues that preclude approval.

## 6. Clinical Pharmacology/Biopharmaceutics

No clinical pharmacology data were submitted in support of this application. The Applicant requested and was granted a waiver for clinical bioequivalence studies according to 21 CFR § 320.22 (b)(1) during the first review cycle.

## 7. Clinical Microbiology

N/A

## 8. Clinical/Statistical-Efficacy

No new clinical efficacy studies were submitted in support of this application. The Applicant is relying on the Agency's prior findings of safety and efficacy for the referenced product, Ofirmev. This is acceptable as the proposed product has the same active ingredient, concentration, proposed indication, and proposed dosing instructions.

## 9. Safety

No new clinical safety studies were submitted or were required for this Complete Response.

## 10. Advisory Committee Meeting

No advisory committee meeting was held for the 505(b)(2) application as no unusual scientific or regulatory issues requiring discussion in that forum arose.

## 11. Pediatrics

This application does not trigger the requirements of the Pediatric Research Equity Act.

## 12. Other Relevant Regulatory Issues

At the time of the Complete Response action in February, 2015, there were two unexpired patents for NDA 22450, Ofirmev, the listed drug relied upon by this 505(b)(2) NDA. While the Applicant submitted Paragraph 4 certification, the Applicant has been sued for patent infringement by Cadence Pharmaceuticals, the holder of NDA 22450. Litigation regarding these patents has not been resolved and is ongoing.

## 13. Labeling

A review was conducted by the Division of Pediatric and Maternal Health to assist with Pregnancy and Lactation Labeling Rule (PLLR) Conversion during the first review cycle. The recommended changes will be incorporated into the draft package insert during the next review cycle. Recommendations from DMEPA will be incorporated into the product labeling during the next review cycle as well, once the deficiencies precluding approval have been addressed.

## 14. Decision/Action/Risk Benefit Assessment

- Regulatory Action – Complete Response

- Risk Benefit Assessment
  There is insufficient information from CMC and nonclinical perspectives to assess the safety of the drug product. The Applicant has not provided adequate information to determine if extractables from the (b) (4) Based on their extraction study, as much as approximately (b) (4) mcg/vial (b) (4) mcg/day) of unknown material could be present (b) (4) This exceeds the threshold of toxicological concern of (b) (4) mcg/day and, therefore, requires adequate safety justification based on a toxicological risk assessment for the identified materials.

  In addition, there were deficiencies noted from the facility inspection of the drug product manufacturing site Agila Specialties Private Limited (FEI: 3007648351) and the Agila Specialties Private Limited Control Testing Laboratory (FEI: 3003813519), sited by the Office of Compliance.

  Until these deficiencies are adequately addressed, the product may not be approved. Additionally, the patent infringement litigation must be resolved prior to approval.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

None at this time

- Recommendation for other Postmarketing Requirements and Commitments

None at this time

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/s/

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ELLEN W FIELDS
03/10/2016

# Summary Review for Regulatory Action

| | |
|---|---|
| **Date** | (electronic stamp) |
| **From** | Sharon Hertz, MD |
| **Subject** | Division Director Summary Review |
| **NDA#/Supplement #** | 206610/000 |
| **Applicant Name** | Agila Specialties Private Limited |
| **Date of Submission** | May 5, 2014 |
| **PDUFA Goal Date** | March 5, 2015 |
| **Proprietary Name / Established (USAN) Name** | Acetaminophen |
| **Dosage Forms / Strength** | Lyophilized powder for injection, 1 g/vial |
| **Proposed Indication(s)** | 1. Management of mild to moderate pain<br>2. Management of moderate to severe pain with adjunctive opioid analgesics<br>3. Reduction of fever |
| **Action/Recommended Action:** | Complete Response |

| **Material Reviewed/Consulted** OND Action Package, including: | |
|---|---|
| Pharmacology Toxicology Review | Carlic Huynh, PhD, R. Daniel Mellon, PhD |
| CMC Review<br>OBP Review | Ciby J. Abraham, PhD, Julia Pinto, PhD<br>Kelly Kitchens, PhD, Tapash Ghosh, PhD |
| CMC Microbiology Review | Vinayak Pawar, PhD, Stephen E. Langille, PhD |
| Clinical Pharmacology Review | Srikanth Nallani, PhD, Yun Xu, PhD |
| OSE/DMEPA | James Schlick, MBA, RPh, Vicky Borders-Hemphill, PharmD |
| DPMH | Leyla Sahin, MD, Lynne Yao, MD |
| | |

OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Errors Prevention
DSI=Division of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OPDP=Office of Prescription Drug Promotion
DCDP=Division of Consumer Drug Promotion
OMP=Office of Medical Policy Initiatives
DMPP=Division of Medical Policy Programs

# Signatory Authority Review Template

## 1. Introduction

The first parenteral acetaminophen product, Ofirmev, Cadence Pharmaceuticals, (NDA 22450), was approved on November 2, 2010. Ofirmev was also submitted as a 505(b)(2) application, referencing the Agency's previous findings of efficacy and safety for Tylenol (NDA 19872) and scientific literature. Ofirmev is a sterile, clear, colorless, preservative-free, isotonic formulation of acetaminophen. Each 100 mL glass vial contains 1000 mg acetaminophen (10 mg/mL). The product that is the subject of this NDA is a lyophilized powder rather than a solution, and is intended to have greater stability and a longer shelf-life than the referenced product. The nature of this formulation change precludes submission of a 505(j) application.

