CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 203133

Name: Dextromethorphan Polistirex Extended Release Oral Suspension, 30 mg/5mL

Sponsor: Amneal Pharmaceuticals LLC

Approval Date: July 28, 2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 203133

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Reviews / Information Included in this Review

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 203133

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 203133

ANDA APPROVAL

Amneal Pharmaceuticals LLC
50 Horseblock Road
Brookhaven, NY 11719
Attention: Pavan Kumar
Director, Regulatory Affairs

Dear Sir:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on July 8, 2011, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Dextromethorphan Polistirex Extended-Release Oral Suspension, (equivalent to Dextromethorphan Hydrobromide, 30 mg/5 mL) [OTC].

Reference is also made to the complete response letter issued by this office on July 14, 2015, and to your amendments received on July 14 and November 10, 2016; and February 6, April 24, and June 8, 2017.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for over-the-counter (OTC) use as recommended in the submitted labeling. Accordingly the ANDA is **approved**, effective on the date of this letter. The Office of Bioequivalence has determined your Dextromethorphan Polistirex Extended-Release Oral Suspension, (equivalent to Dextromethorphan Hydrobromide, 30 mg/5 mL) [OTC], to be bioequivalent to the reference listed drug (RLD), Delsym Extended-Release Oral Suspension, 30 mg/5 mL, of Reckitt Benckiser LLC. Your dissolution testing should be incorporated into the stability and quality control program using the FDA-recommended method and specification for your application (see enclosure).

Under section 506A of FD&C Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

REPORTING REQUIREMENTS

Post marketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1st of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf. The SPL will be accessible via publicly available labeling repositories.

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: www.fda.gov/ectd.

Sincerely yours,

{See appended electronic signature page}

For Vincent Sansone, PharmD
Acting Deputy Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

ENCLOSURE:

DISSOLUTION

The "interim" dissolution specifications are as follows:

Medium	500 mL of 0.1N HCl at 37ºC ± 0.5ºC for 1 hour followed with addition of 400 mL of phosphate buffer (final pH 6.8) containing 0.25 M Sodium chloride after 1 hour sampling
USP Apparatus	II (Paddle)
RPM	50
Temperature	37°C±0.5°C
Specifications	Acid Stage: 1 hr (b) (4) Buffer Stage: 30 min: (b) (4); 60 min: (b) (4); 360 min (6 hrs) NLT (b) (4)

The "interim" dissolution test(s) and tolerances should be finalized by submitting dissolution data for the first three production size batches. Data should be submitted as a Supplement – Changes Being Effected when there are no revisions to the "interim" specifications or when the final specifications are more stringent than the "interim" specifications. In all other instances, the information should be submitted in a Prior Approval Supplement.

Heidi Lee

Digitally signed by Heidi Lee
Date: 7/28/2017 01:46:16PM
GUID: 52795fe90009070673e7de063d080d1f

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 203133

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 203133

COMPLETE RESPONSE

Amneal Pharmaceuticals
85 Adams Avenue
Hauppauge, NY 11788
Attention: Alpesh Patel
Vice President, Global Regulatory Affairs

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) dated July 7, 2011, received July 8, 2011, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Dextromethorphan Polistirex Extended-release Oral Suspension, 30 mg/5 mL (OTC).

We acknowledge receipt of your amendments dated August 24, September 1, and September 16, 2011; April 24, June 14, and August 8, 2012; and January 4 and February 12, 2013.

We have completed our review of this ANDA, as amended, and have determined that we cannot approve this ANDA in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

1. (b) (4)

2.

10 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

BIOEQUIVALENCE

Deficiencies Related to the Bioequivalence (BE) Studies

1. You did not submit **ALL** analytical raw numerical data. Please provide complete (100%) raw numerical data, in the instrument printout format, including original and repeated analysis for all samples, including the data of peak area/height for the analyte, peak area/height for the internal standard, ratio of the peak area/height for the analyte to the peak area/height for the internal standard, dilution factor (if any), and the corresponding concentration for each assayed and reassayed sample of all samples, calibration standard concentration samples, and quality control samples for your fasting (#ARL/10/408) and fed (#ARL/10/409) BE studies.

2. You did not submit concentration and pharmacokinetic data of dextromethorphan in SAS transport files (.xpt) for fasting (#ARL/10/408) study subjects. Instead, you provided concentration and pharmacokinetic data of dextromethorphan in SAS transport files (.xpt) for fed (#ARL/10/409) study in duplicated. Therefore, please submit dextromethorphan concentration and pharmacokinetic data for the fasting study in SAS transport format.

Deficiency Related to the Formulation

3. (b) (4)

For Future Submissions

4. You used a non-standard high-fat vegetarian breakfast in the fed BE study (#ARL/10/409). Currently, there is no adequate data from which to conclude that a high-fat vegetarian breakfast served prior to dosing in BE studies under a fed state will have the same effect on drug absorption as the standard FDA high-fat breakfast using meat as the main protein source. Therefore, the DBIII does not encourage the use of vegetarian meals for breakfast in future fed BE study.

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

DISSOLUTION

The Division of Bioequivalence has completed its review of the dissolution testing portion of your submission. We acknowledge you will conduct dissolution testing for your test product using the following FDA-recommended dissolution method and specifications:

Dissolution Medium:	500 mL of 0.1N HCl at 37ºC ± 0.5ºC for 1 hour followed with addition of 400 mL of phosphate buffer (final pH 6.8) containing 0.25 M Sodium chloride after 1hr sampling.
USP Apparatus:	II (Paddle)
RPM:	50
Temperature:	37°C± 0.5°C
Specifications	Acid Stage: 1 hr (b) (4) Buffer Stage: 30 min: (b) (4); 60 min: (b) (4); 360 min (6 hrs) NLT (b) (4)

LABELING

1. GENERAL COMMENTS
   a. Please include a Format Legend with each of your submissions for the container labels and carton labeling to help us verify your compliance with the labeling format requirements of 21 CFR 201.66.
   b. Please revise the established name to read "Dextromethorphan Polistirex Extended-release Oral Suspension" [use a lower case letter "r" for the word "release"].
   c. (b) (4)
   d. Please explain the tamper evident feature of your packaging configuration to ensure your compliance with 21 CFR 211.132. Also, include an additional and prominent tamper-evident statement on the principal display panel.
   e. (b) (4)
2. CONTAINER (89 mL and 148 mL)
   a. Please refer to the GENERAL COMMENTS where appropriate.
   b. Active Ingredient: Please revise to read "…30 mg dextromethorphan hydrobromide, USP." [add "USP"].
   c. Other Information: (b) (4)
3. CARTON (1 x 89 mL and 1 x 148 mL)
   a. Please refer to the GENERAL COMMENTS where appropriate.
   b. Please add the product strength to the top panel with the established name.
   c. Active ingredient: Please revise to read "30 mg dextromethorphan hydrobromide, USP" [add ", USP"].

d. Uses, second bullet: Please revise to read "…to help you get to sleep" [add "to" before the word "sleep"].

e. Directions: Please add "mL = milliliter" as the last bullet point, per RLD labeling.

f. Other information: Please revise to read "Dosing cup provided" (b) (4) (b) (4)

g. Inactive ingredients: Please add "sodium polystyrene sulfonate" to the list.

h. Inactive ingredients: Please include the following in the list: "hydrochloric acid or sodium hydroxide solution, if required, to adjust the pH".

i. Dosing chart on the right panel: Please add the following text: "mL = milliliter".

j. Please revise the picture of the dosing cup in accordance with the recommendations in section 4 below.

4. DOSING CUP (10 mL)

a. We acknowledge the document entitled, "PROTOCOL/REPORT OF SUITABILITY OF THE GRADUATION OF DOSAGE CUPS FOR LIQUID DOSAGE FORMS" and the "Specification Sheet" in section 3.2.P.7 of your submission. However, to help us further evaluate your proposed dosing cup, please provide a photograph of the actual, to be marketed dosing cup (front and back) as well as a comparison with the RLD's dosing cup. Please submit to both chemistry and labeling for full evaluation.

b. We recommend that you add the established name above the dosing values.

c. We recommend that you replace the current picture of the dosing cup on the container labels and carton labeling with one that depicts the front of the actual dosing cup, displaying the dosing values.

5. SPL

a. Please revise the SPL in accordance with your revised labels and labeling.

b. Data elements/Inactive Ingredients: Please add "sodium polystyrene sulfonate", "hydrochloric acid", and "sodium hydroxide" to the list.

Submit your revised labeling electronically in final print format.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained.

Prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the Electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17.

FACILITY INSPECTIONS

Office of Compliance has no further questions at this time. The compliance status of each facility named in the application may be re-evaluated upon re-submission.

OTHER

A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

RESUBMISSION
MINOR
COMPLETE RESPONSE AMENDMENT
CHEMISTRY / BIOEQUIVALENCE / LABELING

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the ANDA under 21 CFR 314.65. You may also request an extension of time in which to resubmit the ANDA. A resubmission response must fully address all the deficiencies listed.

The drug product may not be legally marketed until you have been notified in writing that this ANDA is approved.

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give

priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self identification or fee payment.

Additionally, we note that the failure of any facility referenced in the application to self-identify and pay applicable fees means that FDA will not consider the GDUFA application review goal dates to apply to that application.

If you have any questions, call Vikas Arora, Regulatory Project Manager, at (240) 402-8884.

Sincerely yours,

Denise P. Toyer -A

Digitally signed by Denise P. Toyer -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300112898, cn=Denise P. Toyer -A
Date: 2015.07.14 17:06:01 -04'00'

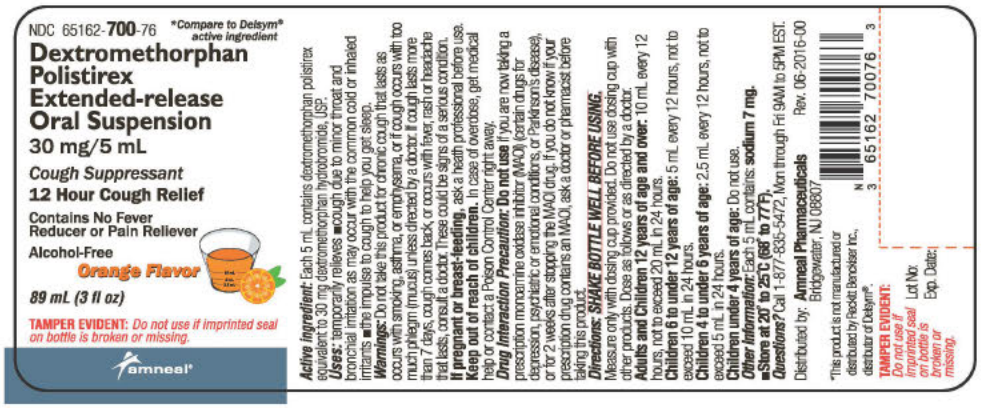
Denise P. Toyer McKan, Pharm.D.
Director, Division of Project Management
Office of Regulatory Operations
Office of Generic Drugs

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

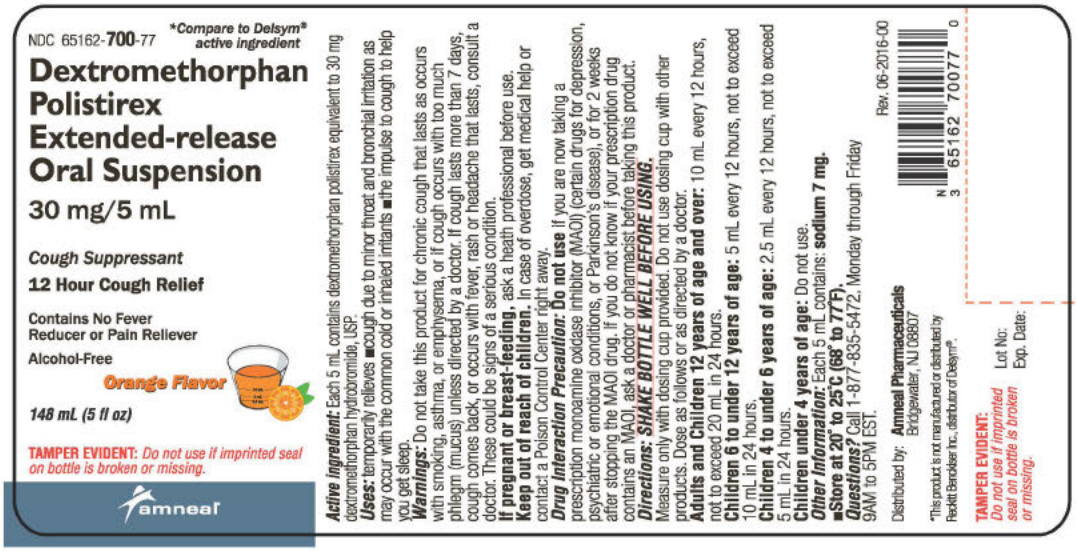
ANDA 203133

LABELING



Label Size 5" x 2"

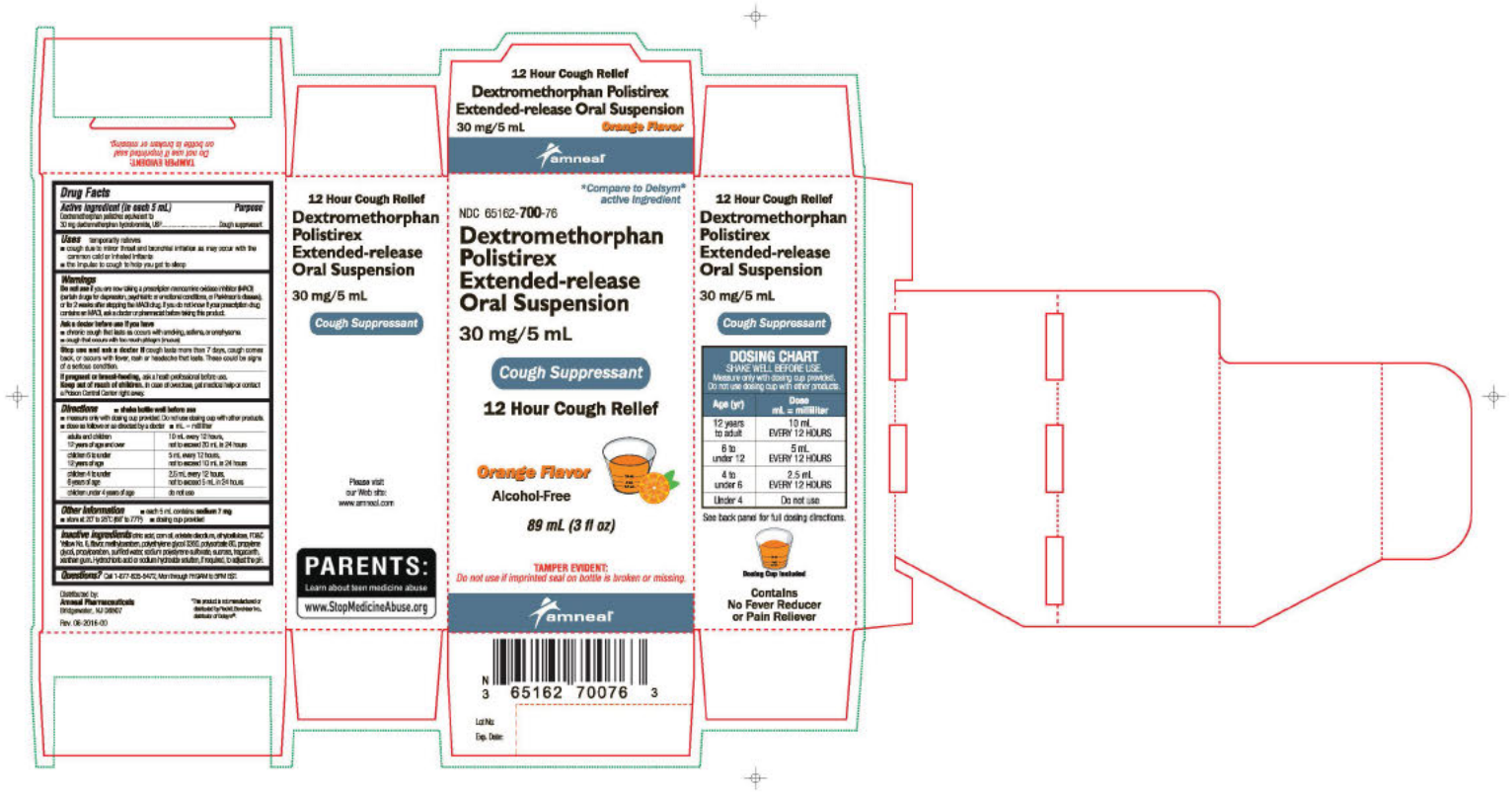
(b) (4)



Label Size 5.5" x 2.75"

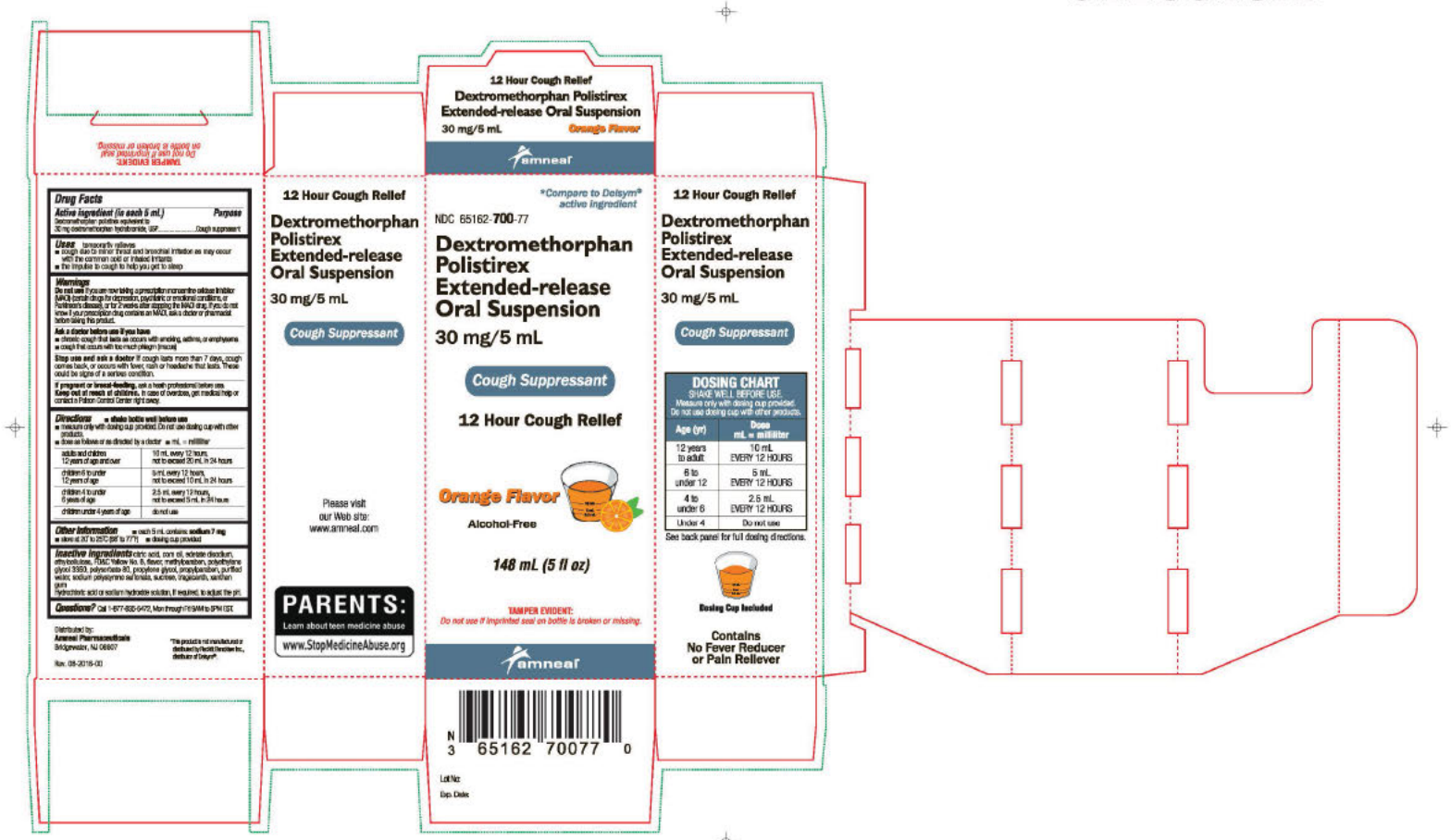
(b) (4)

