CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206610Orig1s000

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA 206610
Supporting document/s:	SDN 30 (Electronic Document Room Sequence Number 29)
Applicant's letter date:	December 6, 2018 (SDN 30)
CDER stamp date:	December 6, 2018 (SDN 30)
Product:	Acetaminophen for Injection
Indication:	The management of (b) (4) pain, the management of moderate to severe pain with adjunctive opioid analgesics, and reduction of fever
Applicant:	Mylan Laboratories Ltd.
Review Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Reviewer:	Carlic K. Huynh, PhD
Team Leader:	Newton H. Woo, PhD
Supervisor:	R. Daniel Mellon, PhD
Division Director:	Sharon Hertz, MD
Project Manager:	Christopher Hilfiger

Template Version: September 1, 2010

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Executive Summary:
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, and 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.

Background and Prior Regulatory History:
The Applicant, Mylan Laboratories Ltd., is developing a lyophilized powder formulation of Acetaminophen for Injection that needs to be reconstituted for the following indications: management of (b) (4) pain, management of moderate to severe pain with adjunctive opioid analgesics, and reduction of fever. This is a fifth cycle review for this product. The reader is referred to the previous nonclinical reviews for a complete regulatory background for this NDA submission (see nonclinical reviews dated February 17, 2015, February 26, 2016, January 31, 2017, and December 1, 2017). From the Complete Response letter from the fourth cycle review dated December 6, 2017, the following nonclinical deficiency was communicated to the Applicant:

> **NONCLINICAL**
> 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. An adequate safety justification was not provided for several leachable/extractable compounds that includes (b) (4) because the referenced studies cannot be independently evaluated. Further, adequate safety justification was not provided for the presumed drug product-related impurities (b) (4) QSAR evaluations for general toxicity are not acceptable.
>
> Information needed to address these deficiencies:
> Conduct a 14-day repeat-dose intravenous toxicology study testing an extract of (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 (b) (4)

compound in the solutions administered to the animals to ensure that the safety of the compounds leached from (b) (4) have been adequately qualified for safety in the study.

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the prescribing information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Applicant's Response to Deficiency:
To address the nonclinical deficiency, the Applicant has changed (b) (4) of their proposed product (see table below from the Applicant's submission) and submitted new leachables data for (b) (4).

(b) (4)

As shown in the table above, the Applicant changed (b) (4). A leachables study conducted with (b) (4) showed that there were no leachable compounds detected. The reader is referred to the quality review for further details and the adequacy of the leachable study.

As there are no leachable compounds originating from (b) (4) that exceeds the qualification threshold of (b) (4) mcg/day and the methods used in the leachables study were deemed adequate, there re no nonclinical safety concerns with potential leachables.

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. However, the evaluation with (b) (4) suggest no significant interactions between the acetaminophen (b) (4) and (b) (4) (see Applicant's Table below).

Elemental Impurities:
In the current submission, the Applicant submitted an assessment of elemental impurities with expired submission batch samples to represent the worst-case scenario. Samples were reconstituted with 98 mL of water for injection and placed inverted for a period of 12 hours at room temperature. Taking into consideration the maximum acetaminophen daily dose of 4 g, the maximum daily intakes of different elemental impurities are summarized below.

(b) (4)

All elemental impurities were below ICH Q3D limits and were below the control threshold (b) (4) of PDE). Therefore, levels of the elemental impurities above are deemed acceptable and no further controls of elemental impurities are warranted.

Labeling:
The Applicant submitted labeling that is the same as the referenced product, Ofirmev®. As such, there are no nonclinical issues or recommended changes with the proposed label.

Overall Conclusions:
The Applicant has elected to change (b) (4)
There were no leachable compounds coming from (b) (4) used that were above the qualification threshold. There are no labeling issues as the proposed labeling is identical to Ofirmev®. Thus, the proposed product is recommended for approval from the Pharmacology Toxicology perspective.

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/s/

CARLIC K HUYNH
05/01/2019 04:54:34 PM

NEWTON H WOO
05/01/2019 05:01:07 PM

RICHARD D MELLON
05/01/2019 05:13:38 PM
I concur.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA 206610
Supporting document/s:	SDN 21 (Electronic Document Room Sequence Number 20)
Applicant's letter date:	June 7, 2017 (SDN 21)
CDER stamp date:	June 7, 2017 (SDN 21)
Product:	Acetaminophen for Injection
Indication:	Management of (b) (4) pain. The management of moderate to severe pain with adjunctive opioid analgesics. The reduction of fever
Applicant:	Mylan Laboratories Ltd.
Review Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Reviewer:	Carlic K. Huynh, PhD
Team Leader:	Newton H. Woo, PhD
Supervisor:	R. Daniel Mellon, PhD
Division Director:	Sharon Hertz, MD
Project Manager:	Christopher Hilfiger

Template Version: September 1, 2010

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Executive Summary:

This is the fourth cycle review of NDA 206610. 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 from (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) 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. 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) 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 reader is referred to the end of the document for the deficiency and information to resolve the deficiency to be communicated to the Applicant.

Background and Prior Regulatory History:

The Applicant, Mylan Laboratories Ltd., is developing a lyophilized powder formulation of Acetaminophen for Injection for the following indications: management of (b) (4) pain, management of moderate to severe pain with adjunctive opioid analgesics, and reduction of fever. This is a fourth cycle review for this product. The reader is referred to the previous nonclinical reviews for a complete regulatory

background for this NDA submission (see nonclinical reviews dated February 17, 2015, February 26, 2016, and January 31, 2017). From the Complete Response letter from the third cycle review dated February 1, 2017, the following nonclinical deficiency was communicated to the Applicant:

NONCLINICAL

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 study 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 [redacted] are present in the final product using an analytical method able to detect [redacted] mcg/day.