## 2. Background

A number of sponsors have demonstrated interest in the development of intravenous acetaminophen products that differ sufficiently in formulation and/or presentation from existing approved products that a 505(b)(2) application is necessary rather than a 505(j) application. The key aspects in the review of these products are to evaluate whether changes in the formulation or presentation change the efficacy or safety profile of the product. In particular, review of these applications focuses on the type and amount of impurities and degradants, the amount and type of any extractables and leachables, and the risk for medication errors based on the presentation.

## 3. CMC/Device

Sections of this review are from the review by Dr. Ciby Abraham. The drug substance is adequately supported by reference to DMF (b) (4)

The drug product is a sterile white to off white lyophilized powder or cake in 100 mL/28 mm (b) (4) glass vial with a rubber stopper and flip off aluminum red seal. The product is (b) (4). The lyophilized powder is reconstituted by adding 98 mL of water for injection and shaking it for (b) (4) fully dissolve. The shelf life of the lyophilized powder is 24 months at 20 C to 25 C (68 F to77°F). The solution is stable for 12 hours at 20°C to 25°C.

This product contains (b) (4), excipients not present in the referenced product.

As stated in the review by Dr. Abraham:

We recommend a complete response from a Chemistry, Manufacturing, and Control (CMC) perspective for the following reasons. The sponsor provides a (b) (4) extractable study that shows a maximum of (b) (4) ug of unidentified material that may be present (b) (4) lyophilized acetaminophen. CMC sent out an information request on 11/25/2014 and had two teleconferences on 12/5/2014 and 1/22/2015 with the sponsor addressing this issue. The sponsor stated they will characterize the unidentified material but has not provided any information to date. Therefore, in order to resolve the complete response, the sponsor will need to provide the full characterization of the unidentified material that is present in their product from their (b) (4). Evaluation of the compound(s) and specifications will be evaluated by CMC and the pharmacology/toxicology group.

The Office of Compliance has given an overall recommendation of withhold for the drug product manufacturing site Agila Specialties Private Limited (FEI: 3007648351) and for Agila Specialties Private Limited Control Testing Laboratory (FEI: 3003813519).

The product quality microbiology reviewer found no deficiencies and that Applicant "has met regulatory expectations for the performance of process simulations in support of the aseptic manufacture of the subject drug product."

I concur with the conclusions reached by the chemistry reviewer regarding the lack of acceptability of the manufacturing of the drug product. Manufacturing site inspections were unacceptable. These deficiencies preclude approval of this product at this time.

## 4. Nonclinical Pharmacology/Toxicology

From Dr. Huynh's review:

There were no new toxicology studies submitted or required for this drug product formulation as the reconstituted formulation is virtually identical to the referenced drug product. During review of the DMF, two drug substance impurities were identified that contain structural alerts for mutagenicity, specifically (b) (4). In communications with the DMF holder, these specifications have been reduced to acceptable levels in the DMF. The drug substance specifications for residual solvents in the DMF are acceptable. However, the drug substance acceptance specifications have not been updated by the Applicant as of the date of this review to reflect the tightened specifications now in the DMF. This is an approval issue. The drug product specifications are acceptable and within the range of the referenced drug product.

There also remains an outstanding issue with identification of the extractables studies done on (b) (4) (see the CMC review). To date, it is not clear what, if anything, from this (b) (4) is present in the final drug product and the worst-case scenario proposed by the Applicant is that up to (b) (4) mcg/vial (b) (4)

mcg/day) of unidentified material may be present in the product. This exceeds the threshold for toxicological concern of (b) (4) mcg/day recommended by the Division. Until this is clarified, we cannot recommend approval.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that the following deficiencies must be addressed prior to approval:

1. The drug substance (b) (4) is reported to be clastogenic and, therefore, your proposed drug substance specification of NMT (b) (4) % is unacceptable.

2. The drug substance impurity (b) (4) is predicted to be mutagenic via QSAR analysis and therefore, the proposed specification of NMT (b) (4) % is unacceptable.

3. An adequate characterization of potential leachables from t (b) (4) has not been provided. The worst-case scenario based on the extraction study suggests that approximately (b) (4) mcg/vial (b) (4) mcg/day) of unknown material could be present (b) (4). This exceeds the threshold of toxicological concern of (b) (4) mcg/day and therefore, requires adequate safety justification based on a toxicological risk assessment for the identified materials.