0126017A


12 Hour Cough Relief
Dextromethorphan Polistirex
Extended-release Oral Suspension
30 mg/5 mL
Orange Flavor
amneal
Drug Facts
Active Ingredient (in each 5 mL)
Purpose
Cough suppressant
Uses
Warnings
Directions
Other Information
Inactive Ingredients
Questions?
Distributed by:
Amneal Pharmaceuticals
Bridgewater, NJ 08807
Rev. 06-2016-00
12 Hour Cough Relief
Dextromethorphan Polistirex Extended-release Oral Suspension
30 mg/5 mL
Cough Suppressant
Please visit our Web site: www.amneal.com
PARENTS:
Learn about teen medicine abuse
www.StopMedicineAbuse.org
*Compare to Delsym® active ingredient
NDC 65162-700-76
Dextromethorphan Polistirex Extended-release Oral Suspension
30 mg/5 mL
Cough Suppressant
12 Hour Cough Relief
Orange Flavor
Alcohol-Free
89 mL (3 fl oz)
TAMPER EVIDENT:
Do not use if imprinted seal on bottle is broken or missing.
amneal
N 3 65162 70076 3
Lot No.
Exp. Date:
12 Hour Cough Relief
Dextromethorphan Polistirex Extended-release Oral Suspension
30 mg/5 mL
Cough Suppressant
DOSING CHART
SHAKE WELL BEFORE USE.
Measure only with dosing cup provided.
Do not use dosing cup with other products.
Age (yr)
Dose mL = milliliter
12 years to adult
10 mL EVERY 12 HOURS
6 to under 12
5 mL EVERY 12 HOURS
4 to under 6
2.5 mL EVERY 12 HOURS
Under 4
Do not use
See back panel for full dosing directions.
Dosing Cup Included
Contains No Fever Reducer or Pain Reliever

(b) (4)

0126018A


TAMPER EVIDENT:
Do not use if imprinted seal on bottle is broken or missing.
Drug Facts
Active Ingredient (in each 5 mL)
Purpose
Dextromethorphan polistirex equivalent to 30 mg dextromethorphan hydrobromide, USP
Cough suppressant
Uses
temporarily relieves
cough due to minor throat and bronchial irritation as may occur with the common cold or inhaled irritants
the impulse to cough to help you get to sleep
Warnings
Do not use if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your prescription drug contains an MAOI, ask a doctor or pharmacist before taking this product.
Ask a doctor before use if you have
chronic cough that lasts as occurs with smoking, asthma, or emphysema
cough that occurs with too much phlegm (mucus)
Stop use and ask a doctor if cough lasts more than 7 days, cough comes back, or occurs with fever, rash or headache that lasts. These could be signs of a serious condition.
If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.
Directions
shake bottle well before use
measure only with dosing cup provided. Do not use dosing cup with other products.
dose as follows or as directed by a doctor
mL = milliliter
adults and children 12 years of age and over: 10 mL every 12 hours, not to exceed 20 mL in 24 hours
children 6 to under 12 years of age: 5 mL every 12 hours, not to exceed 10 mL in 24 hours
children 4 to under 6 years of age: 2.5 mL every 12 hours, not to exceed 5 mL in 24 hours
children under 4 years of age: do not use
Other Information
each 5 mL contains: sodium 7 mg
store at 20° to 25°C (68° to 77°F)
dosing cup provided
Inactive Ingredients citric acid, corn oil, edetate disodium, ethylcellulose, FD&C Yellow No. 6, flavor, methylparaben, polyethylene glycol 3350, polysorbate 80, propylene glycol, propylparaben, purified water, sodium polystyrene sulfonate, sucrose, tragacanth, xanthan gum
hydrochloric acid or sodium hydroxide solution, if required, to adjust the pH.
Questions? Call 1-877-888-9472, Mon through Fri 9 AM to 5 PM EST.
Distributed by:
Amneal Pharmaceuticals
Bridgewater, NJ 08807
Rev. 08-2016-00
*The product is not manufactured or distributed by Reckitt Benckiser Inc., distributor of Delsym®.
12 Hour Cough Relief
Dextromethorphan Polistirex Extended-release Oral Suspension
30 mg/5 mL
Cough Suppressant
Please visit our Web site: www.amneal.com
PARENTS:
Learn about teen medicine abuse
www.StopMedicineAbuse.org
12 Hour Cough Relief
Dextromethorphan Polistirex Extended-release Oral Suspension
30 mg/5 mL
Orange Flavor
amneal
*Compare to Delsym® active ingredient
NDC 65162-700-77
Dextromethorphan Polistirex Extended-release Oral Suspension
30 mg/5 mL
Cough Suppressant
12 Hour Cough Relief
Orange Flavor
Alcohol-Free
148 mL (5 fl oz)
TAMPER EVIDENT:
Do not use if imprinted seal on bottle is broken or missing.
amneal
N 3 65162 70077 0
Lot No:
Exp. Date:
12 Hour Cough Relief
Dextromethorphan Polistirex Extended-release Oral Suspension
30 mg/5 mL
Cough Suppressant
DOSING CHART
SHAKE WELL BEFORE USE.
Measure only with dosing cup provided.
Do not use dosing cup with other products.
Age (yr) | Dose mL = milliliter
12 years to adult | 10 mL EVERY 12 HOURS
6 to under 12 | 5 mL EVERY 12 HOURS
4 to under 6 | 2.5 mL EVERY 12 HOURS
Under 4 | Do not use
See back panel for full dosing directions.
Dosing Cup Included
Contains No Fever Reducer or Pain Reliever

(b) (4)

Dextromethorphan Polistirex Extended-release Suspension
12 Hour Cough Relief
Orange

Drug Facts

Active ingredient (in each 5 mL)

Dextromethorphan polistirex equivalent to 30 mg dextromethorphan hydrobromide, USP

Purpose

Cough suppressant

Uses

Temporarily relieves

- cough due to minor throat and bronchial irritation as may occur with the common cold or inhaled irritants
- the impulse to cough to help you get to sleep

Warnings

Do not use if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your prescription drug contains an MAOI, ask a doctor or pharmacist before taking this product.

Ask a doctor before use if you have

- chronic cough that lasts as occurs with smoking, asthma or emphysema
- cough that occurs with too much phlegm (mucus)

Stop use and ask a doctor if cough lasts more than 7 days, cough comes back, or occurs with fever, rash or headache that lasts. These could be signs of a serious condition.

If pregnant or breast-feeding, ask a health professional before use.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

- **shake bottle well before use**

- measure only with dosing cup provided. Do not use dosing cup with other products.
- dose as follows or as directed by a doctor
- mL = milliliter

adults and children 12 years of age and over	10 mL every 12 hours, not to exceed 20 mL in 24 hours
children 6 to under 12 years of age	5 mL every 12 hours, not to exceed 10 mL in 24 hours
children 4 to under 6 years of age	2.5 mL every 12 hours, not to exceed 5 mL in 24 hours
children under 4 years of age	do not use

Other information

- each 5 mL contains: **sodium 7 mg**
- store at 20° to 25°C (68° to 77°F)
- dosing cup provided

Inactive ingredients

citric acid, corn oil, edetate disodium, ethylcellulose, FD&C Yellow No. 6, flavor, methylparaben, polyethylene glycol 3350, polysorbate 80, propylene glycol, propylparaben, purified water, sodium polystyrene sulfonate, sucrose, tragacanth, xanthan gum
Hydrochloric acid or sodium hydroxide solution, if required, to adjust the pH.

Questions?

Call 1-877-835-5472, Mon through Fri 9AM to 5PM EST.

Distributed by:
Amneal Pharmaceuticals
Bridgewater, NJ 08807

Rev. 06-2016-00

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 203133

LABELING REVIEWS

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	7/25/16
ANDA Number(s)	203133
Review Number	2
Applicant Name	Amneal Pharmaceuticals
Established Name & Strength(s)	Dextromethorphan Polistirex Extended-release Oral Suspension, (equivalent to Dextromethorphan Hydrobromide, 30 mg/5 mL) [OTC]
Proposed Proprietary Name	None
Submission Received Date	7/14/16
Labeling Reviewer	Manizheh Siahpoushan
Labeling Team Leader	Theresa Liu (acting)

Review Conclusion

☐ ACCEPTABLE – No Comments.

☒ ACCEPTABLE – Include Post Approval Comments

☐ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for the Letter to Applicant.

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Easily Correctable Deficiency if all other OGD reviews are acceptable. Otherwise, the labeling minor deficiencies will be included in the Complete Response (CR) letter to the applicant.

☐ On Policy Alert List

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

N/A

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with Choose an item. all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

However, prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address –

http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submission dated July 14, 2016.

1.3 POST APPROVAL REVISIONS

These comments will NOT be sent to the applicants at this time.
These comments will be addressed post approval (in the first labeling supplement review).

CONTAINER LABELS AND CARTON LABELING

1. Established name presentation (including the dosing cup): (b) (4) "Extended-release" (b) (4) (b) (4)
2. We recommend including a description of your container closure system's tamper evident feature in the tamper evident statement [e.g., "TAMPER EVIDENT: Do not use if the seal on bottle imprinted with XX is broken or missing" ("XX" to be replaced with your tamper evident feature)]. For guidance, we refer you to the RLD's which states: "TAMPER EVIDENT: Do not use if the neckband printed with √ is broken or missing."
3. Directions (carton labeling): (b) (4) "do not use dosing cup with other products".

2. PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment to firm's response as well as any new deficiencies found in this cycle. Include the previous review cycle and the review's submission date(s) [e.g. "The below comments are from the labeling review C3 based on the submission dated 7/4/15"].

Reviewer Comments: Deficiencies identified in the 2/5/14 labeling review (C1) and the applicant's responses to the 7/14/15 CR, submitted on 7/14/16 are as follow:

1. **GENERAL COMMENTS**

   a. **Please include a Format Legend with each of your submissions for the container labels and carton labeling to help us verify your compliance with the labeling format requirements of 21 CFR 201.66.**

   b. **Please revise the established name to read "Dextromethorphan Polistirex Extended-release Oral Suspension" [use a lower case letter "r" for the word "release"].**

   c. (b) (4)

   d. **Please explain the tamper evident feature of your packaging configuration to ensure your compliance with 21 CFR 211.132. Also, include an additional and prominent tamper-evident statement on the principal display panel.**

   e. (b) (4)

   Amneal's Response:

   Amneal acknowledges the Agency's comments.

   As recommended by the agency, Amneal has revised the labeling as mentioned above.

   Regarding the tamper evident feature of Amneal's packaging configuration, Amneal's product is having a shrink band around the bottle neck and cap, same like the RLD.

   Please refer to **Module 1.14.2.1** for the revised final container and carton labels.

   For side-by-side comparison of Amneal's revised container and carton labels vs. Amneal's previously submitted container and carton labels, please refer to **Module 1.14.1.2**.

2. **CONTAINER (89 mL and 148 mL)**

   a. **Please refer to the GENERAL COMMENTS where appropriate.**

   b. **Active Ingredient: Please revise to read "…30 mg dextromethorphan hydrobromide, USP." [add "USP"].**

   c. **Other Information:** (b) (4)

   Amneal's Response:

   Amneal acknowledges the Agency's comments.

   As recommended by the agency, Amneal has revised the labeling as mentioned above.

   Please refer to **Module 1.14.2.1** for the revised final container labels.

   For side-by-side comparison of Amneal's revised container labels vs. Amneal's previously submitted container labels, please refer to **Module 1.14.1.2**.

3. **CARTON (1 x 89 mL and 1 x 148 mL)**

   a. **Please refer to the GENERAL COMMENTS where appropriate.**

   b. **Please add the product strength to the top panel with the established name.**

   c. **Active ingredient: Please revise to read "30 mg dextromethorphan hydrobromide, USP" [add ", USP"].**

   d. **Uses, second bullet: Please revise to read "…to help you get to sleep" [add "to" before the word "sleep"].**

   e. **Directions: Please add "mL = milliliter" as the last bullet point, per RLD labeling.**

   f. **Other information: Please revise to read "Dosing cup provided" (b) (4) (b) (4)**

   g. **Inactive ingredients: Please add "sodium polystyrene sulfonate" to the list.**

   h. **Inactive ingredients: Please include the following in the list: "hydrochloric acid or sodium hydroxide solution, if required, to adjust the pH".**

   i. **Dosing chart on the right panel: Please add the following text: "mL = milliliter".**

   j. **Please revise the picture of the dosing cup in accordance with the recommendations in section 4 below.**

   Amneal's Response:

   Amneal acknowledges the Agency's comments.

   As recommended by the agency, Amneal has revised the labeling as mentioned above.

   Please refer to **Module 1.14.2.1** for the revised final carton labels.

   For side-by-side comparison of Amneal's revised carton labels vs. Amneal's previously submitted carton labels, please refer to **Module 1.14.1.2**.

4. **DOSING CUP (10 mL)**

a. **We acknowledge the document entitled, "PROTOCOL/REPORT OF SUITABILITY OF THE GRADUATION OF DOSAGE CUPS FOR LIQUID DOSAGE FORMS" and the "Specification Sheet" in section 3.2.P.7 of your submission. However, to help us further evaluate your proposed dosing cup, please provide a photograph of the actual, to be marketed dosing cup (front and back) as well as a comparison with the RLD's dosing cup. Please submit to both chemistry and labeling for full evaluation.**

Amneal's Response:

As requested by the Agency, photographs of the actual, to be marketed dosing cup (front and back) as well as a comparison with the RLD's dosing cup is provided in **Module 1.14.1.2**

The same information is also provided in **Module 3.2.P.7** for chemistry review.

b. **We recommend that you add the established name above the dosing values.**

Amneal's Response:

(b) (4)

photographs of the actual, to be marketed dosing cup (front and back) as well as a comparison with the RLD's dosing cup is provided in **Module 1.14.1.2**. As per FDA's request in the CR letter, the samples of the product and dosing cup were sent to FDA on July 14, 2016. (b) (4)

(b) (4)

(b) (4) The updated drawing of dosing cup showing the appearance of text is provided in **Module 3.2.P.7**

c. **We recommend that you replace the current picture of the dosing cup on the container labels and carton labeling with one that depicts the front of the actual dosing cup, displaying the dosing values.**

Amneal's Response:

As requested by the Agency, the picture of the dosing cup on the container and carton labeling have been replaced with the ones that depict the front of the actual dosing cup, displaying the dosing values. Please refer to **Module 1.14.2.1** for revised carton and container labels.

5. **SPL**

a. **Please revise the SPL in accordance with your revised labels and labeling.**

b. **Data elements/Inactive Ingredients: Please add "sodium polystyrene sulfonate", "hydrochloric acid", and "sodium hydroxide" to the list.**

Amneal's Response:

Amneal acknowledges Agency's comment. The SPL file has been revised in accordance with revised labels and labeling. As suggested by the Agency, data elements for "sodium polystyrene sulfonate", "hydrochloric acid", and "sodium hydroxide" were added to the list. The SPL file is provided in **Module 1.14.2.3**.

Submit your revised labeling electronically in final print format.

The responses and the revised labels and labeling are satisfactory, pending CMC assessment, as indicated in section 2.2.

2.1 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were **NOT** requested in the previous labeling review?
NO

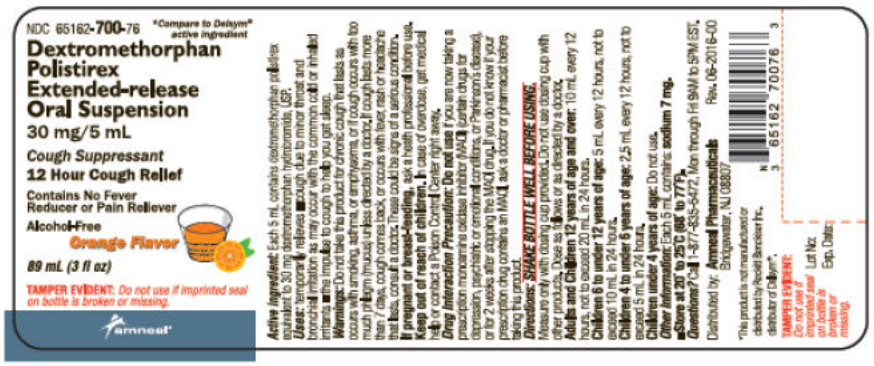
If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

Reviewer Comments: The container labels and carton labeling were revised as requested by the Agency. Additionally, the distributor's information has been updated. The first labeling review did not request the applicant to include a description of the container closure system's tamper evident feature in their tamper evident statement. For example, the RLD's states: "**TAMPER EVIDENT: Do not use if the** neckband printed with is broken or missing." Post approval revisions will be requested.