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(b) (4)

Overall Conclusions:
There were no changes with the formulation, drug substance specifications, and drug product specifications from the previous review cycles. The Applicant continues to use the same arguments from the previous review cycles and has not analyzed the final lyophilized drug product for potential compounds derived from (b) (4). In this submission, the Applicant provided an updated toxicological risk assessment based on the limit of quantitation of several compounds identified in the (b) (4) material but not present in the (b) (4) r material, several of which were deemed inadequate. In addition, there were 2 unknowns in the extractable study and 4 unknowns from the leachable study that were addressed in this submission. Three of the unknowns from the leachable study were acetaminophen-related compounds (b) (4) It is not known if the 2 unknowns from the extractable study are similar to any of the 4 unknowns from the leachable study.

Taken together, the safety justification submitted for several compounds were deemed inadequate with several unknown compounds appearing to be reaction products with (b) (4). Therefore, the nonclinical pharmacology toxicology team recommends a Complete Response.

We have tried on three separate review cycles to have the Applicant simply determine if the compounds from the (b) (4) extraction study are present in the final drug product. The Applicant has not done this assessment and their alterative approach has only raised more questions about the potential reactivity of (b) (4) with the drug product solution. Therefore, to address the safety of this drug product, as currently manufactured, we recommend a 14-day repeat dose intravenous toxicology study testing (b) (4) with the compounds identified in the (b) (4). This will still require that the Applicant identify the compound with the (b) (4) in order to complete the study.

Recommendations:
The following nonclinical deficiencies are to be communicated to the Applicant:

1. 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 include (b) (4) because the

referenced studies cannot be independently evaluated or for the presumed drug product-related impurities (b) (4) compound. QSAR evaluations for general toxicity are not acceptable.

Information needed to address this deficiency:

1. Conduct a 14-day repeat-dose intravenous toxicology study testing an extract (b) (4) and must define a NOAEL for the levels of each of these compounds that a person would be exposed to on a mg/m^2 basis. The study must include a dosing regimen that mimics the clinical dosing regimen. The study report must also include quantitative analysis of the above compounds with an identification of the (b) (4) compound in the solutions administered to the animals to ensure that the safety of the compounds leached from (b) (4) have been adequately qualified for safety in the study.

References

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(b) (4)

(b) (4)

(b) (4)

(b) (4)

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(b) (4)

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Van Duuren BL and Katz C. 1972. Replication of Low-Level Carcinogenic Activity Bioassays. *Cancer Research.* 32:880-881.

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/s/

CARLIC K HUYNH
12/01/2017

NEWTON H WOO
12/01/2017

RICHARD D MELLON
12/01/2017
I concur.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	206610
Supporting document/s:	SDN 13, 14, and 15 (Electronic Document Room Sequence Number 12, 13, and 14)
Applicant's letter date:	September 10, 2015 (SDN 13), November 5, 2015 (SDN 14), and February 5, 2016 (SDN 15)
CDER stamp date:	September 10, 2015 (SDN 13), November 5, 2015 (SDN 14), and February 5, 2016 (SDN 15)
Product:	Acetaminophen for Injection
Indication:	Management of (b) (4) pain, management of moderate to severe pain with adjunctive opioid analgesics, and reduction of fever
Applicant:	Mylan Laboratories Ltd.
Review Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Reviewer:	Carlic K. Huynh, PhD
Team Leader:	Newton H. Woo, PhD
Supervisor:	R. Daniel Mellon, PhD
Division Director:	Sharon Hertz, MD
Project Manager:	Christopher Hilfiger

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1 Executive Summary

1.1 Introduction

The Applicant, now Mylan Laboratories Ltd. after its acquisition of Agila Specialties Private Ltd., is developing an intravenous formulation of acetaminophen for Injection that is a lyophilized powder (1 g/vial) to be reconstituted immediately prior to use. The Applicant is submitting an application via the 505(b)(2) pathway, relying upon the Agency's previous findings of safety and efficacy to Cadence Pharmaceuticals' OFIRMEV (NDA 22450). This is the second cycle review of this NDA. Sections that have already been reviewed have been omitted in this Pharmacology/Toxicology review (for other sections see Pharmacology/Toxicology Review dated February 17, 2015).

The first cycle deficiencies and information required to address the deficiencies are reproduced from the complete response letter from February 2015:

NONCLINICAL

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

   To address this deficiency, update the drug substance specification for (b) (4) . We recommend that you contact your DMF holder to determine an appropriate specification.

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.

   To address this deficiency, either update your drug substance specification for (b) (4) to NMT (b) (4) mcg/day (NMT (b) (4) %) 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 (b) (4) . Based on your extraction study, as much as approximately (b) (4) mcg/vial (b) (4) mcg/day) of unknown material could be present in the drug product vials. 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, identify the extractables from the (b) (4) extraction study and determine if they are present in the drug product formulation. Quantitate and characterize any unidentified foreign material from (b) (4) 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 (b) (4) mcg/day.

1.2 Brief Discussion of Nonclinical Findings

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 [redacted], 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 [redacted] 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 [redacted] 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 [redacted] mcg/day for genotoxic compounds as well as proposed by the [redacted] 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 [redacted] 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.