**Information needed to resolve the deficiencies**

1. Updated drug substance specification for (b) (4) to as low as technically feasible. We recommend that the Applicant contact the DMF holder to determine an appropriate specification.

2. Updated drug substance specification for (b) (4) to NMT (b) (4) mcg/day (NMT (b) (4) %) or an adequate Ames assay to demonstrate that the compound is not mutagenic.

3. Identification of the extractables from (b) (4) extraction study and determine if they are present in the drug product formulation and submission of an adequate toxicological risk assessment for any leachable that is above the Toxicological Threshold of Concern of (b) (4) mcg/day.

## 5. Clinical Pharmacology/Biopharmaceutics

No clinical pharmacology data were submitted in support of this application. The Applicant requested a waiver for clinical bioequivalence studies according to 21 CFR § 320.22 (b)(1), based on the following:

- The proposed drug product is a clear, sterile solution after reconstitution and dilution; it is intended solely for administration by injection (intravenous infusion).

- The proposed drug product claims the same active ingredients in the same concentration as presented on the labeling of the reference drug product, Ofirmev (acetaminophen) for Injection that is the subject of an approved NDA 22450 held by Cadence Pharms, and approved November 2, 2010.

Dr. Kitchens noted that the mean osmolality of the proposed drug product (312 mOsmol/kg) is 13.9% greater than the reported osmolality of the reference drug product (274 mOsmol/kg). This was discussed with the review team and it was determined that this difference in osmolality would not pose any safety concerns.

Dr. Kitchens stated that the proposed drug product meets the criteria for a biowaiver because the drug product is a parenteral solution intended solely for administration by injection and that it contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application or abbreviated new drug application. She found that the Applicant has provided adequate information to support the biowaiver request. Therefore, the waiver for in vivo bioavailability/bioequivalence studies for Acetaminophen for Injection, 1 g/vial, is granted.

I concur with the conclusions reached by the biopharmaceutics reviewer that the Applicant's request for a biowaiver from clinical bioequivalence studies be granted.

## 6. Clinical Microbiology

N/A

## 7. Clinical/Statistical-Efficacy

No new clinical efficacy studies were submitted in support of this application. The Applicant is relying on the Agency's prior findings of safety and efficacy for the referenced product, Ofirmev. This is acceptable as the proposed product has the same active ingredient, concentration, proposed indication, and proposed dosing instructions.

## 8. Safety

No new clinical safety studies were submitted in support of this application. The Applicant is relying on the Agency's prior findings of safety and efficacy for the referenced product, Ofirmev. This is acceptable as the proposed product has the same active ingredient, concentration, proposed indication, and proposed dosing instructions. However, as there are two drug substance impurities that are potentially clastogenic or mutagenic and the potential leachables from (b) (4) have not been adequately characterized, it is not yet known whether this product can be expected to have comparable safety to the referenced product.

## 9. Advisory Committee Meeting

No advisory committee meeting was held for the 505(b)(2) application as no unusual scientific or regulatory issues requiring discussion in that forum arose.

## 10. Pediatrics

This application does not trigger the requirements of the Pediatric Research Equity Act.

## 11. Other Relevant Regulatory Issues

There are two unexpired patents for NDA 22450, Ofirmev, the listed drug relied upon by this 505(b)(2) NDA. While the Applicant submitted Paragraph 4 certification, the Applicant has been sued for patent infringement by Cadence Pharmaceuticals, the holder of NDA 22450.

## 12. Labeling

A review was conducted by the Division of Pediatric and Maternal Health to assist with Pregnancy and Lactation Labeling Rule (PLLR) Conversion. The recommended changes will be incorporated into the draft package insert during the next review cycle.

Recommendations from DMEPA will be incorporated into the product labeling during the next review cycle once the deficiencies precluding approval have been addressed.

## 13. Decision/Action/Risk Benefit Assessment

- Regulatory Action – Complete Response

- Risk Benefit Assessment

The proposed specifications for the drug substance impurity (b) (4), which is reported to be clastogenic, and (b) (4), which is predicted to be mutagenic, are high and there has not been an adequate characterization of potential leachables from the (b) (4) which under the worst-case scenario presented by the Applicant, are present in an amount that exceeds the threshold of toxicological concern of (b) (4) mcg/day. The specifications for the two identified drug substance impurities must be lowered, or in the case of (b) (4), qualified for safety. In addition, the extractables from the (b) (4) extraction study must be identified and evaluated for their presence

in the drug product formulation. An adequate toxicological risk assessment must be submitted for any leachable that is above the Toxicological Threshold of Concern of (b) (4) mcg/day.

Until these deficiencies are adequately addressed, the product may not be approved. The last hurdle for this application will have to be resolution of the patent infringement lawsuit.

- Recommendation for Postmarketing Risk Management Activities

None at this time.

- Recommendation for other Postmarketing Study Commitments

None at this time.

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/s/

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SHARON H HERTZ
02/27/2015