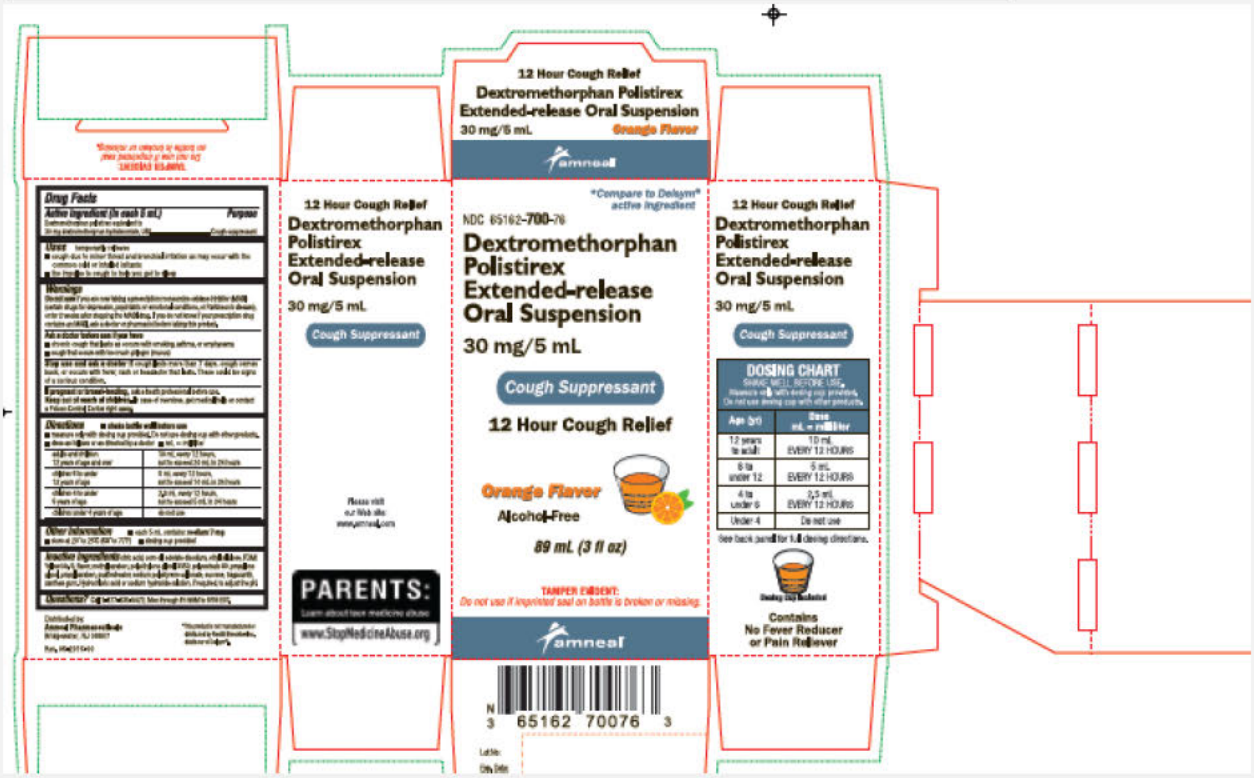
Received on 7/8/11:

(b) (4)

Resubmitted on 7/14/16:



(b) (4)



2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s) [e.g. resolution of any pending chemistry review or issue].

6 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

DISSOLUTION

The Division of Bioequivalence has completed its review of the dissolution testing portion of your submission. We acknowledge you will conduct dissolution testing for your test product using the following FDA-recommended dissolution method and specifications:

Dissolution Medium:	**500 mL of 0.1N HCl at 37°C + 0.5°C for 1 hour followed with addition of 400 mL of phosphate buffer (final pH 6.8) containing 0.25 M Sodium chloride after 1hr sampling.**
USP Apparatus:	**II (Paddle)**
RPM:	**50**
Temperature:	**37°C± 0.5°C**
Specifications	**Acid Stage: 1 hr (b) (4) Buffer Stage: 30 min: (b) (4); 60 min: (b) (4); 360 min (6 hrs) NLT (b) (4)**

Amneal's Response:

Amneal acknowledges the Agency's comment and agrees to perform the dissolution testing as per the above conditions.

From module 1.14.1.2 submitted on 7/14/1:

(b) (4)

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in DLR's SharePoint Drug Facts? NO If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review
Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? NO If Yes, please explain.

3.2 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)
☒ **MOST RECENTLY APPROVED NDA MODEL LABELING** *(If NDA is listed in the discontinued section of the Orange Book, also enter ANDA model labeling information.)* **NDA# /Supplement# (S-000 if original):** 018658/S-030 **Supplement Approval Date:** 6/19/14 **Proprietary Name:** Delsym **Established Name:** dextromethorphan polistirex extended-release suspension **Description of Supplement:** This "Prior Approval" sNDA provides for a revision of the proprietary name layout and updated graphics for the pediatric labeling of the orange and grape-flavored SKUs.
☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING** **ANDA#/Supplement# (S-000 if original):** Click here to enter text. **Supplement Approval Date:** Click here to enter text. **Proprietary Name:** Click here to enter text. **Established Name:** Click here to enter text. **Description of Supplement:**
☐ **TEMPLATE (e.g., BPCA, PREA, Carve-out):** Click here to enter text.
☒ **OTHER (Describe):** There are no pending supplements for this NDA.

Reviewer Assessment:

Is the Prescribing Information same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8)? **NA**
Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old)? **NA**
Does the Model Labeling have combined insert labeling for multiple dosage forms? **NA**

Reviewer Comments:

- The ANDA product is an OTC and does not contain a package insert.
- The revisions to the RLD labels and labeling that are proposed in S-030 do not involve any updates to the drug facts and are only related to the presentation of information with respect to the NDA's [redacted] (b) (4)
- Regarding S-030, as per the "nonclinical" labeling review for S-030, *The sponsor did not make any changes to the drug facts label and these changes will not influence the 'adult" labels. On March 6, 2014, the sponsor submitted updated label to replace the December 23, 2013 submission. On June 2, 2014 the sponsor provided an information request to identify representative labeling which is shown in the chart below.*

(b) (4)

The proposed labeling was compared to the currently approved labeling (dated May 9, 2011) that was approved as part of NDA 18658/S-29.

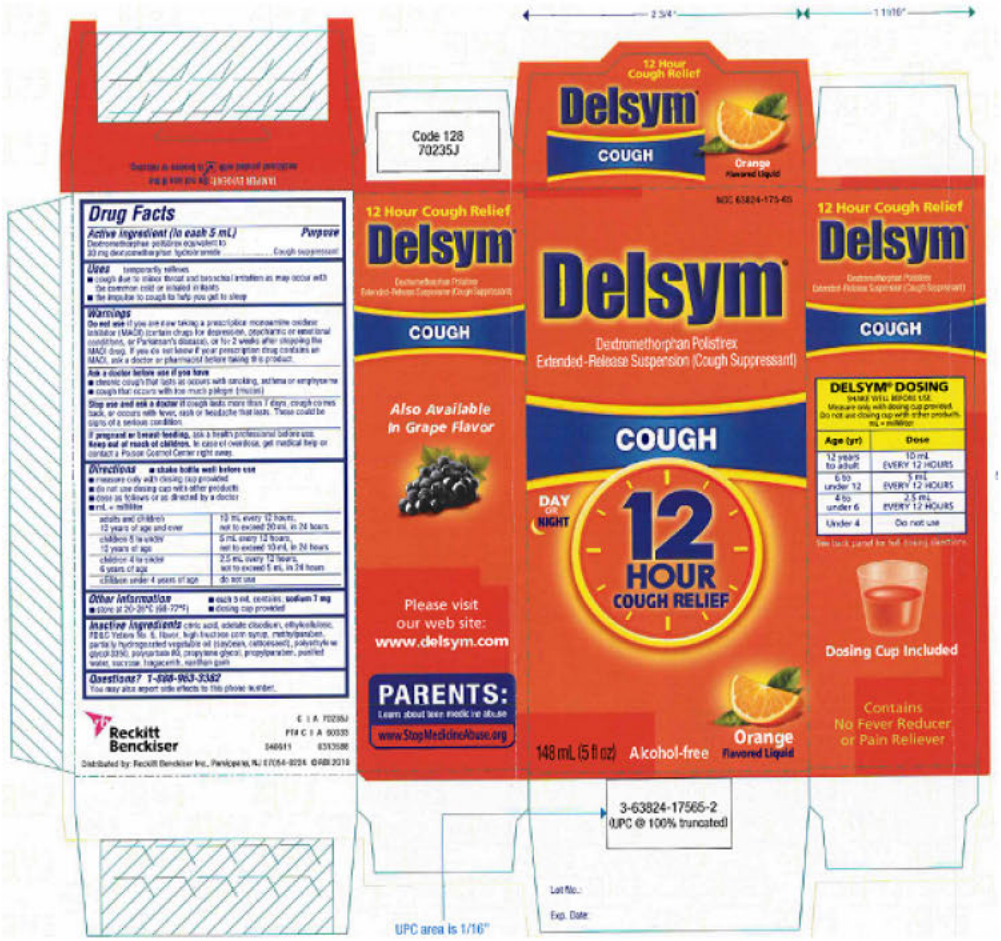
Outer Carton Drug Facts Label

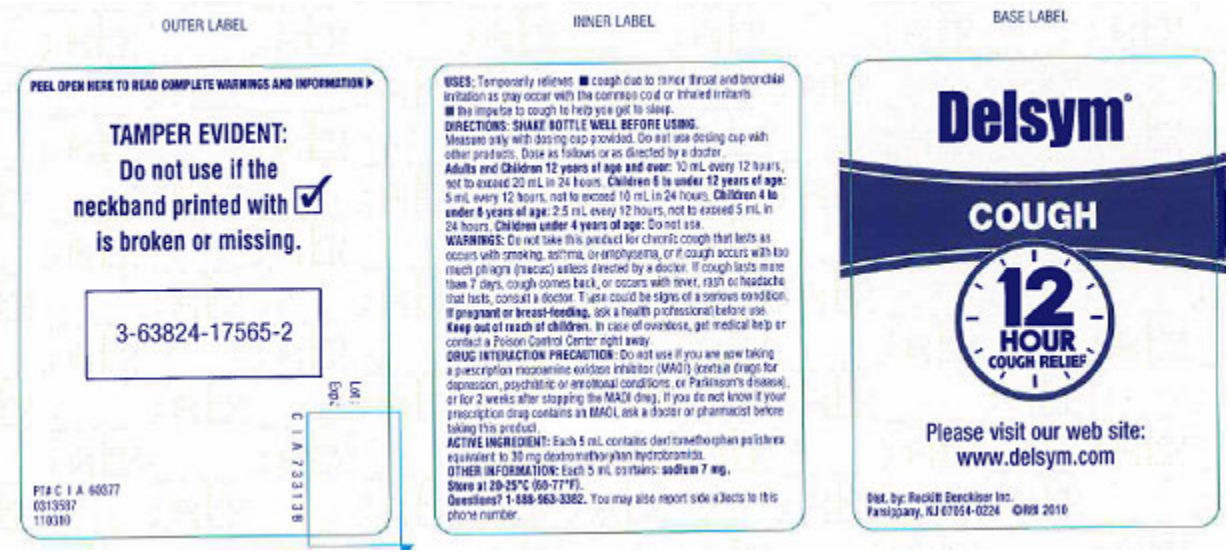
Note: There were no changes to the drug fact panel with respect to content. The annoted format font specifications are in accordance with 21 CFR 201.66. This is acceptable.

3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: see below]

S-029 approved 5/16/11:





Notes from the DMEPA label and labeling review of S-030 dated 4/21/14:

The applicant proposes to add the descriptor "Children's" above the proprietary name "Delsym" (December 20, 2013 submission) and to change graphics and location of text on the principal display panel (March 6, 2014 submission) on the pediatric orange-flavored and grapeflavored product packaging labels and labeling while making no changes to the Drug Facts label.

CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed container labels and carton labeling are acceptable from a medication errors perspective.

Proposed Children's Delsym Grape 5 oz Bottle Label

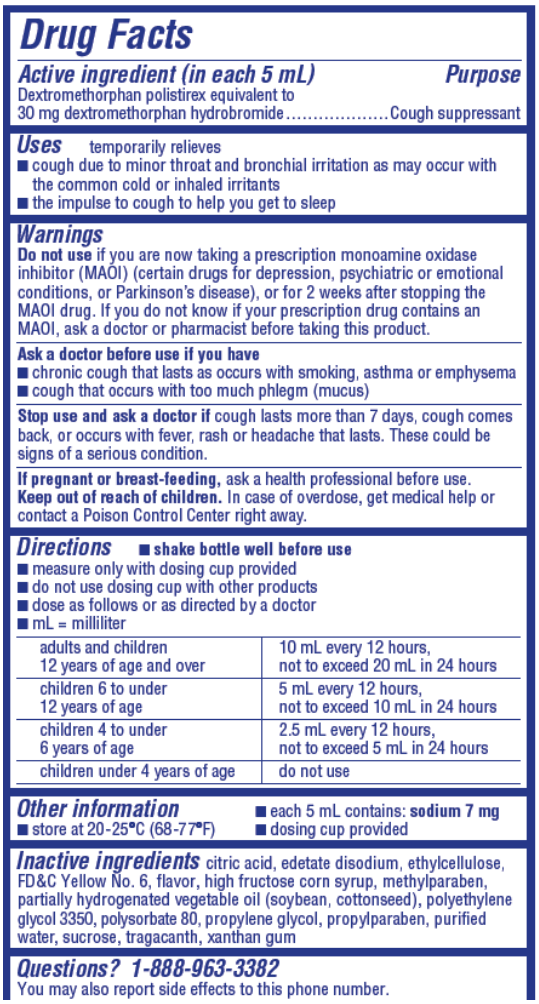
FRONT LABEL

Proposed Children's Delsym Grape 5 oz Carton Labeling

Proposed Children's Delsym Orange 5 oz Bottle Label Carton Labeling

FRONT LABEL

Proposed Children's Delsym Orange 5 oz Carton Labeling



Drug Facts

Active ingredient (in each 5 mL) — **Purpose**
Dextromethorphan polistirex equivalent to 30 mg dextromethorphan hydrobromide ..... Cough suppressant

Uses temporarily relieves
- cough due to minor throat and bronchial irritation as may occur with the common cold or inhaled irritants
- the impulse to cough to help you get to sleep

Warnings
Do not use if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your prescription drug contains an MAOI, ask a doctor or pharmacist before taking this product.

Ask a doctor before use if you have
- chronic cough that lasts as occurs with smoking, asthma or emphysema
- cough that occurs with too much phlegm (mucus)

Stop use and ask a doctor if cough lasts more than 7 days, cough comes back, or occurs with fever, rash or headache that lasts. These could be signs of a serious condition.

If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions ■ **shake bottle well before use**
- measure only with dosing cup provided
- do not use dosing cup with other products
- dose as follows or as directed by a doctor
- mL = milliliter

adults and children 12 years of age and over	10 mL every 12 hours, not to exceed 20 mL in 24 hours
children 6 to under 12 years of age	5 mL every 12 hours, not to exceed 10 mL in 24 hours
children 4 to under 6 years of age	2.5 mL every 12 hours, not to exceed 5 mL in 24 hours
children under 4 years of age	do not use

Other information
- store at 20-25°C (68-77°F)
- each 5 mL contains: **sodium 7 mg**
- dosing cup provided

Inactive ingredients citric acid, edetate disodium, ethylcellulose, FD&C Yellow No. 6, flavor, high fructose corn syrup, methylparaben, partially hydrogenated vegetable oil (soybean, cottonseed), polyethylene glycol 3350, polysorbate 80, propylene glycol, propylparaben, purified water, sucrose, tragacanth, xanthan gum

Questions? 1-888-963-3382
You may also report side effects to this phone number.

3.4 UNITED STATES PHARMACOPEIA (USP) & PHARMACOPEIA FORUM (PF)

We searched the USP and PF to determine if the drug product under review is the subject of a USP monograph or proposed USP monograph.

Table 2: USP and PF Search Results

	Date Searched	Monograph ? YES or NO	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
USP	7/25/2016	NO	NA	NA
PF	7/25/2016	NO	NA	NA

Reviewer Comments:
None.

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 7/25/2016.

Table 3 provides Orange Book patents for the Model Labeling and ANDA patent certifications.

(For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	**Patent Expiration**	**Patent Use Code**	**Patent Use Code Definition**	**Patent Certification**	**Date of Patent Cert Submission**	**Labeling Impact**
5980882	Apr 16, 2017			PIV	7/8/11	None

Reviewer Assessment:

Is the applicant's "patent carve out" acceptable? **NA**

Reviewer Comments:

None.

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	**Exclusivity Expiration**	**Exclusivity Code Definition**	**Exclusivity Statement**	**Date of Exclusivity Submission**	**Labeling Impact**
Click here to enter text.					

Reviewer Assessment:

Is the applicant's "exclusivity carve out" acceptable? **NA**

Reviewer Comments:

There is no unexpired exclusivity for this product.

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the inactive ingredients, dosage form description, package sizes, and manufacturer/distributor/packer statements of the Prescribing Information or Drug Facts for OTC products when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or Inactive Ingredients (OTC)? **NO**
Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED or package size(s) for OTC? **NO**
Are there changes to the manufacturer/distributor/packer statements? **YES**
If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)		
Previous Labeling Review	**Currently Proposed**	**Assessment**

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)		
(b) (4)	citric acid, corn oil, edetate disodium, ethylcellulose, FD&C Yellow No. 6, flavor, methylparaben, polyethylene glycol 3350, polysorbate 80, propylene glycol, propylparaben, purified water, sodium polystyrene sulfonate, sucrose, tragacanth, xanthan gum Hydrochloric acid or sodium hydroxide solution, if required, to adjust the pH.	Updated as requested by the Agency. The chemist has been notified of these additions. Acceptable from a labeling perspective.

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
Previous Labeling Review	**Currently Proposed**	**Assessment**
(b) (4) round bottles of 89 mL and 148 mL	(b) (4) round bottles of 89 mL and 148 mL	No changes noted.

Table 7: Manufacturer/Distributor/Packer Statements		
Previous Labeling Review	**Currently Proposed**	**Assessment**
(b) (4)	Distributed by: Amneal Pharmaceuticals Bridgewater, NJ 08807 Rev. 06-2016-00	The distributor's updated information is acceptable.

5. COMMENTS FOR CHEMISTRY REVIEWER

Describe issue(s) sent to and/or received from the chemistry (also known as drug product quality) reviewer:

Reviewer Comments:

An email was sent on 7/25/16 to notify the chemist that the Inactive Ingredients section of the Drug Facts on the carton labeling has been updated to include "sodium polystyrene sulfonate" and "hydrochloric acid or sodium hydroxide solution, if required, to adjust the pH", as previously requested by labeling.

6. COMMENTS FOR OTHER REVIEW DISCIPLINES

Describe questions/issue(s) sent to and/or received from other discipline reviewer(s):

Reviewer Comments:
None.

7. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for all labeling pieces for this application.