1.3 Recommendations

1.3.1 Approvability

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 [redacted] extraction study are actually in the final drug product formulation.

Deficiencies

You have not provided an adequate study to determine if extractables from the [redacted] are actually present in the final drug product formulation. 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.

Information needed to resolve the deficiencies
To address this deficiency:

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

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

3. Quantitate and characterize any unidentified foreign material from [redacted] 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] 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.

1.3.2 Additional Nonclinical Recommendations

None.

1.3.3 Labeling

Recommendations for labeling have not changed since the first cycle review. It is noted that in the first cycle the conversion of the label to conform to the PLLR format was voluntary. However, as of June 30, 2015, all NDAs are required to submit labeling that complies with the PLLR format. Refer to the action letter for final drug product labeling.

2 Drug Information

2.1 Drug

CAS Registry Number
103-90-2

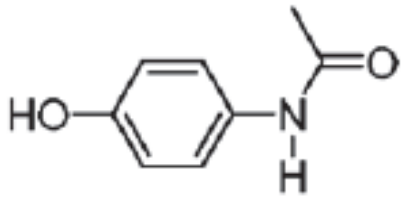
Generic Names
Acetaminophen, paracetamol

Code Name

Chemical Names
N-acetyl-p-aminophenol
4'-hydroxyacetanilide
p-hydroxyacetanilide
p-acetamidophenol
p-acetaminophenol
p-acetylaminophenol

Molecular Formula/Molecular Weight
$C_8H_9NO_2$ / 151.16 g/mol

Structure



Pharmacologic Class
There is no FDA-established pharmacological class for acetaminophen. We recommend not including an established class given the lack of clear understanding of the mechanism of action of acetaminophen.

2.2 Relevant INDs, NDAs, BLAs and MFs

IND#	Drug	Status	Division	Indication	Status Date	Sponsor
116240	Acetaminophen for Injection, 1g/vial	Presubmission	DAAAP	Management of moderate to severe pain with adjunctive opioid analgesics/the reduction of fever	August 20, 2012	Agila Specialties Private Ltd.

NDA#	Drug Name	Div	Strength (route)	Marketing Status	AP Date	Indication	Company
22450	Ofirmev® (acetaminophen for injection)	DAAAP	1000 mg/ 100 mL (10 mg/mL) (IV infusion)	Prescription	November 2, 2010	Management of mild to moderate pain, management of moderate to severe pain with adjunctive opioid analgesics, reduction of fever	Cadence Pharmaceuticals, Inc.

MF#	Subject of MF	Holder	Submit Date	Reviewer's Comment
(b) (4)				

2.3 Drug Formulation

The drug formulation has not been altered since the first cycle review. The instructions for reconstitution remain the same where the contents of the vial are dissolved in 98 mL of sterile water and the reconstituted solution should be used within 12 hours of preparation.

2.4 Comments on Novel Excipients

There are no novel excipients in the formulation.

2.5 Comments on Impurities/Degradants of Concern

Drug Substance Impurities

The information in this section on drug substance impurities has been reproduced from the first cycle review.

The following table illustrates the drug substance impurities (adapted from the Applicant's submission):

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As noted in the table above, the levels of the residual solvents are acceptable as per ICH Q3C.

Drug Product Degradants
The drug product specifications were not changed from the first cycle review. There are no safety concerns with the drug product specifications.

Container Closure System
The components of the contain closure system remain unchanged from the first cycle review.

Since the lyophilized powder will not be reconstituted until use, and since the reconstituted powder should be used within 12 hours, an extractables and leachables assessment of the container closure system is not required as stated in the first cycle review.

Manufacturing Process
The Applicant submitted a characterization of the potential extractables from employed during manufacturing. This characterization was performed because the Applicant had previously reported in the first cycle review that approximately mcg/vial (mcg/day) of unknown material could be present from extraction studies on .
The characterization includes a toxicological risk assessment on all potential extractables, which represents a worse-case scenario according to the Applicant. It is important to note that at the time of this review, the Applicant has not determined whether any of the potential extractables that were identified in the extraction study are actually in the final drug product as leachables.

In the Applicant's extractables assessment, the extraction condition that represents a worse-case scenario was used (b) (4)) and that a patient would receive the maximum daily dose of 4 g/day (4 vials/day) of acetaminophen was considered. The following table illustrates the compounds that were detected in the (b) (4) extraction study and were analyzed in the toxicological risk assessment (modified from the Applicant's submission):

Compound/ Element	Analytical Method	CAS Number	Exposure at MDD of 4 g/day of APAP (mcg/day)
(b) (4)			

As shown in the table above, most of the compounds were below the Toxicological Threshold of Concern (TTC) of (b) (4) mcg/day and all were below the (b) (4) mcg/day limit on genotoxic impurities in acute products as per ICH M7.

However, (b) (4) and 2 unknown compounds that were detected using (b) (4) analysis were not identified (bolded in red in above table). (b) (4) and are not considered to contain a structural alert for mutagenicity. It is noted that the levels of these (b) (4) are below the TTC of (b) (4) mcg/day at the MTDD of (b) (4) day of APAP and further justification is not needed if their levels remain below the TTC. Moreover, an assessment of the final product was not completed to evaluate what compounds from (b) (4), if any, are present in the final drug product. This assessment of leachables would determine whether any of the extractable compounds identified in the table above are present in the final drug product and whether their levels are above the threshold of toxicological concern of (b) (4) mcg/day. This study is still underway and a final report will not be completed prior to the PDUFA goal date for this review cycle.