For each row, you **MUST** choose an item "Final, Draft, or "NA". If you enter "NA" under the second column, you do NOT need to enter "NA" for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Final	89 mL and 148 mL bottles	7/14/16	Satisfactory
Blister	NA	Click here to enter text.	Click here to enter text.	Click here to enter text.
Carton	Final	1 x 89 mL and 1 x 148 mL	7/14/16	Satisfactory
(Other – specify)	NA	Click here to enter text.	Click here to enter text.	Click here to enter text.
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	NA	Click here to enter text.	Click here to enter text.	Click here to enter text.
Medication Guide	NA	Click here to enter text.	Click here to enter text.	Click here to enter text.
Patient Information	NA	Click here to enter text.	Click here to enter text.	Click here to enter text.
SPL Data Elements		6/2016	7/14/16	Satisfactory

Manizheh Siahpoushan

Digitally signed by Manizheh Siahpoushan
Date: 7/25/2016 04:20:48PM
GUID: 50814c7000007a4f0582207115192fdf

Theresa Liu

Digitally signed by Theresa Liu
Date: 7/27/2016 10:11:17AM
GUID: 508da70a00028d58911de18a598cda6f

Labeling Deficiencies determined on February 4, 2014, based on your submission dated July 7, 2011 (received July 8, 2011):

1. GENERAL COMMENTS

a. Please include a Format Legend with each of your submissions for the container labels and carton labeling to help us verify your compliance with the labeling format requirements of 21 CFR 201.66.

b. Please revise the established name to read “Dextromethorphan Polistirex Extendedrelease Oral Suspension” [use a lower case letter “r” for the word “release”].

c. [redacted] (b) (4)

d. Please explain the tamper evident feature of your packaging configuration to ensure your compliance with 21 CFR 211.132. Also, include an additional and prominent tamper-evident statement on the principal display panel.

e. [redacted] (b) (4)

[redacted]

2. CONTAINER (89 mL and 148 mL)

a. Please refer to the GENERAL COMMENTS where appropriate.

b. Active Ingredient: Please revise to read “…30 mg dextromethorphan hydrobromide, USP.” [add “USP”].

c. Other Information: [redacted] (b) (4)

3. CARTON (1 x 89 mL and 1 x 148 mL)

a. Please refer to the GENERAL COMMENTS where appropriate.

b. Please add the product strength to the top panel with the established name.

c. Active ingredient: Please revise to read “30 mg dextromethorphan hydrobromide, USP” [add “, USP”].

d. Uses, second bullet: Please revise to read "…to help you get to sleep" [add "to" before the word "sleep"].

e. Directions: Please add "mL = milliliter" as the last bullet point, per RLD labeling.

f. Other information: Please revise to read "Dosing cup provided" (b) (4)

g. Inactive ingredients: Please add "sodium polystyrene sulfonate" to the list.

h. Inactive ingredients: Please include the following in the list: "hydrochloric acid or sodium hydroxide solution, if required, to adjust the pH".

i. Dosing chart on the right panel: Please add the following text: "mL = milliliter".

j. Please revise the picture of the dosing cup in accordance with the recommendations in section 4 below.

4. DOSING CUP (10 mL)

a. We acknowledge the document entitled, "PROTOCOL/REPORT OF SUITABILITY OF THE GRADUATION OF DOSAGE CUPS FOR LIQUID DOSAGE FORMS" and the "Specification Sheet" in section 3.2.P.7 of your submission. However, to help us further evaluate your proposed dosing cup, please provide a photograph of the actual, to be marketed dosing cup (front and back) as well as a comparison with the RLD's dosing cup. Please submit to both chemistry and labeling for full evaluation.

b. We recommend that you add the established name above the dosing values.

c. We recommend that you replace the current picture of the dosing cup on the container labels and carton labeling with one that depicts the front of the actual dosing cup, displaying the dosing values.

5. SPL

a. Please revise the SPL in accordance with your revised labels and labeling.

b. Data elements/Inactive Ingredients: Please add "sodium polystyrene sulfonate",

“hydrochloric acid”, and “sodium hydroxide” to the list.

Reference ID: 3448226

Submit your revised labeling electronically in final print format.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained.

Prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the Electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17.

Office of Generic Drugs

REVIEW OF PROFESSIONAL LABELING (First Cycle)

ANDA Number:	203133
Date of Submission:	July 7, 2011 (received July 8, 2011)
Applicant:	Amneal Pharmaceuticals
Established Name and Strength:	Dextromethorphan Polistirex Extended-release Oral Suspension, 30 mg/5 mL (OTC)

Labeling Comments below are considered:

☒ Minor Deficiency *

* Please note that the RPM may change the status from Minor Deficiency to Easily Correctable Deficiency if other disciplines are acceptable.

☐ No Comments (Labeling Approval Summary or Tentative Approval Summary)

RPM Note - Labeling comments to be sent to the firm start below:

Labeling Deficiencies determined on February 4, 2014, based on your submission dated July 7, 2011 (received July 8, 2011):

1. GENERAL COMMENTS

   a. Please include a Format Legend with each of your submissions for the container labels and carton labeling to help us verify your compliance with the labeling format requirements of 21 CFR 201.66.

   b. Please revise the established name to read "Dextromethorphan Polistirex Extended-release Oral Suspension" [use a lower case letter "r" for the word "release"].

   c. (b) (4)

   d. Please explain the tamper evident feature of your packaging configuration to ensure your compliance with 21 CFR 211.132. Also, include an additional and prominent tamper-evident statement on the principal display panel.

   e. (b) (4)

2. CONTAINER (89 mL and 148 mL)
    a. Please refer to the GENERAL COMMENTS where appropriate.
    b. Active Ingredient: Please revise to read "…30 mg dextromethorphan hydrobromide, USP." [add "USP"].
    c. Other Information: (b) (4)
3. CARTON (1 x 89 mL and 1 x 148 mL)
    a. Please refer to the GENERAL COMMENTS where appropriate.
    b. Please add the product strength to the top panel with the established name.
    c. Active ingredient: Please revise to read "30 mg dextromethorphan hydrobromide, USP" [add ", USP"].
    d. Uses, second bullet: Please revise to read "…to help you get to sleep" [add "to" before the word "sleep"].
    e. Directions: Please add "mL = milliliter" as the last bullet point, per RLD labeling.
    f. Other information: Please revise to read "Dosing cup provided" (b) (4)
    g. Inactive ingredients: Please add "sodium polystyrene sulfonate" to the list.
    h. Inactive ingredients: Please include the following in the list: "hydrochloric acid or sodium hydroxide solution, if required, to adjust the pH".
    i. Dosing chart on the right panel: Please add the following text: "mL = milliliter".
    j. Please revise the picture of the dosing cup in accordance with the recommendations in section 4 below.
4. DOSING CUP (10 mL)
    a. We acknowledge the document entitled, "PROTOCOL/REPORT OF SUITABILITY OF THE GRADUATION OF DOSAGE CUPS FOR LIQUID DOSAGE FORMS" and the "Specification Sheet" in section 3.2.P.7 of your submission. However, to help us further evaluate your proposed dosing cup, please provide a photograph of the actual, to be marketed dosing cup (front and back) as well as a comparison with the RLD's dosing cup. Please submit to both chemistry and labeling for full evaluation.
    b. We recommend that you add the established name above the dosing values.
    c. We recommend that you replace the current picture of the dosing cup on the container labels and carton labeling with one that depicts the front of the actual dosing cup, displaying the dosing values.
5. SPL
    a. Please revise the SPL in accordance with your revised labels and labeling.
    b. Data elements/Inactive Ingredients: Please add "sodium polystyrene sulfonate", "hydrochloric acid", and "sodium hydroxide" to the list.

Submit your revised labeling electronically in final print format.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained.

Prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the Electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17.

Note RPM - Labeling comments end here

REVISIONS NEEDED POST APPROVAL? No

NOTES/QUESTIONS TO THE CHEMIST/BIO REVIEWER/MICRO REVIEWER:
None.

Review Summary

Labeling Submitted	Date submitted	Final or Draft	Recommendation
CONTAINER (89 mL and 148 mL)	July 7, 2011 (received July 8, 2011)	Draft	Not Acceptable
CARTON (1 x 89 mL and 1 x 148 mL)	July 7, 2011 (received July 8, 2011)	Draft	Not Acceptable
SPL	July 7, 2011 (received July 8, 2011)	N/A	Not Acceptable

FOR THE RECORD:

1. **MODEL LABELING**

   The review is based on Delsym (NDA 018658/S-029 approved on May 16, 2011), held by Reckitt Benckiser. S-029 provided for change in the graphical layout for both the 3 fl. oz- and 5 fl. oz "adult" and "pediatric" orange and grape flavored carton and immediate container labels. In addition, this sNDA provides for the replacement of the term "vegetable oil" with "partially hydrogenated soybean oil" on the list of inactive ingredients found on the Drug Facts label.

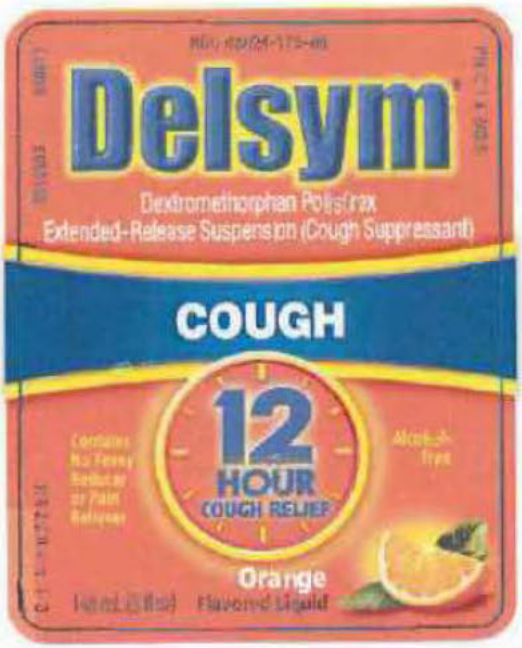
   S-028 (CMC supplement) approved on November 10, 2010, provided for alternate oval shaped immediate containers for the 3- and 5-fluid ounce packaging sizes: " *Your May 12,*

2010 correspondence notified us that the labels for the 5-fluid ounce grape and orange-flavored (pediatric) cartons and immediate containers are representative of the labels for the 3-fluid ounce grape and orange-flavored (pediatric) cartons and immediate containers. Also, the labels for the 3-fluid ounce (adult graphic) grape and orange-flavors cartons and immediate containers are representative of the labels for the 5-fluid ounce grape and orange-flavored (adult graphic) cartons and immediate containers. Any changes approved for this representative labeling will be incorporated into the labeling of the other package sizes, which are identical with the exception of the volume."

Pending RLD Supplements: S-030 submitted on December 23, 2013, proposes the following changes: Revision of the brand name to "Children's Delsym® and adding the modifier "Children's" above the brand name "Delsym®" on the pediatric labeling of the orange and grape-flavored SKUs.

RLD Container Labels

Container labels and carton labeling approved on 5/16/2011 (attached to the approval letter) :



OUTER LABEL

PEEL OPEN HERE TO READ COMPLETE WARNINGS AND INFORMATION ▶

TAMPER EVIDENT:
Do not use if the neckband printed with ☑ is broken or missing.

3-63824-17565-2

Lot:

Pt# C I A 60377
0313587
110310

INNER LABEL

USES: Temporarily relieves ■ cough due to minor throat and bronchial irritation as may occur with the common cold or inhaled irritants ■ the impulse to cough to help you get to sleep.

DIRECTIONS: SHAKE BOTTLE WELL BEFORE USING. Measure only with dosing cup provided. Do not use dosing cup with other products. Dose as follows or as directed by a doctor.

Adults and Children 12 years of age and over: 10 mL every 12 hours, not to exceed 20 mL in 24 hours. **Children 6 to under 12 years of age:** 5 mL every 12 hours, not to exceed 10 mL in 24 hours. **Children 4 to under 6 years of age:** 2.5 mL every 12 hours, not to exceed 5 mL in 24 hours. **Children under 4 years of age:** Do not use.

WARNINGS: Do not take this product for chronic cough that lasts as occurs with smoking, asthma, or emphysema, or if cough occurs with too much phlegm (mucus) unless directed by a doctor. If cough lasts more than 7 days, cough comes back, or occurs with fever, rash or headache that lasts, consult a doctor. These could be signs of a serious condition.

If pregnant or breast-feeding, ask a health professional before use.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

DRUG INTERACTION PRECAUTION: Do not use if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your prescription drug contains an MAOI, ask a doctor or pharmacist before taking this product.

ACTIVE INGREDIENT: Each 5 mL contains: dextromethorphan polistirex equivalent to 30 mg dextromethorphan hydrobromide.

OTHER INFORMATION: Each 5 mL contains: **sodium 7 mg.**

Store at 20-25°C (68-77°F).

Questions? 1-888-963-3382. You may also report side effects to this phone number.

BASE LABEL

Delsym®

COUGH

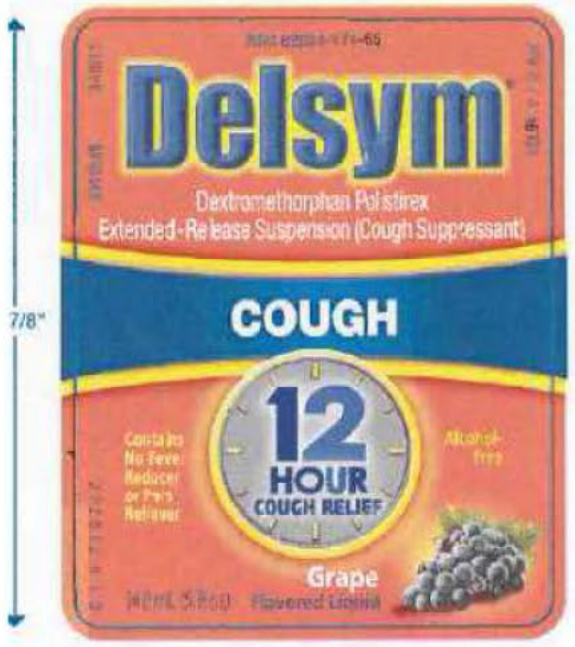
12
HOUR
COUGH RELIEF

Please visit our web site:
www.delsym.com

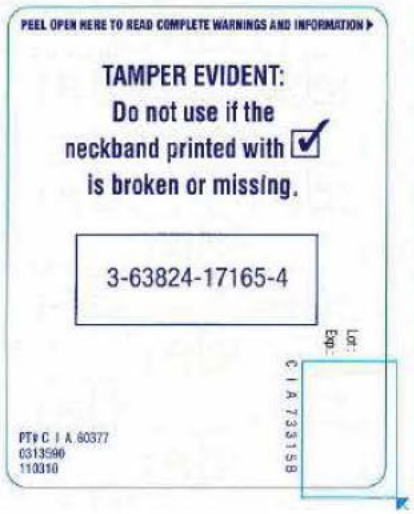
Dist. by: Reckitt Benckiser Inc.
Parsippany, NJ 07054-0224 ©RBI 2010


Right justified
Drug Facts
Active ingredient (In each 5 mL)
Purpose
Dextromethorphan polistirex equivalent to 30 mg dextromethorphan hydrobromide
Cough suppressant
Uses
temporarily relieves
cough due to minor throat and bronchial irritation as may occur with the common cold or inhaled irritants
the impulse to cough to help you get to sleep
Warnings
Do not use if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your prescription drug contains an MAOI, ask a doctor or pharmacist before taking this product.
Ask a doctor before use if you have
chronic cough that lasts as occurs with smoking, asthma or emphysema
cough that occurs with too much phlegm (mucus)
Stop use and ask a doctor if cough lasts more than 7 days, cough comes back, or occurs with fever, rash or headache that lasts. These could be signs of a serious condition.
If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.
Directions
shake bottle well before use
measure only with dosing cup provided
do not use dosing cup with other products
dose as follows or as directed by a doctor
mL = milliliter
adults and children 12 years of age and over: 10 mL every 12 hours, not to exceed 20 mL in 24 hours
children 6 to under 12 years of age: 5 mL every 12 hours, not to exceed 10 mL in 24 hours
children 4 to under 6 years of age: 2.5 mL every 12 hours, not to exceed 5 mL in 24 hours
children under 4 years of age: do not use
Other information
each 5 mL contains: sodium 7 mg
store at 20-25°C (68-77°F)
dosing cup provided
Inactive ingredients citric acid anhydrous, D&C Red #33, edetate disodium, ethylcellulose, FD&C Blue #1, flavor, high fructose corn syrup, methylparabens, partially hydrogenated vegetable oil (soybean, cottonseed), polyethylene glycol 3350, polysorbate 80, propylene glycol, propylparaben, purified water, sucrose, tragacanth, xanthan gum
Questions? 1-888-963-3382
You may also report side effects to this phone number
Reckitt Benckiser
Distributed by: Reckitt Benckiser Inc., Parsippany, NJ 07054-0224 ©RBI 2010
C I A 71975D
PT# C I A 80333
040511
6313591
2.5 pt. box barline
Bullets: 5 pt. solid square Zapf Dingbats
.5 pt. hairline
2 3/4"
1 11/16"
5 11/1
Code 128
71975D
12 Hour Cough Relief
Delsym
COUGH
Grape Flavored Liquid
NDC 63824-171-65
Dextromethorphan Polistirex Extended-Release Suspension (Cough Suppressant)
Also Available In Orange Flavor
Please visit our web site: www.delsym.com
PARENTS:
Learn about teen medicine abuse
www.StopMedicineAbuse.org
DAY OR NIGHT
12 HOUR COUGH RELIEF
148 mL (5 fl oz) Alcohol-free Grape Flavored Liquid
DELSYM® DOSING
SHAKE WELL BEFORE USE.
Measure only with dosing cup provided.
Do not use dosing cup with other products.
mL = milliliter
Age (yr) | Dose
12 years to adult: 10 mL EVERY 12 HOURS
6 to under 12: 5 mL EVERY 12 HOURS
4 to under 6: 2.5 mL EVERY 12 HOURS
Under 4: Do not use
See back panel for full dosing directions
Dosing Cup Included
Contains No Fever Reducer or Pain Reliever
3-63824-17165-4
(UPC @ 100% truncated)
0.5 pt. hairline
UPC area is 1/16" below score and is
Lot No.:
Exp. Date:

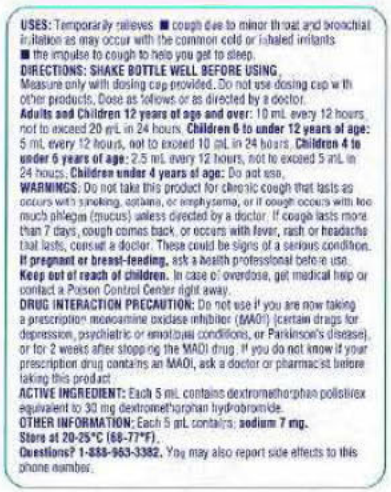
FRONT LABEL



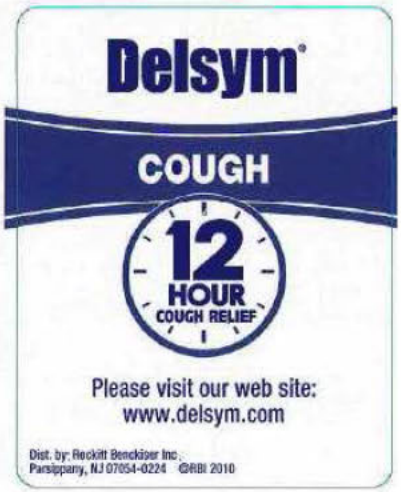
OUTER LABEL



INNER LABEL



BASE LABEL

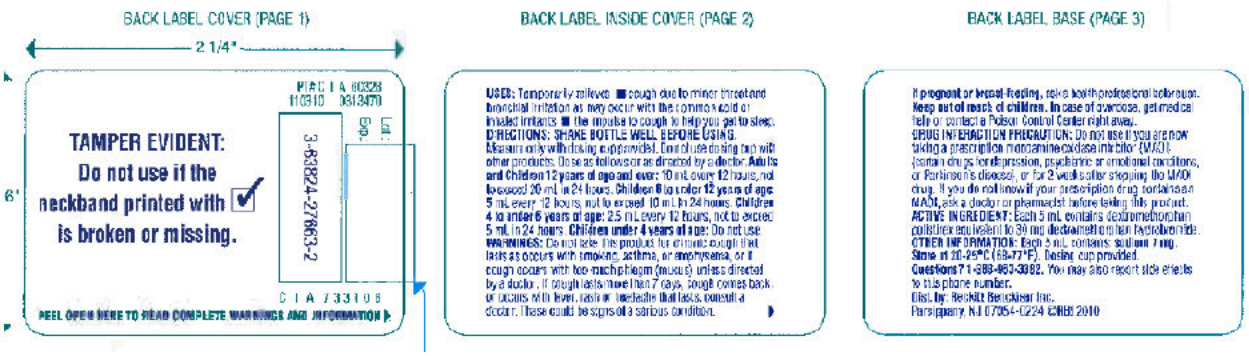


2 3/4"
1 11/16"
4 5/16"
Code 128
70234G
Drug Facts
Active ingredient (in each 5 mL)
Purpose
Dextromethorphan polistirex equivalent to 30 mg dextromethorphan hydrobromide
Cough suppressant
Uses temporarily relieves
■ cough due to minor throat and bronchial irritation as may occur with the common cold or inhaled irritants
■ the impulse to cough to help you get to sleep
Warnings
Do not use if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your prescription drug contains an MAOI, ask a doctor or pharmacist before taking this product.
Ask a doctor before use if you have
■ chronic cough that lasts as occurs with smoking, asthma or emphysema
■ cough that occurs with too much phlegm (mucus)
Stop use and ask a doctor if cough lasts more than 7 days, cough comes back, or occurs with fever, rash or headache that lasts. These could be signs of a serious condition.
If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.
Directions ■ shake bottle well before use
■ measure only with dosing cup provided
■ do not use dosing cup with other products
■ dose as follows or as directed by a doctor
■ mL = milliliter
adults and children 12 years of age and over
10 mL every 12 hours, not to exceed 20 mL in 24 hours
children 6 to under 12 years of age
5 mL every 12 hours, not to exceed 10 mL in 24 hours
children 4 to under 6 years of age
2.5 mL every 12 hours, not to exceed 5 mL in 24 hours
children under 4 years of age
do not use
Other information
■ store at 20-25°C (68-77°F)
■ each 5 mL contains: sodium 7 mg
■ dosing cup provided
Drug Facts (continued)
Inactive ingredients citric acid anhydrous, D&C Red #33, edetate disodium, ethylcellulose, FD&C Blue #1, flavor, high fructose corn syrup, methylparaben, partially hydrogenated vegetable oil (soybean, cottonseed), polyethylene glycol 3350, polysorbate 80, propylene glycol, propylparaben, purified water, sucrose, tragacanth, xanthan gum
Questions? 1-888-963-3382
You may also report side effects to this phone number
Also Available In Orange Flavor
PARENTS:
Learn about teen medicine abuse
www.StopMedicineAbuse.org
Reckitt Benckiser
Distributed by: Reckitt Benckiser Inc.
Parsippany, NJ 07054-0224
©RB 2010
12 Hour Cough Relief
Delsym
COUGH For Children & Adults
Grape Flavored Liquid
NDC 63824-172-63
Dextromethorphan Polistirex
Extended-Release Suspension (Cough Suppressant)
DAY OR NIGHT
12 HOUR COUGH RELIEF
89 mL (3 fl oz)
Alcohol-free
DELSYM® DOSING
Age (yr)
Dose
12 years to adult
10 mL EVERY 12 HOURS
6 to under 12
5 mL EVERY 12 HOURS
4 to under 6
2.5 mL EVERY 12 HOURS
Under 4
Do not use
Please visit our web site! www.delsym.com
Dosing Cup Included
Contains No Fever Reducer or Pain Relievers
3-63824-27263-4
(UPC @ 100% truncated)
Lot No.:
Exp. Date:
UPC area is 1/16"

Delsym
COUGH
12 HOUR
Grape

FRONT LABEL

2 1/4"



MedWatch (Checked on 2/4/14): No safety updates noted.

2. **USP** (Checked on 2/4/14): Drug product is not compendial.

   PF (Checked on 2/4/14): No updates noted.

3. **PATENT AND EXCLUSIVITY**

   Patent Data – NDA 018658

Patent No	Patent Expiration	Patent Use Code	Use	How filed	Labeling Impact
5980882	Apr 16, 2017			IV	None

Exclusivity Data– NDA 018658

There are no unexpired exclusivities listed in the Orange book for this drug product.

2. Paragraph IV Certification - Amneal certifies that, in its opinion and to the best of its knowledge, **US Patent Number 5980882** is invalid, unenforceable, and/or will not be infringed by the manufacture, use, or sale of Dextromethorphan Polistirex Extended Release

As required by FDC Act § 505(j)(2)(B)(i)-(iv) and 21 C.F.R. §§ 314.94(a)(12)(i)(A)(4) and 314.95, Amneal hereby states that not later than 20 days after the date of the postmark on the letter from FDA acknowledging that this submission is sufficiently complete to permit a substantive review, the company will send the required notice to the holder of NDA N018658 and to the owner of **US 5980882**. This notice, which will be sent by certified mail, return receipt requested, shall meet the requirements of FDC Act § 505(j)(2)(B)(iv) and 21 C.F.R. §§ 314.95(a) and (c).

Re: Dextromethorphan Polistirex Extended Release Oral Suspension, Equivalent to 30 mg/5 mL of Dextromethorphan Hydrobromide

Patent Amendment: Notice of Legal Action

ANDA # 203133: Sequence # 0005

In accordance with 21 CFR 314.107(f)(2), Amneal Pharmaceuticals hereby provides the Agency with a copy of the complaint served on Amneal Pharmaceuticals by **Reckitt Benckiser Inc.**, NDA **holder of the Reference Listed Drug** (**please see attached**) for **Delsym®** (Dextromethorphan Polistirex Extended Release Oral Suspension, equivalent to 30 mg/5 mL of Dextromethorphan Hydrobromide). Reference is made to the Patent Amendment dated October 7, 2011 (Sequence # 0004) in which Amneal notified the Agency of receipt of the patent notice by **Reckitt Benckiser Inc.** (b) (4)

4. **INACTIVE INGREDIENTS**

The listing of inactive ingredients on the carton labeling does not appear to be consistent with the listing of inactive ingredients found in the statement of components and composition. We will make recommendations.

Inactive ingredients

(b) (4)

Table 14. Description and Composition of the Drug Product

Ingredients	Quantity in mg/ 5 mL	mg per dose (Dose: 10 mL)	Quantity in %w/v	Quantity in %w/w[1]
Dextromethorphan Hydroboromide	30.00	60.00		
Sodium Polystyrene Sulfonate, USP				
Polyethylene Glycol 3350 NF				
Ethylcellulose, NF				
Corn Oil, NF				
Tragacanth NF				
Xanthan Gum, NF				
Propylene Glycol, USP				
Methylparaben, NF				
Propylparaben, NF				
Sucrose, NF				
Edetate Disodium, USP				
Citric Acid, USP				
Polysorbate-80 NF				
FD & C Yellow # 6				
Flavor				
Hydrochloric Acid, NF OR Sodium Hydroxide NF				
Purified Water, USP				

Each excipient is within the potency limits listed for an oral dosage form in the most current FDA/CDER Inactive Ingredient Guide (IIG).

Ingredients	Quantity %w/w	Maximum Potency From FDA's Inactive Ingredient database	Functions
Sodium Polystyrene Sulfonate, USP (b) (4)			(b) (4)
Polyethylene Glycol 3350 (b) (4) NF			
Ethylcellulose, NF (b) (4)			
Corn Oil, NF			
Tragacanth (b) (4) NF			
Xanthan Gum, NF			
Propylene Glycol, USP			
Methylparaben, NF			
Propylparaben, NF			
Sucrose, NF			
Edetate Disodium, USP			
(b) (4) Citric Acid, USP			
Polysorbate-80 (b) (4)			
FD & C Yellow # 6			
(b) (4) Flavor (b) (4)			

(b) (4)

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CONCLUSION:

From the above results (Table 13) of the sodium contents from the R&D batch, PE batch and ANDA submission batches; it was evident that the sodium content in the "Dextromethorphan Polistirex Extended Release Suspension Equivalent to 30 mg/5 mL of Dextromethorphan HBr" is about 7 mg in both RLD and Amneal's Proposed Generic Product.

Based on the above results; Amneal's container labels of Dextromethorphan Polistirex Extended Release suspension, equivalent to 30 mg/5 mL of the Dextromethorphan Hydrobromide are incorporated to include the statement of sodium contents as ***"7 mg of sodium per 5 mL of suspension"*** same as RLD Delsym®.

Note: Firm has included the following statement on the container labels and carton labeling:

Other Information: Each 5 mL contains: **sodium 7 mg.**

5. **MANUFACTURING FACILITY**

Company Name/ Address	Functions
	(b) (4)

6. **FINISHED PRODUCT DESCRIPTION**

RLD:

Available in grape and orange flavors.

ANDA:

The generic ANDA (b) (4) orange flavor, (b) (4)

Product Characteristics			
Color	ORANGE	**Score**	
Shape		**Size**	
Flavor	ORANGE	**Imprint Code**	

Package Size	89 mL Package Size		148 mL Package Size	
Batch #	ANDA Batch # BB-ST-10012A 	RLD Batch # 53045 	ANDA Batch # BB-ST-10012B 	RLD Batch # 54554 
Strength	30 mg/ 5 mL	30 mg/ 5 mL	30 mg/ 5 mL	30 mg/ 5 mL
Description	Orange colored suspension	Orange colored suspension	Orange colored suspension	Orange colored suspension
Density	1.120 g/mL	1.136 g/mL	1.120 g/mL	1.137 g/mL
Viscosity	270 cP	347 cP	280 cP	340 cP
pH	3.7	3.6	3.7	3.62

7. **STORAGE STATEMENT AND DISPENSING RECOMMENDATIONS**

RLD:

store at 20°-25°C (68°-77°F)

ANDA:

store at 20° to 25°C (68° to 77°F)

Satisfactory accelerated stability data (40ºC/75% RH) at 1, 2 & 3 months and 6 months controlled room temperature stability data for the drug product, Dextromethorphan Polistirex ER Suspension, equivalent to Dextromethorphan Hydrobromide Based on our satisfactory accelerated studies, a (b) (4) expiration-dating period is proposed and will be confirmed by controlled room temperature condition stability data (25ºC/60% RH). Our controlled room temperature Condition stability data will support the recommended storage conditions specified in the labeling:

Store at 20° C to 25° C (68° F to 77° F). Please refer following tables for overall stability trend and 3M accelerated comparison between 'upright' vs. 'sideways' orientation.

8. **PRODUCT LINE**

RLD:

5 fl oz (148 mL) grape (adult graphic)
5 fl oz (148 mL) grape (pediatric graphic)
3 fl oz (89 mL) grape (adult graphic)
3 fl oz (89 mL) grape (pediatric graphic)
3 fl oz (89 mL) orange (adult graphic)
3 fl oz (89 mL) orange (pediatric graphic)
5 fl oz (148 mL) orange (adult graphic)
5 fl oz (148 mL) orange (pediatric graphic)

ANDA:

1	NDC:65162-700-76	1 in 1 CARTON
1		89 mL in 1 BOTTLE
2	NDC:65162-700-77	1 in 1 CARTON
2		148 mL in 1 BOTTLE

9. **CONTAINER/CLOSURE**

The proposed container/closure systems consist of a 3 fl oz (b) (4) Round bottle *{Package size **3 fl oz (89 mL)**}* and 5 fl oz (b) (4) Round bottle *{Package size 5 fl oz **(148 mL)**}* (b) (4)

(b) (4)

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Device Suitability Testing			
Dosage cup used in this study * **Batch No. :** **QC Receiving No.:**			
Sr. No.	**Test**	**Specification**	**Results**
1.	Description	10 mL Dosage Cup with 2.5 mL, 5 mL and 10 mL graduations printed in black ink. (b) (4) [redacted]	Complies
2.	Graduation visibility and readability of marking	2.5 mL, 5 mL and 10 mL graduations printed in black ink.	Complies

*Attached COA

☒ The marking on the dosage cups meets the requirements of the delivery of specified volume.

Specification Sheet

(b) (4)

[redacted]

10. **RELATED APPLICATIONS**

None identified.

11. **SPL DATA ELEMENTS**

Revisions requested.

12. **CITIZENS PETITION/PROPRIETARY NAME/CONSULTS**

None.

Date of Review: February 4, 2014

Primary Reviewer: Manizheh Siahpoushan

Team Leader: Ruby (Chi-Ann) Wu

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

/s/

MANIZHEH SIAHPOUSHAN
02/05/2014

CHI-ANN Y WU
02/05/2014
for Wm. Peter Rickman

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 203133

CHEMISTRY REVIEWS

Recommendation:
ANDA: 203133 (Sequence # 0019)

☒ **Approval**
☐ **Information Request – Minor (30 days for applicant to respond)**
☐ **Complete Response - Minor**
☐ **Complete Response – Major**

ANDA # 203133

Amendment Review

Drug Name/Dosage Form	**Dextromethorphan Polistirex Extended Release Oral Suspension**
Strength	Equivalent to 30 mg Dextromethorphan Hydrobromide per 5 mL
Reviewer(s)	Mohammed Abd El-Shafy , Ph.D. /Sanna T Sander, Ph.D.
Applicant	**Amneal Pharmaceuticals ("Amneal")**

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Quality Amendment, Sequence # : 0019 (21)	06/08/2017
Quality Amendment, Sequence #: 0017 (20)	05/02/2017
Quality Amendment, Sequence #: 0016 (18)	02/06/2017
Quality Amendment, Sequence #: 0014 (16)	07/14/2016

DMFs:

DMF #	HOLDER	ITEM REFERENCED	STATUS*	*REVIEW COMPLETE	Reviewer
(b) (4)			Adequate (Rev#10)	03/28/2014 *05/25/2016 NAI* 07/06/2017	Ahmed, M B Gaddam
			Adequate (Rev #16, #17)	01/05/2016 *06/21/2017 NAIAQ*	Takiar, NB Skanchy, D
Type III DMF	Refer to Section 2.3.P.7 below for the list of Type III DMFs referenced by the applicant				

(b) (4)	Adequate [2]	01/12/2009	BERTHA, CRAIG M
	N/A (sufficient information in ANDA)	N/A	N/A

(b) (4)

CONSULTS:

** Last checked 03OCT2016*

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION*	DATE*	REVIEWER
Microbiology	N/A (oral, non-sterile dosage form)	N/A	N/A
Methods Validation	N/A	N/A	N/A
Labeling	Adequate	07/27/2016	SIAHPOUSHAN, MANIZHEH
Bioequivalence	Dissolution - Adequate, *DBE Specifications accepted*	01/16/2013	WAHBA, ZAKARIA Z
	BE adequate	12/15/2016	Chunsheng Zhao
Toxicology/Clinical	Consult regarding level of (b) (4)	12/14/2011	Wafa Harrouk, Ph.D.
EA	Categorical Exclusion request per 21CFR25.31(a) see Section 1.12.14	N/A	N/A
Radiopharmaceutical	N/A	N/A	N/A
Samples Requested	Visual samples requested	Rev #01, Comment #32	Sander, Sanna T

(b) (4)

(b) (4)

FACILITIES:

Overall Recommendation:
Approve (12/14/2016) . [No change 06/02/2017 or 06/13/2017]

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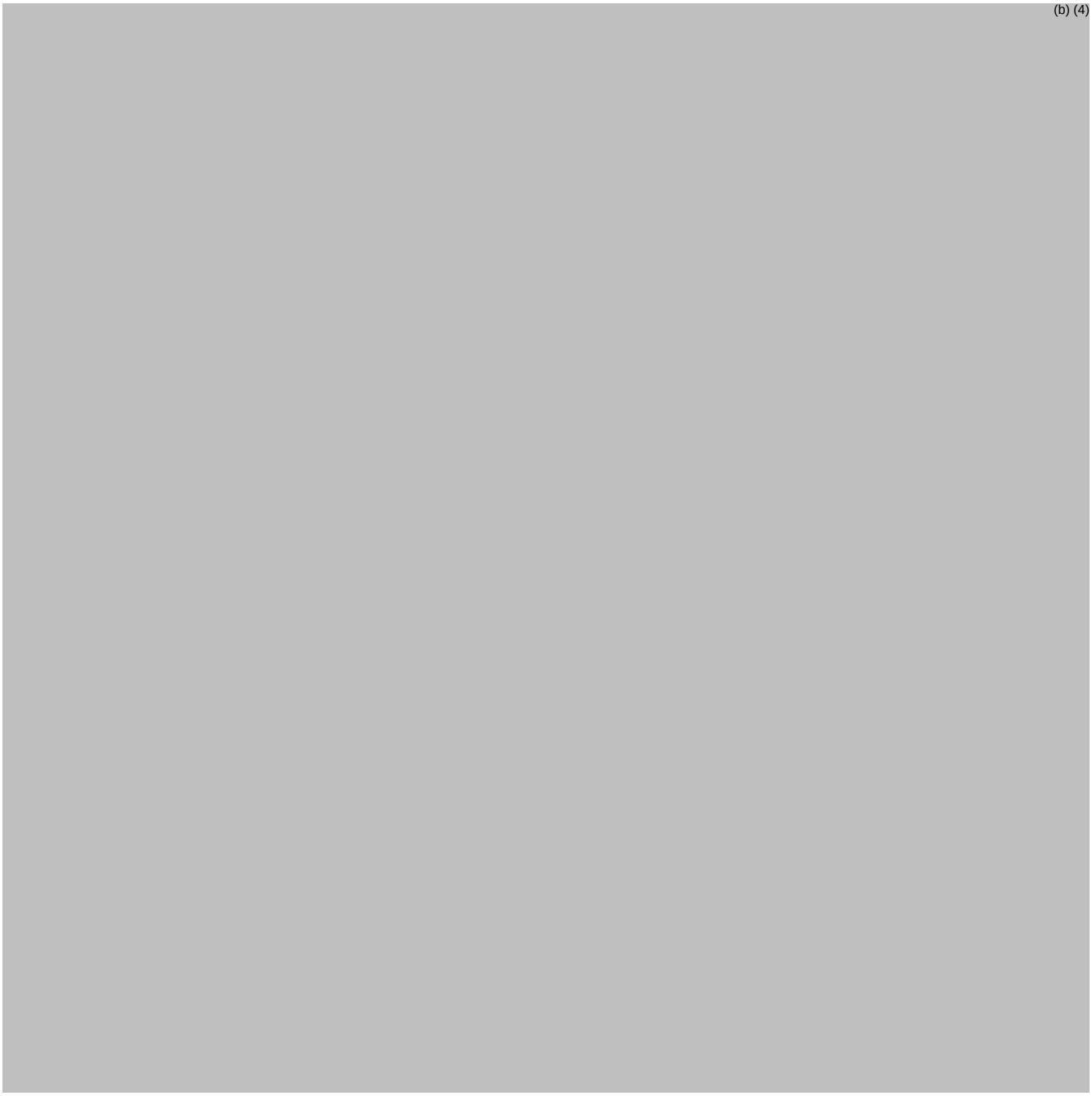
Note – A DPQ Review Summary and current status is included at the end of this review within the Primary / Secondary reviewer assessments (link : DP Review Summary after Sequence 0019:), and after the updated summary of current Module 3/eCTD information (link : C. UPDATED SUBMISSION (Sequence 0014 to 0019) -- included are recent DS/DP specifications, in process tests etc.