2.6 Proposed Clinical Population and Dosing Regimen

The indication is the management of (b) (4) pain, management of moderate to severe pain with adjunctive opioid analgesics, and reduction of fever. The acute use product is proposed to be administered in a hospital setting, with a typical duration of use (b) (4). The proposed clinical population will be adults and adolescents as well as children aged 2 to 12 years.

2.7 Regulatory Background

This is a 505(b)(2) application referencing the Agency's previous findings of safety to Ofirmev® (NDA 22450).

At the conclusion of the first cycle review, a complete response letter was issued (dated February 27, 2015) with the following nonclinical deficiencies:

NONCLINICAL

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 [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] extraction 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.

A follow-up TCON was conducted with the Applicant on November 20, 2015 to address these deficiencies. In particular, the Division reiterated our request that the Applicant determine whether the extractables identified in [redacted] extraction studies were in the final drug product formulation. In an email dated February 2, 2016 (with a follow-up submission, SDN 15, which was received by the Agency on February 5, 2016), the Applicant submitted a feasibility plan with estimated timelines for the study and submission of the data (final study reports). However, an additional information request was sent to the Applicant February 8, 2016 that requested the following:

1. We note in your feasibility test plan that you omitted compounds that were classified as GRAS in your summary table. However, omitting compounds based on GRAS designation is not acceptable given that your product is for intravenous use. Therefore, submit a toxicological risk assessment for all leachable compounds that exceed the [redacted] mcg/day qualification threshold.

2. Table 1 of the February 5, 2016 submission shows that a different [redacted] is used for the worst case studies [redacted]) than [redacted]

(b) (4). Clarify whether the same (b) (4) is used in both the manufacturing process and the extraction studies. If (b) (4) has changed, then provide additional data to demonstrate the continued integrity of (b) (4), updated manufacturing process data, and updated batch analysis data generated with the new (b) (4). Alternatively, if (b) (4) is different in the extraction studies from that used in the manufacturing process, then provide a justification for the change (b) (4) for the extraction studies.

3. Provide a firm date that you will submit to the Agency the study report that evaluates whether any of the extractable compounds from the (b) (4) extraction study are in your lyophilized drug product formulation at release and a summary of the levels and associated maximum daily intake of each leachable present in your reconstituted drug product.

In a correspondence from the Applicant (email dated February 23, 2016), the Applicant stated that the final report could not be submitted until after the PDUFA deadline.

3 Studies Submitted

3.1 Studies Reviewed

There were no nonclinical studies submitted in this NDA. A toxicological risk assessment was submitted on the extractables identified; however, as several extractables were not identified, and it is not even known if these compounds are present in the final drug product, a detailed review of their toxicology assessment was not completed. This will be done once we know what, if anything, is actually present in the drug product formulation.

3.2 Studies Not Reviewed

There were no nonclinical studies submitted in this NDA.

3.3 Previous Reviews Referenced

The first cycle Pharmacology/Toxicology NDA review dated February 17, 2015.

11 Integrated Summary and Safety Evaluation

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. Previously, 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 from the previous review

cycle. In this 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. The drug product specifications are acceptable and within the range of the referenced drug product.

The Applicant submitted results from an extractables study done on a (b) (4) To justify the safety of these potential leachables, the Applicant assumed the worst case scenario with the extraction study and submitted a toxicological risk assessment of the extractables that exceed the Toxicological Threshold of Concern (TTC) of (b) (4) mcg/day. However, several of these extractables have not been identified and therefore the toxicological risk assessment does not account for all extraction compounds. Moreover, the Applicant has not determined whether any of the extractables identified in (b) (4) extraction study are present in their lyophilized drug product formulation.

Therefore, from a pharmacology toxicology perspective, the proposed drug product cannot be approved at this time and a Complete Response is recommended.

12 Appendix/Attachments

Reference List

Haworth S, Lawlor T, Mortelmans K, Speck W, and Zieger E. 1983. Salmonella Mutagenicity Test Results for 250 Chemicals. Environmental Mutagenesis. Supplement 1:3-142.

McCann J, Choi E, Yamasaki E, and Ames BN. 1975. Detection of carcinogens as mutagens in the Salmonella/microsome test: assay of 300 chemicals. Proc Natl Acad Sci U S A. **72**:5135-5139.

Zeiger E, Anderson B, Haworth S, Lawlor T, and Mortelmans K. 1988. Salmonella mutagenicity tests: IV. Results from the testing of 300 chemicals. Environmental and Molecular Mutagenesis. 11(Suppl 12):1-157.

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

/s/

CARLIC K HUYNH
02/25/2016

NEWTON H WOO
02/25/2016

RICHARD D MELLON
02/26/2016
I concur.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	206610
Supporting document/s:	SDN 1, 2, 3, and 4 (EDR Sequence Number 0, 1, 2, and 3)
Applicant's letter date:	May 3, 2014 (SDN 1), July 18, 2014 (SDN 2), July 25, 2014 (SDN 3), and August 7, 2014 (SDN 4)
CDER stamp date:	May 5, 2014 (SDN 1), July 18, 2014 (SDN 2), July 25, 2014 (SDN 3), and August 7, 2014 (SDN 4)
Product:	Acetaminophen for Injection
Indication:	Management of (b) (4) pain, management of moderate to severe pain with adjunctive opioid analgesics, and reduction of fever
Applicant:	Agila Specialties Private Ltd.
Review Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Reviewer:	Carlic K. Huynh, PhD
Acting Team Leader:	Newton H. Woo, PhD
Supervisor:	R. Daniel Mellon, PhD
Acting Division Director:	Sharon Hertz, MD
Project Manager:	Christopher Hilfiger

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of 206610 are owned by Agila Specialties Private Ltd. or are data for which Agila Specialties Private Ltd. has obtained a written right of reference. Any information or data necessary for approval of 206610 that Agila Specialties Private Ltd. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of 206610.

TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction

The Applicant, Agila Specialties Private Limited, is developing an intravenous formulation of acetaminophen for Injection (1 g/vial). Agila's acetaminophen product is a lyophilized powder that is reconstituted immediately prior to use. The Applicant is submitting an application via the 505(b)(2) pathway, proposing to rely upon the Agency's previous findings of safety and efficacy to Cadence Pharmaceuticals' OFIRMEV (NDA 22450). The proposed nonclinical portions of the label for the Agila APAP for injection lyophilized powder formulation are the same as the referenced OFIRMEV product labeling.

1.2 Brief Discussion of Nonclinical Findings

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 a (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.

The proposed label for the Agila APAP formulation is the same as the referenced OFIRMEV for the mutagenesis, carcinogenesis, impairment of fertility, and pregnancy sections. The format of the recommended labeling is in the recently finalized Pregnancy Labeling and Lactation Rule (PLLR) format, which is not required at this time. This will be discussed with the entire team during labeling.

1.3 Recommendations

1.3.1 Approvability

From a nonclinical pharmacology toxicology perspective, there are inadequate data to support approval of this drug product and we recommend a Complete Response.

Deficiencies

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

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

3. You have not provided an adequate characterization of potential leachables from the [redacted]. Your worst-case scenario based on your extraction study suggests that approximately [redacted] mcg/vial [redacted] mcg/day) of unknown material could be [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.

Information needed to resolve the deficiencies

1. Update the drug substance specification for [redacted] to as low as technically feasible. We recommend that you contact your DMF holder to determine an appropriate specification.

2. 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. Identify the extractables from [redacted] extraction study and determine if they are present in the drug product formulation. Submit an adequate toxicological risk assessment for any leachable that is above the Toxicological Threshold of Concern of [redacted] mcg/day.

1.3.2 Additional Nonclinical Recommendations

None at this time.

1.3.3 Labeling

Although there are no new nonclinical data that must be added to the drug product labeling, this label will be edited to comply with the new Final Pregnancy and Lactation Labeling Rule. This is voluntary at this time; however, as per OND policy we are requesting Applicants to consider these changes now rather than wait until the required deadlines. The labeling recommendations below have not been discussed with the

entire team or the Applicant and therefore may not represent final drug product labeling. The reader is referred to the action letter for final drug product labeling.

Applicant's proposed labeling	***Reviewer's proposed changes***	***Rationale for changes***
(b) (4)		

4 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

2 Drug Information

2.1 Drug

CAS Registry Number
103-90-2

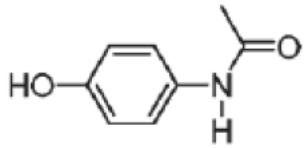
Generic Name
Acetaminophen, paracetamol

Code Name

Chemical Name
N-acetyl-p-aminophenol
4'-hydroxyacetanilide
p-hydroxyacetanilide
p-acetamidophenol
p-acetaminophenol
p-acetylaminophenol

Molecular Formula/Molecular Weight
$C_8H_9NO_2$ / 151.16 g/mol

Structure



Pharmacologic Class
There is no FDA-established pharmacological class for acetaminophen. We recommend not including an established class given the lack of clear understanding of the mechanism of action of acetaminophen.

2.2 Relevant INDs, NDAs, BLAs and MFs

IND#	Drug	Status	Division	Indication	Status Date	Sponsor
116240	Acetaminophen for Injection, 1g/vial	Presubmission	DAAAP	Management of moderate to severe pain with adjunctive opioid analgesics/the reduction of fever	August 20, 2012	Agila Specialties Private Ltd.

NDA#	Drug Name	Div	Strength (route)	Marketing Status	AP Date	Indication	Company
22450	Ofirmev® (acetaminophen for injection)	DAAAP	1000 mg/ 100 mL (10 mg/mL) (IV infusion)	Prescription	November 2, 2010	Management of mild to moderate pain, management of moderate to severe pain with adjunctive opioid analgesics, reduction of fever	Cadence Pharmaceuticals, Inc.