(b) (4)



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CHECKLIST FOR THE CHEMISTRY REVIEW:

ANDA 203133

Dextromethorphan Polistirex Extended Release Oral Suspension equivalent to 30 mg/5 mL of Dextromethorphan Hydrobromide

Camille Smith, RBPM

Function	**Performed By (Initial and Date)**	**Check appropriate box**
Is this package for new strength PAS?	RBPM	☐ Yes ☒ No
DMF adequate?	RBPM	☒ Yes ☐ No *(see comments)
Any outstanding consults?	RBPM	☐ Yes *(see comments) ☒ No
Final recommended dissolution method/specification acknowledged by Firm?	DD, BC or designee	☒ Yes* ☐ No ☐ N/A
Are all facility inspections acceptable?	RBPM	☒ Yes ☐ No
Is microbiology recommendation adequate for sterile products?	RBPM	☐ Yes ☐ No ☒ N/A
Are there comparability protocols provided? If yes, how many?	DD, BC, or designee	☐ Yes How many:_____ ☒ No *
If USP monograph exists, do the specifications conform to the current USP?	DD, BC or designee	☐ Yes ☒ No *(see comments) ☐ N/A
Is the final review uploaded into the current IT platform?	RBPM	☒ Yes ☐ No
* Dissolution specifications accepted with Seq 0016 amendment. No USP monograph for DP (as of USP40); applicant acknowledged Drug Product will be compliant with elemental impurities (b) (4) starting 01Jan2018 (no supporting data to date). No comparability protocols as of Seq 0019.		

Division	Name	Date
OMPT/CDER/OPQ/OLDP/DMRP/MRBIII	Sanna Sander	7-17-2017

Camille Smith

Digitally signed by Camille Smith
Date: 7/16/2017 02:46:15PM
GUID: 56268f11002393c2a965ba586399e57f

Sanna Sander

Digitally signed by Sanna Sander
Date: 7/17/2017 05:45:20PM
GUID: 51dc6d2e0000c649fbc009a8f0773910

A. Check List

Solid IR/Oral Sol. RPN < 60 or Injection/Ophthalmic Q1/Q2 = RLD – 2 Tier	☐
First Generic – 3 Tier	☐
Other Criteria under "Exceptions List" for Table 1 of SOP – 3 Tier **[RPN > 60]**	☒

B. Approvability: – ***No, MINOR [1] Deficiency / IR LETTER (30 days)***

ANDA 203133

Dextomethorphan Polistirex Extended Release Oral Suspension,
Equivalent to 30 mg Dextromethorphan HBR per 5 mL

Amneal Pharmaceuticals

Sanna T Sander, Ph.D.
OPQ-OLDP-DMRP

[1] Defined as per Memo of Thu 3/26/2015 regarding MAJOR versus MINOR deficiencies, applicable to MR Drug Products only

Table of Contents

Chemistry Review Data Sheet

1. ANDA ######: 203133

2. REVIEW #: 01

3. REVIEW DATE: 12/22/2014

4. REVIEWER: Sanna T. Sander, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Document(s)	Document Date
N/A	N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
New/ANDA	07/07/2011 (Sequence 0000)
Quality/Quality Information	09/01/2011 (Sequence 0002)
Quality/Quality Information	09/16/2011 (Sequence 0003)
Quality/Dissolution Data	02/12/2013 (Sequence 0011)

7. NAME & ADDRESS OF APPLICANT:

Name:	Amneal Pharmaceuticals
Address:	85 Adams Avenue, Hauppauge, NY 11788 USA
Representative:	Alpesh Patel, Vice President, Global Regulatory Affairs. alpesh@amneal.com
Telephone:	(b) (6)

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name:	N/A
Non-Proprietary Name (USAN):	Dextromethorphan Polistirex Extended Release Oral Suspension

9. LEGAL BASIS FOR SUBMISSION:

Reference Listed Drug:

Active Ingredient:	DEXTROMETHORPHAN POLISTIREX
Dosage Form;Route:	SUSPENSION, EXTENDED RELEASE;ORAL
Proprietary Name:	**DELSYM**
Applicant:	**RECKITT BENCKISER**
Strength:	EQ 30MG HBR/5ML
Application Number:	**N018658**
Approval Date:	Oct 8, 1982
Reference Listed Drug	Yes
RX/OTC/DISCN:	OTC

Patent Data:

Appl No	Prod No	Patent No	Patent Expiration	DS Claim	DP Claim	Patent Use Code	Delist Requested
N018658	001	5980882	Apr 16, 2017		Y		

Exclusivity Data: There is no unexpired exclusivity for this product.

10. PHARMACOL. CATEGORY: Cough Suppressant, Antitussivum

11. DOSAGE FORM: Suspension

12. STRENGTH/POTENCY: Equivalent to 30 mg Dextromethorphan HBR per 5ML

13. ROUTE OF ADMINISTRATION: Oral

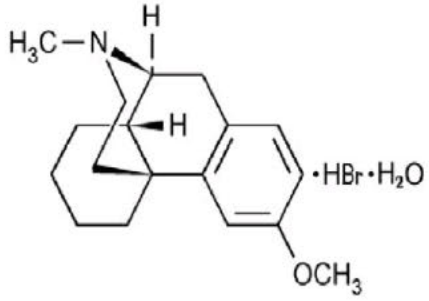
14. Rx/OTC DISPENSED: **OTC**

15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCT TRACKING: Not a NANO product

15c. PRECEDENT: Not a Precedent

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name	Morphinan, 3-methoxy-17-methyl-, (9,13,14)-, hydrobromide, monohydrate 3-Methoxy-17-methyl-9,13,14-morphinan hydrobromide monohydrate
CAS#	[6700-34-1]
USAN:	Dextromethorphan Hydrobromide, USP
Molecular Structure:	
Molecular Formula:	$C_{18}H_{25}NO \cdot HBr \cdot H_2O$
Molecular Weight:	370.32

Note – from A091135 and included for information here by Reviewer:

(b) (4)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMF(s): ** Last checked 24DEC2014*

DMF #	HOLDER	ITEM REFERENCED	STATUS*	*REVIEW COMPLETE	Reviewer
		(b) (4)	Adequate	03/28/2014 *additional LOAs received*	AHMED, MOHAMMED K
			Adequate *with IR*	04/14/2011 *Response received 05/03/11, & AR's*	TAKIAR, NEERU B
Type III DMF	Refer to Section 2.3.P.7 below for the list of Type III DMFs referenced by the applicant				
		(b) (4)	Adequate [2]	01/12/2009	BERTHA, CRAIG M
			N/A (sufficient information in ANDA)	N/A	N/A

1 (b) (4)

[2] Later submissions not reviewed – sufficient information included in or requested for A203133.

B. Other Documents referenced:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
RLD	NDA018658	Delsym [R], by Reckitt Benckiser
Previously Approved ANDA (Only ANDA in Orange book)	A091135	Dextromethorphan Polistirex ER Oral Suspension
Previously Approved ANDA referencing Dextromethorphan (b) (4)	ANDA090575	Promethazine Hydrochloride and Dextromethorphan Hydrobromide Oral Solution, 6.25 mg/5 mL and 15 mg/5 mL by Amneal Pharma, approved 02/.08/2011

18. STATUS

** Last checked 24DEC2014*

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION*	DATE*	REVIEWER
Microbiology	N/A (oral, non-sterile dosage form)	N/A	N/A
Methods Validation	N/A	N/A	N/A
Labeling	Inadequate (minor)	02/05/2014	SIAHPOUSHAN, MANIZHEH
Bioequivalence	Dissolution - Adequate, *DBE Specifications accepted*	01/16/2013	WAHBA, ZAKARIA Z
	BE pending	N/A	N/A
Toxicology/Clinical	Consult regarding level of (b) (4)	12/14/2011	Wafa Harrouk, Ph.D.
EA	Categorical Exclusion request per 21CFR25.31(a) see Section 1.12.14	N/A	N/A
Radiopharmaceutical	N/A	N/A	N/A
Samples Requested	Visual samples requested *[Dextromethorphan HBr is not listed as a controlled substance per http://www.deadiversion.usdoj.gov /schedules/]*	Rev #01	Sander, Sanna T

[1] Excerpt from the Consult Report:

(b) (4)

(b) (4)

[redacted]

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ☒ Yes ☐ No If no, explain reason(s) below: N/A

20. EES INFORMATION*

** GDRP and facility alerts last checked 24DEC2014*

Overall Recommendation:
None of the facilities below are Alert listed on 24 DEC2014*

2 Page(s) have been Withheld as b4 (CCI/TS) immediately following this page

Chemistry Review for ANDA 203133

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

(b) (4)

(b) (4)

(b) (4) The orange flavor suspension (b) (4) for the commercial (b) (4)

(b) (4)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

(b) (4)

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(b) (4)

[redacted]

(b) (4)

[redacted]

Steps	(b) (4)
Packaging	Supplied in [Multi-Dose container] : Orange Flavor Suspension. 89 mL (3 oz) and 148 mL (4 oz): (b) (4) (b) (4) **A dosing cup is provided**. A (b) (4) shrink band is added around the cap, (b) (4) *Note – current submission includes orange flavor suspension* (b) (4) (b) (4)
Labeled Storage	Store at 20° to 25°C (68° to 77°F)
Analytical Methods	(b) (4)
Proposed DP expiration	(b) (4)
Maximum Daily Dose:	MDD Dextromethorphan HBr: (Adult) No more than 20 mL in 24 hours, per RLD labeling [3], equivalent to 120 mg DXM HBr per day

[3] *Package insert :* 'DOSAGE & ADMINISTRATION: (b) (4)

Per MDD [120 mg Dextromethorphan HBr per day] and ICH guideline Q3A/B:

ICH Guideline Threshold for	Reporting Threshold **(RT)**	Identification Threshold **(IT)**	Qualification Threshold **(QT)**
Drug Substance	0.05%	0.10% *	0.15% *
Drug Product	0.1%	0.2% **	0.2% **

* Per *ICH Q3A: at ≤2g/day MDD: IT is '0.10 % OR 1.0 mg whichever is lower', QT is '0.15 % OR 1.0 mg whichever is lower'. Calculation: 1.0 mg / 60 mg = 1.6% is higher. Thus, DS limits of IT = 0.10 % and QT=0.15 % apply.*

** Per *ICH Q3B: at >10mg to2g/day MDD: IT is '0.2 % OR 2 mg whichever is lower', at > 100 mg to 2 g/day, QT is '0.2 % OR 3 mg, whichever is lower'. Calculations: 2 mg / 120 mg =1.67 %; 3 mg / 120 mg = 2.5 %; thus, DP limits of IT =QT= 0.2 % apply.*

B. Description of How the Drug Product is Intended to be Used

Indication	Dextromethorphan Polistirex Suspension is a cough suppressant which temporarily relieves • cough due to minor throat and bronchial irritation as may occur with the common cold or inhaled irritants • the impulse to cough to help you get to sleep
Duration of Therapy	Duration of therapy is labeled for up to one week ('stop use and ask a doctor if cough lasts more than 7 days, cough comes back, or occurs with fever, rash or headache that lasts. These could be signs of a serious condition').
Dosing Instructions and Special Dosing Instructions	**SHAKE BOTTLE WELL BEFORE USING.** ***Directions*** ■ **shake bottle well before use** ■ measure only with dosing cup provided. Do not use dosing cup with other products. ■ dose as follows or as directed by a doctor ■ mL = milliliter adults and children 12 years of age and over: 10 mL every 12 hours, not to exceed 20 mL in 24 hours children 6 to under 12 years of age: 5 mL every 12 hours, not to exceed 10 mL in 24 hours children 4 to under 6 years of age: 2.5 mL every 12 hours, not to exceed 5 mL in 24 hours children under 4 years of age: do not use ***Other information*** ■ store at 20-25°C (68-77°F) ■ each 5 mL contains: **sodium 7 mg** ■ dosing cup provided
Alternate Administration	No alternate administration of the Dextromethorphan Polistirex Suspension is labeled.

FDA recommended Dissolution Method for Dextromethorphan Polistirex Suspension (Extended Release)

USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Sam (
II (Paddle)	50	0.1 N HCl	500	30, 60,

(b) (4)

D. Basis for Approvability or Not-Approval Recommendation

The CMC section of this ANDA is currently not approvable per updated risk assessment and currently implemented control strategy which includes deficiencies to be addressed.

(b) (4)

Chemistry Assessment

I. Review of Common Technical Document-Quality (Ctd-Q) Module 3.2

2.3 Introduction to the Quality Overall Summary

Proprietary Name of Drug Product	N/A
Non-Proprietary Name of Drug Product	**Dextromethorphan Polistirex Extended Release Oral Suspension,** equivalent to 30 mg /5 mL of Dextromethorphan Hydrobromide
Non-Proprietary Name of Drug Substance	Dextromethorphan Hydrobromide
Company Name	Amneal Pharmaceuticals, USA
Dosage Form	Oral Suspension
Strength(s)	equivalent to 30 mg/5 mL of Dextromethorphan Hydrobromide
Route of Administration	Oral
Proposed Indication(s)	Temporarily relieves • cough due to minor throat and bronchial irritation as may occur with the common cold or inhaled irritants • the impulse to cough to help you get to sleep
Maximum Daily Dose	Up to 120 mg / day (Refer to Module 1.14.1.3 – Amneal's Package insert)

(b) (4)

ADMINISTRATIVE

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date: Sanna T Sander, January 16, 16 April 2015
Chemistry Team Leader Name/Date: N/A
Project Manager Name/Date: Brijet Burton
DD/DDD Name/Date: Bhagwant Rege, 08 April 2015

TYPE OF LETTER: NOT APPROVABLE (MINOR / IR [14])

[14] As per Memo of Thu 3/26/2015 regarding MAJOR versus MINOR deficiencies for MR Drug Products only (by B Rege, G Smith, S Rosencrance), this ANDA has MINOR deficiencies as we do not ask for a reformulation (albeit for several additional controls).

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 203133

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	203113	
Drug Product Name	Dextromethorphan Polistirex Extended Release Oral Suspension	
Strength(s)	EQ 30 mg dextromethorphan hydrobromide (HBr)/5 mL	
Applicant Name	Amneal Pharmaceuticals	
Applicant Address	85 Adams Avenue Hauppauge, NY USA 11788	
Applicant Point of Contact	Alpesh Patel, Vice President - Global Regulatory Affairs	
Contact's Telephone Number	(b) (6)	
Contact's Fax Number	(631) 527-3523	
Contact's Email Address	alpesh@amneal.com	
Original Submission Date(s)	July 08, 2011 (Original Submission) August 25, 2011 (1st telephone amendment) September 02, 2011 (2nd telephone amendment, Pharm/Tox report for sodium polystyrene sulfonate) April 24, 2012 (1st dissolution amendment, already reviewed) June 15, 2012 (2nd dissolution amendment, already reviewed) August 9, 2012 (3rd dissolution amendment, already reviewed) January 7, 2013 (4th dissolution amendment, already reviewed)	
Submission Date(s) of Amendment(s) Under Review	07/14/2016 (Post Complete Response Amendment) 11/10/2016 (Response to ECD)	
Reviewer	Chunsheng Zhao, Ph.D.	
Study Number (s)	ARL/10/408	ARL/10/409
Study Type (s)	Fasting	Fed
Strength (s)	2 x EQ 30 mg HBr/5 mL	2 x EQ 30 mg HBr/5 mL
Clinical Site	Accutest Research Laboratories (I) Pvt. Ltd.	
Clinical Site Address	A-31, M.I.D.C., T.T.C., Industrial Area, Khairane, Navi Mumbai-400 709, INDIA.	
Analytical Site	(b) (4)	
Analytical Site Address		
OSIS Status	**Backlog, Year 1 and Year 2 ANDAs** ☐ **Pending** ☒ **Complete**	**Year 3 ANDAs** ☐ **To Be Determined by OSIS** ☐ **Pending For Cause Inspection**
OVERALL REVIEW RESULT	**ADEQUATE**	
REVISED/NEW DRAFT GUIDANCE INCLUDED	**NO**	
DEFICIENCY	☐ **Major**	

CLASSIFICATION	☐ Minor IR Eligible? ☐ Yes ☐ No (Deficiency to be communicated in an ECD letter) ☒ Not Applicable		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
1, 2, 4, 9, 10, 12, 16, 17	**FASTING**	**EQ 30 mg HBr/5 mL**	**ADEQUATE**
1, 2, 4, 9, 10, 12, 16, 17	**FED**	**EQ 30 mg HBr/5 mL**	**ADEQUATE**

REVIEW OF AN AMENDMENT

1. EXECUTIVE SUMMARY

This is a review of an amendment related to the deficiencies issued to the firm in the Complete Response (CR) letter dated 07/14/2015[1]. The deficiency comments include: 1) lack of complete (100%) analytical raw data for the fasting (#ARL/10/408) and fed (#ARL/10/409) BE studies; 2) lack of concentration and pharmacokinetic SAS dataset of dextromethorphan for the fasting study (#ARL/10/408), (b) (4) (b) (4) orange flavored test product formulation was provided).

In the original submission dated 07/08/2011, Amneal Pharmaceuticals submitted the results of fasting (#ARL/10/408) and fed (#ARL/10/409) bioequivalence (BE) studies comparing the test product, Dextromethorphan Polistirex Extended Release Oral Suspension, EQ 30 mg HBr/5 mL to the corresponding reference product, RECKITT BENCKISER LLC's Delsym® (dextromethorphan polistirex) Extended Release Suspension, EQ 30MG HBr/5mL. Each of the BE studies was designed as a single-dose, two-way crossover study in healthy male and female subjects.

In the amendment dated 07/14/2016, the firm's response to the CR letter is found inadequate due to lack of analytical raw numerical data for the fed BE study (#ARL/10/409). The deficiency was communicated to the firm via an Easily Correctible Deficiency (ECD) letter on 11/08/2016, and the firm submitted its response on 11/10/2016. The firm's response is found adequate. As a result, the firm's fasting (#ARL/10/408) and fed (#ARL/10/409) BE studies are considered adequate.

Per original BE review[2], the office of study integrity and surveillance (OSIS) inspection status of the clinical and analytical sites for the current ANDA is considered completed.

As a result, the application is **adequate** without deficiency.

---

[1] GDRP ANDA 203133, Final Decision, Denise Toyer McKan, Completed: 7/14/2015. http://panorama fda.gov/task/view?ID=542136470047406b6dd7f1a8623d20d8d

[2] GDRP ANDA 203133, Bioequivalence Primary Review, Yun Wang, Completed: 2/24/2015. http://panorama fda.gov/task/view?ID=5421364700474401dfd8c6cba43c65580

2. TABLE OF CONTENTS

3. SUBMISSION SUMMARY

3.1 Background

- According to the Orange Book (OB), this is an over-the-counter (OTC) product[3]. There is product-specific draft bioequivalence (BE) guidance available for Dextromethorphan Polistirex Extended Release Oral Suspension[4]. The guidance recommends the BE should be established based on 90% CI of parent drug dextromethorphan, and the active metabolite (dextrorphan) data as supportive evidence of comparable therapeutic outcome.

  In the original submission, the firm submitted the results of fasting (No. ARL/10/408) and fed (No. ARL/10/409) BE studies comparing a test product , Amneal Pharmaceuticals' Dextromethorphan Polistirex Extended Release Oral Suspension, EQ 30 mg HBr/5 mL, to the corresponding reference product, RECKITT BENCKISER LLC's Delsym® (dextromethorphan polistirex) Extended Release Oral Suspension, EQ 30MG HBr/5mL. Each of the BE studies was designed as a single-dose, two-way crossover study in healthy male and female subjects.

- The firm submitted the plasma concentration and pharmacokinetic (PK) data for the parent drug, dextromethorphan and active metabolite, dextrorphan. The data for the active metabolite (dextrorphan) is provided as supportive evidence. BE evaluation was made based on the data of the parent compound (dextromethorphan). The results of dextromethorphan are summarized in the tables below (firm calculated):

Fasting Study (ARL/10/408)

Parent Drug: Dextromethorphan Dextromethorphan Polistirex Extended Release Suspension, EQ 30 mg HBr/5 mL Dose (2X EQ 30 mg Dextromethorphan HBr), N=53 (Male = 44 and Female = 9) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasted Bioequivalence Study (Study No. ARL/10/408)					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng*hr/mL)	25.06	23.31	107.53	102.60	112.69
AUC0-inf (ng*hr/mL)	25.51	23.74	107.44	102.57	112.54
Cmax (ng/mL)	1.97	1.77	111.26	106.58	116.14

[3] Electronic Orange Book, search: Delsym; Last accessed Feb 10, 2015

[4] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm085592.pdf

Fed Study (ARL/10/409)

Parent Drug: Dextromethorphan Dextromethorphan Polistirex Extended Release Suspension, EQ 30 mg HBr/5 mL Dose (2 X EQ 30 mg Dextromethorphan HBr), N=53 (Male = 43 and Female = 10) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study (Study No. ARL/10/409)					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng*hr/mL)	34.92	33.63	103.84	96.8629	111.3172
AUC0-inf (ng*hr/mL)	35.53	34.21	103.87	96.9404	111.2928
Cmax (ng/mL)	2.38	2.29	104.16	95.8039	113.2506

- Per original BE review [**GDRP, ANDA 203133, Bioequivalence Primary Review, Yun Wang(4), Completion Date: 2/24/2015**][5], the PK parameters of the test and reference for the active metabolite (dextrorphan) were comparable. However, the application was found inadequate due to 1) inadequate fasting and fed BE studies as a result of lack of complete analytical raw data for both the fasting and fed BE studies, and lack of concentration and pharmacokinetic data of dextromethorphan in SAS transport files (.xpt) for fasting BE study; (b) (4) orange flavored test product formulation was provided).

- The deficiencies were communicated to the firm via Complete Response (CR) letter issued on 07/14/2015[6]. The firm then submitted its responses for aforementioned deficiencies issued by the Division of Bioequivalence III (DBIII) in an amendment dated 07/14/2016. The firm's response was originally found inadequate due to failure to submit 100% raw numerical data for its fed BE study (#ARL/10/409), and the deficiency was communicated to the firm via an ECD letter on 11/08/2016. The firm submitted its response to the ECD letter on 11/10/2016.

3.2 Drug Product Information and Relevant DB History

The drug information[7] has not changed since the most recent review completed on 2/24/2015. For more information, please refer to the following reviews and draft guidance:

- GDRP, ANDA 203133, Wang, Yun, Bioequivalence Primary Review, Completion Date: 2/24/2015.
  http://panorama.fda.gov/task/view?ID=542136470047401dfd8c6cba43c65580

[5] GDRP, ANDA 203133, Bioequivalence Primary Review, Yun Wang(4), Completion Date: 2/24/2015. http://panorama fda.gov/task/view?ID=542136470047401dfd8c6cba43c65580
[6] GDRP, ANDA 203133, http://panorama.fda.gov/task/view?ID=54213647004740b6dd7f1a8623d20d8d
[7] Drugs@FDA, RLD labeling, http://www.accessdata fda.gov/drugsatfda_docs/label/2014/018658Orig1s030lbl_replacement.pdf

- Guidance on Dextromethorphan Polistirex Extended Release Oral Suspension (*Finalized May 2008*) http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm085592.pdf

4. CONTENT OF SUBMISSION

Study Types	Yes/No?	How many?
Single-dose fasting (Pivotal)	-	-
Single-dose fed	-	-
Steady-state	-	-
Single-dose fasting and fed (Pilot)	-	-
In vitro dissolution	-	-
Waiver requests	-	-
BCS Waivers	-	-
Clinical Endpoints	-	-
Failed Studies	-	-
Amendment	Yes	2

5. REVIEW OF CURRENT AMENDMENT

The firm's response to the three (3) deficiencies on 7/14/2016, the ECD letter on 11/10/2016, and the reviewer's evaluations of those responses are provided in this section of the review.

Deficiency #1:

You did not submit ALL analytical raw numerical data. Please provide complete (100%) raw numerical data, in the instrument printout format, including original and repeated analysis for all samples, including the data of peak area/height for the analyte, peak area/height for the internal standard, ratio of the peak area/height for the analyte to the peak area/height for the internal standard, dilution factor (if any), and the corresponding concentration for each assayed and reassayed sample of all samples, calibration standard concentration samples, and quality control samples for your fasting (#ARL/10/408) and fed (#ARL/10/409) BE studies.

Firm's Response to Deficiency #1:

Amneal acknowledges the Agency's comment and requested all analytical raw numerical data from (b) (4)

Please note that as per section VII(c) of the Guidance for Industry "Bio-analytical Method Validation", May 2001; "For pivotal bioequivalence studies for marketing, chromatograms

from 20% of serially selected subjects should be included." Based on this requirement, chromatograms for 20% of subject were included in the reports for both studies.

For Study #ARL/10/408 (Fasting), a total of 58 subjects were enrolled in the study, samples for Subject No. (b) (6) (withdrawn due to adverse event in period II) were discontinued from study and were not analyzed as per Principal Investigator's discretion (refer to the original application Sequence 0000). Please refer to Module 5.3.1.4 for **raw numerical data** for this study in the requested format.

For Study #ARL/10/409 (Fed), a total of 58 subjects were enrolled in the study. The samples from 4 subjects; Subject No (b) (6) (withdrawn due to non-compliance to fed condition in period I), Subject No. (b) (6) (withdrawn due to adverse event in period I), Subject No. (b) (6) (withdrawn due to personal reasons before dosing in period I) and Subject No. (b) (6) (withdrawn due to adverse event in period II) were discontinued from study and were not analyzed as per Principal Investigator's discretion (refer to the original application Sequence 0000).

Subject No. (b) (6) showed pre-dose concentration greater than 5% of C_{max} in period II. The samples for this subject were analyzed but were not considered for calculation of bioequivalence result as per section **8.0 Statistical Plan** of the Study Protocol. Please refer to Module 5.3.1.4 for **raw numerical data** for this study in the requested format.

Additionally, there were two batches (REPETITION01 and REPETITION02) that were repeated under Code-A (sample outside assay range). The sample list report (Sequence) for these two batches demonstrates that samples were repeated with dilution factor (User Divisor). Please refer to **Module 5.3.1.4** for the sample list report for the Study #ARL/10/409 (Fed).

Reviewer's Comments on Firm's Response to Deficiency #1: The firm's response to Deficiency #1 is **adequate.**

- In the amendment dated 07/14/2016, the firm submitted all raw data for dextromethorphan and dextrorphan in the fasting BE study. However, the firm only provided a repeat list for reassay samples, but not provided the original raw numerical data for repeat samples for the fed BE study. Therefore, the reviewer could not verify the fed study repeats and batch rejection. The firm was then asked to submit the complete raw numerical data for calibration standards, QC samples and study samples, such as peak area of analyte and internal standard, calculated concentration, etc. for all subject samples (assayed and reassayed) in the fed BE study via an ECD letter on 11/08/2016. The firm submitted its response on 11/10/2016 and provided the information.

- The reviewer's evaluation for the fasting study repeat is discussed as below:

    1. Repeat Analysis due to "sample outside assay range":

Per the original BE review, there were one hundred and fifty seven (157) samples in the fasting study that were reanalyzed for dextromethorphan under the reason of "sample outside assay range". The firm submitted all raw data for the fasting BE study. As subject No.(b) (6) was excluded for dextromethorphan due to pre-dose concentrations exceeding 5% of Cmax, which was in accordance with the firm's protocol (Study Code: ARL/10/408, Version 03), the reviewer did not further check reassays for this subject but verified the pre-dose concentration for subject No(b) (6) in Period II (1.595 ng/mL) is more than 5% of Cmax (19.010 ng/mL) of the respe ive period. The reviewer notes that the original measured concentrations of these samples exceed the ULOQ (10.095 ng/mL). The repeat analysis listed in Table 7.8.1 in the firm's fasting BE bioanalytical report were selected according to SOP (b) (4) (Standard Operating Procedure For Repeat Sample Analysis, Effective Date: (b) (4)). All the reassayed values after correction with the dilution factor were ≥85% of the ULOQ.

2. There were also two (2) samples (05/X/T08 and 06/Y/T01) in the fasting study reanalyzed for dextrophan under the reason "Inconsistent Internal Standard Area Response":

7.8.3 Sample Repeat Analysis of Dextrorphan: Analytical Repeat:

Sr. No.	Sample ID	Assay-1 Conc. (ng/mL)	Run ID	Code	Assay-2 Conc. (ng/mL)	Run ID	Final Reported value (ng/mL)
1	05/X/T08	1.181	ARL_10_408_SUB_05	B	1.244	ARL_10_408_SUB_Repetition_03	1.244
2	06/Y/T01	BLQ	ARL_10_408_SUB_06	B	BLQ	ARL_10_408_SUB_Repetition_03	BLQ

The firm's SOP (b) (4) (Repeat Sample Analysis, Effective Date: (b) (4) has predefined the reason as the following:

Analyst/group leader/ designee will calculate the mean internal standard response in the batch by considering all samples of the batch including calibration curve and quality control samples (excluding system suitability and blank samples).

Analyst/group leader/designee will identify the sample in the batch having internal standard response beyond ±50% of mean internal standard response in the batch and those samples will be repeated in singlet.

The reviewer verified the repeats based on the firm's raw data. In addition, the reanalyzed value is consistent with the original value, with only up to 5.33% difference, the reviewer considers it acceptable.

- The reviewer's evaluation for the fed study repeat is discussed as below:

1. Per original BE review, there were one hundred and thirty four (134) samples in the fed study that were reanalyzed for dextromethorphan under the reason of "sample outside assay range". The reviewer notes that the original measured concentrations of these samples exceed the ULOQ (10.151 ng/mL), and the reanalysis of these

samples was per SOP [redacted] (Standard Operating Procedure for Repeat Sample Analysis, Effective Date: [redacted]. All the reassayed values after correction with the dilution factor were ≥85% of the ULOQ.

2. Repeat Analysis due to "inconsistent internal standard area response":

   Per the original BE review, there were nineteen (19) samples reanalyzed for dextromethorphan and 16 samples reanalyzed for dextrorphan in the fed study under the reason of "inconsistent internal standard area response". The reviewer randomly selected some samples repeated due to this reason and checked the original raw data, and considers the reanalysis is per SOP [redacted](Standard Operating Procedure for Repeat Sample Analysis, Effective Date: [redacted]).

3. Batch Rejection

   Per the original BE review, there was one rejected batch in the fed BE study (Run ID: SUB_29) for dextromethorphan and dextrorphan (simultaneous detection) due to interference in CS0 at analyte retention time & multiple reaction monitoring (MRM) more than 20% of LLOQ area. The reviewer checked the raw data for both dextromethorphan and dextrorphan, and confirmed the reason. The rejection of this analytical run is per SOP [redacted](Batch Acceptance of Subject Sample Analysis, Effective Date: [redacted]), which defines the following: *In blank matrix, response of the interfering peaks, if any, at the retention time and MRM of analyte(s) and internal standard should be ≤20% of the extracted CS-I (LLOQ) response for analyte(s) and ≤5% of the extracted mean internal standard response, respectively*.

Deficiency #2:

You did not submit concentration and pharmacokinetic data of dextromethorphan in SAS transport files (.xpt) for fasting (#ARL/10/408) study subjects. Instead, you provided concentration and pharmacokinetic data of dextromethorphan in SAS transport files (.xpt) for fed (#ARL/10/409) study in duplicated. Therefore, please submit dextromethorphan concentration and pharmacokinetic data for the fasting study in SAS transport format.

Firm's Response to Deficiency #2:

Amneal acknowledges the Agency's comment and would like to clarify that this was an inadvertent error. For ease of review, all SAS files and define documents submitted in the original application (Sequence 0000) have been removed using the 'delete' lifecycle function and the correct datasets for both fasting (#ARL/10/408) and fed (#ARL/10/409) studies have been added to the application as 'new' along with the respective define documents. This gives the opportunity to place the files in the appropriate eCTD location with the proper naming convention. Please refer to the define document for **fasting study #ARL/10/408** and **fed study #ARL/10/409** for further information.

Reviewer's Comments on Firm's Response to Deficiency #2: The firm's response to deficiency #2 is **adequate.**

- The firm submitted the concentration and pharmacokinetic data of dextromethorphan and dextrorphan in SAS transport files (dmo-onc.xpt and dmo-pk for dextromethorphan and do-conc.xpt and do-pk for dextrorphan) for fasting (#ARL/10/408) study subjects. The firm did not report the concentration for subject Nos. (b) (6) in their SAS dataset due to pre-dose concentrations exceeding more than 5% of Cmax of corresponding subject. The reviewer verified the concentration from firm submitted raw dataset, which the pre-dose concentration in subject No. (b) (6) Period II, subject No. (b) (6) Period II, subject No (b) (6) Period II, and subject No. (b) (6) Period II, is greater than 5% of their Cmax in corresponding period, which is 16.869, 16.294, 19.010 and 18.164 ng/mL, respectively. The reviewer conducted SAS analysis for BE assessment, as the following, and the results are consistent with the firm's reported results.

Dextromethorphan, N=53*

Dextromethorphan Polistirex Extended Release Suspension, EQ 30 mg HBr/5 mL Dose (10 ml, EQ 60 mg Dextromethorphan HBr) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study (Study No. ARL/10/408), Dextromethorphan N=53 (Male = 44 and Female = 9)					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng*hr/mL)	25.07	23.34	1.07	102.51	112.57
AUC0-inf (ng*hr/mL)	25.51	23.76	1.07	102.51	112.47
Cmax (ng/mL)	1.97	1.77	1.11	106.58	116.14

* Subjects No. (b) (6) were excluded from statistical analysis for dextromethorphan due to pre-dose concentrations exceed more than 5% of Cmax.

Dextrorphan, N=57 (supporting evidence)

Dextromethorphan Polistirex Extended Release Suspension, EQ 30 mg HBr/5 mL Dose (10 ml, EQ 60 mg Dextromethorphan HBr) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study (Study No. ARL/10/408), Dextrorphan N=57 (Male = 48 and Female = 9)					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng*hr/mL)	11.79	10.27	1.15	109.89	120.06
AUC0-inf (ng*hr/mL)	12.24	10.65	1.15	110.13	119.77
Cmax (ng/mL)	1.20	1.00	1.20	115.26	125.11

Arithmetic Mean Parameters and Ratios

Dextromethorphan, N=53

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	ng hr/mL	48.531	164.67	3.32	470.26	42.955	148.80	2.94	340.64	1.13
AUCI	ng hr/mL	49.440	167.23	3.51	492.45	43.794	151.17	3.15	360.46	1.13
CMAX	ng/mL	2.963	101.74	0.28	14.02	2.611	98.08	0.26	11.51	1.13
TMAX	hr	5.500	.	2.00	7.00	5.500	.	3.00	8.00	1.00
KE	hr-1	0.081	30.81	0.03	0.16	0.080	28.42	0.03	0.13	1.01
THALF	hr	9.379	33.78	4.46	20.73	9.429	34.02	5.14	23.09	0.99

Dextrorphan, N=57

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	ng hr/mL	13.124	42.01	2.14	26.87	11.503	42.10	1.86	25.86	1.14
AUCI	ng hr/mL	13.390	40.61	3.38	27.76	11.736	40.65	2.75	26.09	1.14
CMAX	ng/mL	1.446	47.76	0.08	3.44	1.201	44.44	0.07	2.27	1.20
TMAX	hr	5.000	.	2.00	7.00	5.000	.	1.50	14.00	1.00
KE	hr-1	0.111	43.00	0.01	0.22	0.107	38.14	0.01	0.19	1.03
THALF	hr	10.306	148.25	3.08	107.72	9.051	95.98	3.62	46.90	1.14

- As shown from the above tables, the 90% confidence intervals (CIs) of the ratios of Ln-transformed means for LnCmax, LnAUC0-t and LnAUC0-∞ of dextromethorphan in the fasting BE study are within the limits of 80.00-125.00%. The PK parameters of the test and reference for the active metabolite, dextrorphan, were comparable (T/R ratio was within 0.8- 1.25), and therefore are supportive. The 90% CI for the least squares geometric mean of LnCmax for dextrorphan is 115.26-125.11%, which slightly falls out of the BE acceptance range of 80.00 - 125.00%. However, per draft product specific BE guidance of dextromethorphan polistirex[8], BE evaluation was made based on the data of the parent compound (dextromethorphan).

Deficiency #3:

(b) (4)

[redacted]

[8] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm085592.pdf

Firm's Response to Deficiency #3:

Amneal acknowledges the Agency's comment. (b) (4) Please refer to the Amneal's response provided to **Comment #6** in the Product Quality section.