MF#	Subject of MF	Holder	Submit Date	Reviewer's Comment
(b) (4)				

2.3 Drug Formulation

The following table illustrates the formulation of the lyophilized powder, which needs to be reconstituted prior to use (from the Applicant's submission):

Acetaminophen for Injection [1 g/vial]

Ingredient	Reference	Functional Category	Quantity/Unit [per vial]	% W/V
Acetaminophen[1]	USP/BP/Ph.Eur	Active Ingredient	1.000 g	(b) (4)
(b) (4) Cysteine hydrochloride monohydrate (b) (4)	USP/BP/Ph.Eur	(b) (4)	25.000 mg	
Mannitol	USP/BP/Ph.Eur		3.850 g	
Dibasic sodium phosphate (b) (4)	USP/BP/Ph.Eur		(b) (4)	
(b) (4)	USP/BP/Ph.Eur		(b) (4)	
Sodium hydroxide	USNF/BP/Ph.Eur		Q.S. to pH	---
Hydrochloric acid	USNF/BP/Ph.Eur		Q.S. to pH	---
(b) (4)	USP/BP/Ph.Eur		Q.S. to (b) (4)	---
(b) (4)	USPNF/BP/Ph.Eur		Q.S.	---

Q.s.: quantity sufficient

Once reconstituted in 98 mL of sterile water, the formulation is compositionally similar to Ofirmev®. However, there is (b) (4) mg/vial of dibasic sodium phosphate (b) (4)), whereas, Ofirmev® contains 10.4 mg/vial of dibasic sodium phosphate, anhydrous. In discussions with the Chemistry, Manufacture, and Control (CMC) review team, (b) (4) mg of dibasic sodium phosphate (b) (4) 10.4 mg/vial of dibasic sodium phosphate, anhydrous. According to the proposed labeling, the reconstituted solution should be used within 12 hours from preparation. (b) (4)

The daily exposure to (b) (4) cysteine hydrochloride monohydrate and mannitol at the maximum daily dose of 4 g/day of APAP are the same as in Ofirmev® and thus, their levels are qualified and do not represent a safety concern.

Dibasic sodium phosphate (b) (4) are in numerous FDA-approved intravenous formulations at similar concentrations for acute use. Thus, the levels of dibasic sodium phosphate (b) (4) do not represent a safety concern.

2.4 Comments on Novel Excipients

There are no novel excipients in the formulation.

2.5 Comments on Impurities/Degradants of Concern

Drug Substance Impurities

The following table illustrates the drug substance impurities (adapted from the Applicant's submission):

specification has historically been deemed adequate by the Agency. The specification is acceptable for the drug product.

Moreover, the osmolality and pH upon both release and shelf-life are 290 ± 30 mOsmol/kg and a pH range of 4.5 to 6.5. The osmolality and pH of Ofirmev® are 255 to 345 mOsm/kg and pH range of 5.0 to 6.5. Thus, the osmolality and pH of the proposed drug product are similar to Ofirmev® and do not represent a safety concern.

During evaluation of the extractables study on [redacted] (b) (4), it was discovered by the CMC reviewer that approximately [redacted] (b) (4) mcg/vial of material was extracted out, which includes [redacted] (b) (4) material itself. This can potentially be in the final lyophilized powder drug product and result in up to [redacted] (b) (4) mcg/day at the maximum daily dose. Thus, there may be additional [redacted] (b) (4) that would require a toxicological risk assessment. The reader is referred to the CMC review for more information. Until this is clarified and it is assured that these materials are not present in the final drug product formulation, we cannot recommend approval.

Container Closure System

The drug formulation is lyophilized powder that is reconstituted in sterile water prior to use. The following table illustrates the container closure system (from the Applicant's submission):

Component	Description	Manufacturer	DMF #
Glass Vial	100 mL (b) (4) (b) (4)	(b) (4)	
Rubber Closure	(b) (4)		
Flip off Aluminium Seal	(b) (4)		

(b) (4)

Since the lyophilized powder will not be reconstituted until use, and since the reconstituted powder should be used within 12 hours, an extractables and leachables assessment of the container closure system is not required.

2.6 Proposed Clinical Population and Dosing Regimen

The indication is the management of (b) (4) pain, management of moderate to severe pain with adjunctive opioid analgesics, and reduction of fever. Due to the intravenous route of administration, this is not considered a chronic indication. As this product is administered in a hospital setting, the typical duration of use would be (b) (4) (b) (4) The proposed clinical population will be adults and adolescents as well as children aged 2 to 12 years.

2.7 Regulatory Background

This is a 505(b)(2) application referencing the Agency's previous findings of safety to Ofirmev® (NDA 22450).

There was a preIND meeting with this Applicant under IND 116240 scheduled for November 2, 2012. However, the meeting was cancelled by the Sponsor as the Division's preliminary comments were adequate. The following nonclinical comments are from the preliminary comments sent to the Applicants (dated November 2, 2012):

> **We concur that no further nonclinical toxicology studies for acetaminophen will be required to support your proposed 505(b)(2) submission that relies on the Agency's previous finding of safety for Offirmev, as your formulation, once reconstituted, is essentially the same as the referenced product. Refer to the nonclinical comments in Attachment 1 for general recommendations regarding your planned NDA submission.**
>
> **We note that acetaminophen drug products contain the breakdown product (b) (4) , which is a reported genotoxic compound. The USP drug substance specification of NMT (b) (4) % (NMT (b) (4) ppm) will be acceptable to support your NDA. Your drug product specification for (b) (4) should be based on good manufacturing practices and reduced to as low as technically feasible, if it cannot be reduced to reflect a maximal daily intake of NMT (b) (4) mcg/day. Final determination of the adequacy of your drug substance and drug product specifications can be made only following review of your NDA submission.**

There were also additional comments for the pre-NDA stage of drug development to the Applicant (dated November 2, 2012):

1. Your NDA submission should include a detailed discussion of the nonclinical information in the published literature since the data of approval of the referenced drug product 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.

2. 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.

3. Any impurity or degradation product that exceeds ICH qualification thresholds must be adequately qualified for safety as described in ICH Q3A(R2) and ICH Q3B(R2) guidances at the time of NDA submission. Adequate qualification would 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.

4. Genotoxic, carcinogenic or impurities that contain a structural alert for genotoxicity must be either reduced to NMT (b) (4) mcg/day in the drug substance and drug product or adequate safety qualification must be provided. For an impurity with a structural alert for mutagenicity, adequate safety qualification requires a negative in vitro bacterial reverse mutation assay (Ames assay) ideally with the isolated impurity, tested up to the appropriate top concentration of the assay as outlined in ICH S2A guidance document titled "Guidance on Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals." Should the Ames assay produce positive or equivocal results, the impurity specification must be set at NMT (b) (4) mcg/day, or otherwise justified. Justification for a positive or equivocal Ames assay may require an assessment for carcinogenic potential in either a standard 2-year rodent bioassay or in an appropriate transgenic mouse model.

5. In Module 2 of your NDA (2.6.6.8 Toxicology Written Summary/Other Toxicity), 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 and Q3B qualification thresholds along with a determination if the impurity contains a structural alert for mutagenicity. Any proposed specification that exceeds the qualification threshold should be adequately justified for safety from a toxicological perspective.

6. The NDA submission must contain information on potential leachables and extractables from the drug container closure system and/or drug product formulation as outlined in the FDA Guidance for Industry titled "Container Closure Systems for Packaging Human Drugs and Biologics." The evaluation of extractables and leachables from the drug container closure system must include specific assessments for residual monomers, solvents, polymerizers, etc.). Based on identified leachables provide a toxicological evaluation to determine the safe level of exposure via the label-specified 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 specific container closure system or patch, drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing). As many residual monomers are known genotoxic agents, your safety assessment must take into account the potential that these impurities may either be known or suspected highly reactive and/or genotoxic compounds. The safety assessment should be specifically discussed in Module 2.6.6.8 (Toxicology Written Summary/Other Toxicity) of the NDA submission. For additional guidance on extractables and leachables testing, consult the FDA Guidance documents "Container Closure Systems for Packaging Human Drugs and Biologics" and "Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation." Additional methodology and considerations have also been described in the PQRI leachables/extractables recommendations to the FDA, which can be found at http://www.pqri.org/pdfs/LE_Recommendations_to_FDA_09-29-06.pdf.

7. Failure to submit adequate impurity qualification, justification for the safety of new excipient use, or an extractable leachable safety assessment at the time of NDA submission can result in a Refusal-to-File or other adverse action.

3 Studies Submitted

3.1 Studies Reviewed

There were no nonclinical studies submitted in this NDA.

3.2 Studies Not Reviewed

There were no nonclinical studies submitted in this NDA.

3.3 Previous Reviews Referenced

There were no previous reviews referenced.

4 Pharmacology

4.1 Primary Pharmacology

There were no primary pharmacology studies with acetaminophen lyophilized powder submitted in this NDA.

4.2 Secondary Pharmacology

There were no secondary pharmacology studies with acetaminophen lyophilized powder submitted in this NDA.

4.3 Safety Pharmacology

There were no safety pharmacology studies with acetaminophen lyophilized powder submitted in this NDA.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

There were no PK/ADME studies with acetaminophen lyophilized powder submitted in this NDA.

5.2 Toxicokinetics

There were no general toxicology studies with acetaminophen lyophilized powder submitted in this NDA. There were no separate toxicokinetics studies done with acetaminophen lyophilized powder submitted in this NDA.

6 General Toxicology

There were no general toxicology studies with acetaminophen lyophilized powder submitted in this NDA.

7 Genetic Toxicology

There were no genetic toxicology studies with acetaminophen lyophilized powder submitted in this NDA. The following information on the genetic toxicology (mutagenesis) of acetaminophen is from the referenced Ofirmev® label (Cadence Pharma, November 2011):

> Mutagenesis
> Acetaminophen was not mutagenic in the bacterial reverse mutation assay (Ames test). In contrast, acetaminophen tested positive in the in vitro mouse lymphoma assay and the in vitro chromosomal aberration assay using human lymphocytes. In the published literature, acetaminophen has been reported to be clastogenic when administered a dose of 1500 mg/kg/day to the rat model (3.6-times the MHDD, based on a body surface area comparison). In contrast, no clastogenicity was noted at a dose of 750 mg/kg/day (1.8-times the MHDD, based on a body surface area comparison), suggesting a threshold effect.

8 Carcinogenicity

There were no studies on the carcinogenicity of acetaminophen lyophilized powder submitted in this NDA. The following information on the carcinogenicity of acetaminophen is from the referenced Ofirmev® label (Cadence Pharma, November 2011):

> Carcinogenesis
> Long-term studies in mice and rats have been completed by the National Toxicology Program to evaluate the carcinogenic potential of acetaminophen. In 2-year feeding studies, F344/N rats and B6C3F1 mice were fed a diet containing acetaminophen up to 6000 ppm. Female rats demonstrated equivocal evidence of carcinogenic activity based on increased incidences of mononuclear cell leukemia at 0.8 times the maximum human daily dose (MHDD) of 4 grams/day, based on a body surface area comparison. In contrast, there was no evidence of carcinogenic activity in male rats (0.7 times) or mice (1.2-1.4 times the MHDD, based on a body surface area comparison).

9 Reproductive and Developmental Toxicology

There were no fertility studies with acetaminophen lyophilized powder submitted in this NDA. The following information on the impairment of fertility of acetaminophen is from the referenced Ofirmev® label (Cadence Pharma, November 2011):

Impairment of fertility
In studies conducted by the National Toxicology Program, fertility assessments have been completed in Swiss mice via a continuous breeding study. There were no effects on fertility parameters in mice consuming up to 1.7 times the MHDD of acetaminophen, based on a body surface area comparison. Although there was no effect on sperm motility or sperm density in the epididymis, there was a significant increase in the percentage of abnormal sperm in mice consuming 1.7 times the MHDD (based on a body surface area comparison) and there was a reduction in the number of mating pairs producing a fifth litter at this dose, suggesting the potential for cumulative toxicity with chronic administration of acetaminophen near the upper limit of daily dosing.

Published studies in rodents report that oral acetaminophen treatment of male animals at doses that are 1.2 times the MHDD and greater (based on a body surface area comparison) result in decreased testicular weights, reduced spermatogenesis, reduced fertility, and reduced implantation sites in females given the same doses. These effects appear to increase with the duration of treatment. The clinical significance of these findings is not known.

There were no further reproductive and developmental toxicology studies with acetaminophen lyophilized powder submitted in this NDA. The following information on the reproductive and developmental toxicology of acetaminophen is from the pregnancy section of the referenced Ofirmev® label (Cadence Pharma, November 2011):

Pregnancy Category C. There are no studies of intravenous acetaminophen in pregnant women; however, epidemiological data on oral acetaminophen use in pregnant women show no increased risk of major congenital malformations. Animal reproduction studies have not been conducted with IV acetaminophen, and it is not known whether OFIRMEV can cause fetal harm when administered to a pregnant woman. OFIRMEV should be given to a pregnant woman only if clearly needed.

The results from a large population-based prospective cohort, including data from 26,424 women with live born singletons who were exposed to oral acetaminophen during the first trimester, indicate no increased risk for congenital malformations, compared to a control group of unexposed children. The rate of congenital malformations (4.3%) was similar to the rate in the general population. A population-based, case-control study from the National Birth Defects Prevention Study showed that 11,610 children with prenatal exposure to acetaminophen during the first trimester had no increased risk of major birth defects compared to 4,500 children in the control group. Other epidemiological data showed similar results.

While animal reproduction studies have not been conducted with intravenous acetaminophen, studies in pregnant rats that received oral acetaminophen during organogenesis at doses up to 0.85 times the maximum human daily dose (MHDD = 4 grams/day, based on a body surface area comparison) showed evidence of fetotoxicity (reduced fetal weight and length) and a dose-related increase in bone variations (reduced ossification and rudimentary rib changes). Offspring had no evidence of external,

visceral, or skeletal malformations. When pregnant rats received oral acetaminophen throughout gestation at doses of 1.2-times the MHDD (based on a body surface area comparison), areas of necrosis occurred in both the liver and kidney of pregnant rats and fetuses. These effects did not occur in animals that received oral acetaminophen at doses 0.3-times the MHDD, based on a body surface area comparison.

In a continuous breeding study, pregnant mice received 0.25, 0.5, or 1.0% acetaminophen via the diet (357, 715, or 1430 mg/kg/day). These doses are approximately 0.43, 0.87, and 1.7 times the MHDD, respectively, based on a body surface area comparison. A dose-related reduction in body weights of fourth and fifth litter offspring of the treated mating pair occurred during lactation and post-weaning at all doses. Animals in the high dose group had a reduced number of litters per mating pair, male offspring with an increased percentage of abnormal sperm, and reduced birth weights in the next generation pups.

10 Special Toxicology Studies

None.

11 Integrated Summary and Safety Evaluation

There were no new toxicology studies submitted nor required to support this NDA since the osmolality of the reconstituted Agila APAP product is isotonic with no novel excipients, and as such, blood compatibility and local tolerance studies were not deemed necessary. The pH of the Agila APAP product is similar to the referenced OFIRMEV product. The drug substance residual solvent specifications are acceptable. However, the drug substance specifications have been updated in the DMF but not the NDA. These specifications must be revised in order to support approval. The drug product specifications are acceptable and within the range of the referenced drug product.

There is an additional outstanding issue with identification of the extractables studies done on (b) (4) (see the CMC review). As a (b) (4) was lost during the extraction procedures, the CMC reviewer cannot be assured that material from (b) (4) are not present in the final drug product. Therefore, from a nonclinical pharmacology toxicology perspective, there are inadequate data to support an approval recommendation for this application and we recommend a Complete Response.

12 Appendix/Attachments

Reference List

Haworth S, Lawlor T, Mortelmans K, Speck W, and Zieger E. 1983. Salmonella Mutagenicity Test Results for 250 Chemicals. Environmental Mutagenesis. Supplement 1:3-142.

McCann J, Choi E, Yamasaki E, and Ames BN. 1975. Detection of carcinogens as mutagens in the Salmonella/microsome test: assay of 300 chemicals. Proc Natl Acad Sci U S A. **72**:5135-5139.

Zeiger E, Anderson B, Haworth S, Lawlor T, and Mortelmans K. 1988. Salmonella mutagenicity tests: IV. Results from the testing of 300 chemicals. Environmental and Molecular Mutagenesis. 11(Suppl 12):1-157.

The CDER Computational Toxicology Consulting Service QSAR analysis on (b) (4)

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

/s/

CARLIC K HUYNH
02/17/2015

NEWTON H WOO
02/17/2015

RICHARD D MELLON
02/17/2015
I concur.