Reviewer's Comments on Firm's Response to Deficiency #3:

(b) (4) n its response to Comment #6 in the Product Quality section, which is as the following:

(b) (4)

The firm's response to deficiency #3 is **adequate.**

Deficiency #4:
For Future Submissions
You used a non-standard high-fat vegetarian breakfast in the fed BE study (#ARL/10/409). Currently, there is no adequate data from which to conclude that a high-fat vegetarian breakfast served prior to dosing in BE studies under a fed state will have the same effect on drug absorption as the standard FDA high-fat breakfast using meat as the main protein source. Therefore, the DBIII does not encourage the use of vegetarian meals for breakfast in future fed BE study.

Firm's Response to Deficiency #4:

Amneal acknowledges the Agency's comment. Please note that fed study # ARL/10/409 was conducted in February 2011, since then the Agency has discouraged the use non-standard high-fat vegetarian breakfast in fed studies. Amneal has adopted the standard of requesting that all CROs to use meat as the main protein source for high-fat breakfast in fed studies.

Reviewer's Comments on Firm's Response to Deficiency #4:

The firm's response to deficiency #4 is **adequate.**

6. DEFICIENCY COMMENTS

N/A.

7. RECOMMENDATIONS

1. The Division of Bioequivalence III (DBIII) **accepts** the fasting bioequivalence (BE) study (#ARL/10/408) conducted by Amneal Pharmaceuticals on its Dextromethorphan Polistirex Extended Release Oral Suspension, EQ 30MG HBr/5mL, Batch # BB-ST-10012B, comparing it to RECKITT BENCKISER LLC's Delsym® (dextromethorphan polistirex) Extended Release Suspension, EQ 30MG HBr/5mL, Batch # 54554.

2. The DBIII finds the fed BE study (#ARL/10/409) **accepts** the fed BE study (#ARL/10/409) conducted by Amneal Pharmaceuticals on its Dextromethorphan Polistirex Extended Release Oral Suspension, EQ 30MG HBr/5mL, Batch # BB-ST-10012B, comparing it to RECKITT BENCKISER LLC's Delsym® (dextromethorphan polistirex) Extended Release Suspension, EQ 30MG HBr/5mL, Batch # 54554.

8. COMMENTS FOR OTHER OGD DISCIPLINES

Discipline	Comment
N/A	

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:	203133
APPLICANT:	Amneal Pharmaceuticals
DRUG PRODUCT:	Dextromethorphan Polistirex Extended Release Suspension, EQ 30 mg HBr/5 mL

The Division of Bioequivalence III (DBIII) has completed its review and has no further questions at this time.

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Nilufer M. Tampal, Ph.D.
Acting Director, Division of Bioequivalence III
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

9. OUTCOME PAGE

ANDA 203133

Completed Assignment for 203133 ID: 28888

Reviewer: Zhao, Chunsheng

Date Completed:

Verifier: ,

Date Verified:

Division: Division of Bioequivalence

Description: Dextromethorphan Polistirex Extended Release Oral Suspension, EQ 30 mg dextromethorphan hydrobromide (HBr)/5 mL

Items:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Score*	*Subtotal*
28888	7/14/2016	BIO	ANDA Amendment [1]	1	1
28888	9/7/2016	BIOQUALITY	Quality Assessment [1-5]	4.7	4.7
28888	9/7/2016	Complexity	Other [0.5 to 1]	0.5	0.5
28888	9/7/2016	Parallel	Study Amendment [1]	1	1
				Total:	7.5

Easily Correctable Deficiency (ECD)

ANDA No.	203113	
Drug Product Name	Dextromethorphan Polistirex Extended Release Oral Suspension	
Strength(s)	EQ 30 mg dextromethorphan hydrobromide (HBr)/5 mL	
Applicant Name	Amneal Pharmaceuticals	
Applicant Address	85 Adams Avenue Hauppauge, NY USA 11788	
Applicant Point of Contact	Alpesh Patel, Vice President - Global Regulatory Affairs	
Contact's Telephone Number	(b) (6)	
Contact's Fax Number	(631) 527-3523	
Contact's Email Address	alpesh@amneal.com	
Original Submission Date(s)	July 08, 2011 (Original Submission) August 25, 2011 (1st telephone amendment) September 02, 2011 (2nd telephone amendment, Pharm/Tox report for sodium polystyrene sulfonate) April 24, 2012 (1st dissolution amendment, already reviewed) June 15, 2012 (2nd dissolution amendment, already reviewed) August 9, 2012 (3rd dissolution amendment, already reviewed) January 7, 2013 (4th dissolution amendment, already reviewed)	
Submission Date(s) of Amendment(s) Under Review	07/14/2016 (Post Complete Response Amendment)	
Reviewer	Chunsheng Zhao, Ph.D.	
Study Number (s)	ARL/10/408	ARL/10/409
Study Type (s)	Fasting	Fed
Strength (s)	2 x EQ 30 mg HBr/5 mL	2 x EQ 30 mg HBr/5 mL
Clinical Site	Accutest Research Laboratories (I) Pvt. Ltd.	
Clinical Site Address	A-31, M.I.D.C., T.T.C., Industrial Area, Khairane, Navi Mumbai-400 709, INDIA.	
Analytical Site	(b) (4)	
Analytical Site Address		
OSIS Status	**Backlog, Year 1 and Year 2 ANDAs** ☐ **Pending** ☒ **Complete**	**Year 3 ANDAs** ☐ **To Be Determined by OSIS** ☐ **Pending For Cause Inspection**
OVERALL REVIEW RESULT	**INADEQUATE**	
REVISED/NEW DRAFT GUIDANCE INCLUDED	**NO**	

DEFICIENCY CLASSIFICATION	☐ Major ☒ Minor IR Eligible? ☐ Yes ☒ No (Deficiency to be communicated in an ECD letter) ☐ Not Applicable		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
1, 2, 4, 9, 10, 12, 16	FASTING	EQ 30 mg HBr/5 mL	ADEQUATE
1, 2, 4, 9, 10, 12, 16	FED	EQ 30 mg HBr/5 mL	INADEQUATE

The deficiencies presented below represent *EASILY CORRECTABLE DEFICIENCY* identified during the full ANDA review and the current ANDA review cycle will remain open. The following comment should be communicated to the firm.

Deficiency Related to the Fed Bioequivalence (BE) Study (#ARL/10/409)

In the amendment submission date July 14, 2016, you only submitted the complete (100%) raw numerical data for the fasting BE study (#ARL/10/408) and sample list report for two repeated batches for the fed BE study (#ARL/10/409), but did not submit **ALL** analytical raw numerical data for your fed BE study (#ARL/10/409). Please provide complete (100%) raw numerical data, in the instrument printout format, including original and repeated analysis for all samples, including the data of peak area/height for the analyte, peak area/height for the internal standard, ratio of the peak area/height for the analyte to the peak area/height for the internal standard, dilution factor (if any), and the corresponding concentration for each assayed and reassayed sample of all samples, calibration standard concentration samples, and quality control samples for your fed (#ARL/10/409) BE study.

DIVISION OF BIOEQUIVALENCE REVIEW

SIMPLE MODIFIED RELEASE PRODUCTS

ANDA No.	203133		
Drug Product Name	Dextromethorphan Polistirex Extended Release Oral Suspension		
Strength	EQ 30 mg dextromethorphan hydrobromide (HBr)/5 mL		
Applicant Name	Amneal Pharmaceuticals		
Applicant Address	131 Chambers Brook Road Branchburg, NJ 08876 USA Registration No. 3004488497		
Applicant Point of Contact	Alpesh Patel, Vice President (Global Regulatory Affairs)		
Contact's Telephone Number	(b) (6)		
Contact's Fax Number	(908) 231-1085		
Original Submission Dates	July 08, 2011 (Original Submission) August 25, 2011 (1st telephone amendment) September 02, 2011 (2nd telephone amendment, Pharm/Tox report for sodium polystyrene sulfonate) April 24, 2012 (1st dissolution amendment, already reviewed) June 15, 2012 (2nd dissolution amendment, already reviewed) August 9, 2012 (3rd dissolution amendment, already reviewed) January 7, 2013 (4th dissolution amendment, already reviewed)		
Submission Date of Amendment Under Review	N/A		
Reviewer	Yun Wang, Ph.D.		
Study Numbers	ARL/10/408	ARL/10/409	
Study Types	Fasting	Fed	
Strengths	2 x EQ 30 mg HBr/5 mL	2 x EQ 30 mg HBr/5 mL	
Clinical Site	Accutest Research Laboratories (I) Pvt. Ltd.		
Clinical Site Address	A-31, M.I.D.C., T.T.C., Industrial Area, Khairane, Navi Mumbai-400 709, INDIA.		
Analytical Site	(b) (4)		
Analytical Site Address			
OSIS Status	**Complete**		
OVERALL REVIEW RESULT	**INADEQUATE**		
REVISED/NEW DRAFT GUIDANCE INCLUDED	**NO**		

BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
1	Fasting	EQ 30 mg HBr/5 mL	**INADEQUATE**
1	Fed	EQ 30 mg HBr/5 mL	**INADEQUATE**

1 EXECUTIVE SUMMARY

This application contains the results of fasting and fed bioequivalence (BE) studies comparing a test product , Amneal Pharmaceuticals' Dextromethorphan Polistirex Extended Release Oral Suspension, EQ 30 mg HBr/5 mL, to the corresponding reference product, RECKITT BENCKISER LLC's Delsym® (dextromethorphan polistirex) Extended Release Oral Suspension, EQ 30MG HBr/5mL. According to the Orange Book (OB), this is an over-the-counter (OTC) product[1]. Each of the BE studies was designed as a single-dose, two-way crossover study in healthy male and female subjects.

The firm submitted the plasma concentration and pharmacokinetic data for the parent drug, dextromethorphan and active metabolite, dextrorphan. The data for the active metabolite (dextrorphan) is provided as supportive evidence. BE evaluation was made based on the data of the parent compound (dextromethorphan). The results of dextromethorphan are summarized in the tables below (firm calculated):

Fasting Study (ARL/10/408)

Parent Drug: Dextromethorphan Dextromethorphan Polistirex Extended Release Suspension, EQ 30 mg HBr/5 mL Dose (2X EQ 30 mg Dextromethorphan HBr), N=53 (Male = 44 and Female = 9) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasted Bioequivalence Study (Study No. ARL/10/408)					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng*hr/mL)	25.06	23.31	107.53	102.60	112.69
AUC0-inf (ng*hr/mL)	25.51	23.74	107.44	102.57	112.54
Cmax (ng/mL)	1.97	1.77	111.26	106.58	116.14

Fed Study (ARL/10/409)

Parent Drug: Dextromethorphan Dextromethorphan Polistirex Extended Release Suspension, EQ 30 mg HBr/5 mL Dose (2 X EQ 30 mg Dextromethorphan HBr), N=53 (Male = 43 and Female = 10) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study (Study No. ARL/10/409)					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng*hr/mL)	34.92	33.63	103.84	96.8629	111.3172
AUC0-inf (ng*hr/mL)	35.53	34.21	103.87	96.9404	111.2928
Cmax (ng/mL)	2.38	2.29	104.16	95.8039	113.2506

[1] Electronic Orange Book, search: Delsym; Last accessed Feb 10, 2015

The pharmacokinetic parameters of the test and reference for the active metabolite (dextrorphan) were comparable. Therefore, the metabolite data are supportive. However, the firm's fasting and fed BE studies are **inadequate** due to lack of analytical raw data and concentration and pharmacokinetic data of dextromethorphan in SAS transport files (.xpt) for fasting study subjects.

(b) (4)

Office of Study Integrity and Surveillance (OSIS):

The current ANDA is NOT a parent with a pending Office of Study Integrity and Surveillance (OSIS) inspection. Based on evaluation of the submitted data, the OSIS inspections of the clinical sites and analytical site for the current ANDA are not necessary. The studies submitted in the current ANDA do not indicate any conduct issues and no data integrity deficiencies were identified by the reviewer.

(b) (4)

In addition, because the current ANDA is considered low risk based on the data submitted, the OSIS inspection is not expected to impact the current study outcome. The OSIS inspection is complete.

The application is **inadequate** with deficiencies.

(b) (4)

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Drug Product Information[3]

Test Product	Dextromethorphan Polistirex Extended Release Oral Suspension, EQ 30MG HBr/5mL
Reference Product*	**Delsym®** (dextromethorphan polistirex) Extended Release Suspension, EQ 30MG HBr/5mL
RLD Manufacturer	RECKITT BENCKISER LLC
NDA No.	018658
RLD Approval Date	October 8, 1982
Indication[4]	DELSYM® is an OTC product which according to its label temporarily relieves (i) cough due to minor throat and bronchial irritation as may occur with the common cold or inhaled irritants, and (ii) the impulse to cough to help you get to sleep.

* Please note that the Orange Book lists DELSYM® as an over-the counter (OTC) drug product.

3.2 PK/PD Information[5,6]

Bioavailability	Dextromethorphan is rapidly absorbed from the GI tract
Food Effect	May be taken with or without food.
Tmax	Approximately 5-6 hours
Metabolism	It undergoes rapid and extensive hepatic metabolism to demethylated metabolites including the active metabolite, dextrorphan. Dextromethorphan is primarily metabolized by cytochrome P450 2D6 isoenzymes. The rate of metabolism varies between individuals according to phenotype (extensive or poor metabolizers).
Excretion	Excretion is primarily by renal elimination of metabolites; some drug is excreted unchanged.
Half-life	The plasma half-life is normally about 11 hours
Dosage and Administration	Shake well prior to administration. Administer using a calibrated measuring device. Adults and Adolescents (Age >12 years): 10 ml (60 mg) PO every 12 hours, not to exceed 20 ml (120 mg) PO daily. Children (6< Age <12 years): 5 ml (30 mg) PO every 12 hours, up to 10 ml (60 mg) PO daily. Children (4< Age <6 years): 2.5 ml (15 mg) PO every 12 hours, up to 5 ml (30 mg) PO daily. Age < 4 years: Do not use

[3] Electronic Orange Book, search: Delsym; Last accessed Jan 28, 2015.
[4] Delsym® Label: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/018658Orig1s030lbl_replacement.pdf
[5] http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=c0b7f366-31f5-4e87-bdc8-d0ce284e2014; Last accessed Jan 28, 2015.
[6] http://www.clinicalpharmacology-ip.com/Forms/Monograph/monograph.aspx?cpnum=179&sec=monphar&t=0

Maximum Daily Dose	•Adults, Elderly, Adolescents (Age ≥12 years) 120 mg/day PO •Children 6≤ Age <12 years: 60 mg/day PO 4≤ Age <6 years: 30 mg/day PO Age < 4 years: Do not use

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	2 studies

1.	**Type of study:**	Fasting
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	30 mg/5 mL
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	N/A

2.	**Type of study:**	Fed
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	30 mg/5 mL
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	N/A

Analytes to measure (in plasma/serum/blood):	Dextromethorphan and its metabolite Dextrorphan in plasma
Bioequivalence based on:	90% CI of dextromethorphan Please submit the metabolite data as supportive evidence of comparable therapeutic outcome. For the metabolite, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and Cmax.
Waiver request of in-vivo testing:	N/A
Source of most recent recommendations or provide the link to the current draft guidance:	The current BE recommendations for the drug product are listed in the Draft Guidance for Industry: Bioequivalence Recommendations for Specific Products. FDA Guidance for Industry: Draft Guidance on Dextromethorphan Polistirex Extended Release Oral Suspension http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm085592.pdf (recommended May 2008)

Summary of OGD or DB History	Pending ANDAs (Not Yet Reviewed)	Yes (ANDAs (b) (4) and 203133)
	Approved ANDAs	Yes (ANDA 091135)
	Previously Reviewed ANDAs	Yes
	Protocols	No
	Controls	Yes
	Citizen Petitions	No

3.4 Pre-Study Bioanalytical Method Validation

3.4.1 Full Method Validation

Parent Drug: Dextromethorphan

Information Requested	Data
Bioanalytical method validation report location	Module 5.3.1.4, Report No. ARL/REP/MI/019DMX/01
Analyte	Dextromethorphan
Internal standard (IS)	Dextromethorphan-d3
Method description	Solid Phase Extraction, and HPLC-MS/MS
Limit of quantitation	0.010 ng/mL
Average recovery of drug (%)	LQC: 57.47% MQC: 62.31% HQC: 66.09% Average: 61.95%; CV: 6.98%
Average recovery of IS (%)	LQC: 62.82% MQC: 65.15% HQC: 67.35% Average: 65.11%; CV: 3.48%
Standard curve concentrations (ng/mL)	0.010 ng/mL to 10.168 ng/mL
QC concentrations (ng/mL)	LLQC: 0.010 ng/mL LQC: 0.030 ng/mL MQC: 3.041 ng/mL HQC: 7.095 ng/mL H1QC: 9.994 ng/mL
QC Intraday precision range (%)	LLQC: 7.03% LQC: 4.13% MQC: 2.49% HQC: 1.80% H1QC: 1.76%

QC Intraday accuracy range (%)	LLQC: 90.00% LQC: 107.22% MQC: 98.16% HQC: 94.82% H1QC: 97.31%
QC Interday precision range (%)	LLQC: 6.88% LQC: 4.97% MQC: 3.16% HQC: 2.19% H1QC: 3.10%
QC Interday accuracy range (%)	LLQC: 97.22% LQC: 108.52% MQC: 97.08% HQC: 93.04% H1QC: 96.00%
Bench-top stability (hrs)	22 hours @ room temperature
Stock stability (days)	21 hours at room temperature, 7 days @ 2°C to 8°C
Processed stability (hrs)	50 hours at 100C
Freeze-thaw stability (cycles)	3 cycles and 5 cycles at -70°C±10°C
Long-term storage stability (days)	475 days at -70°C±10°C
Dilution integrity	Two times, five times and ten times
Selectivity	% Interference at the retention time (Rt) and MRM in normal blank plasma with Heparin as an anticoagulant For Dextromethorphan ≤ 10.11%, For Dextromethorphan-d3 ≤ 0.43%, % Interference at the Rt and MRM in Hemolysed plasma with Heparin as an anticoagulant For Dextromethorphan ≤ 16.50%, For Dextromethorphan-d3 ≤ 0.24%, % Interference at the Rt and MRM in Lipimic plasma with Heparin as an anticoagulant For Dextromethorphan ≤ 7.97%, For Dextromethorphan-d3 (IS) ≤ 0.23%,

Metabolite: Dextrorphan

Information Requested	Data
Bioanalytical method validation report location	Module 5.3.1.4, Report No. ARL/REP/MI/019DMX/01
Analyte	Dextrorphan
Internal standard (IS)	Dextrorphan-d3
Method description	Solid Phase Extraction, and HPLC-MS/MS
Limit of quantitation	0.010 ng/mL

Average recovery of drug (%)	LQC: 29.43% MQC: 31.34% HQC: 33.06% Average: 31.28% CV: 5.79%
Average recovery of IS (%)	LQC: 32.16% MQC: 30.82% HQC: 33.12% Average: 32.03% CV: 3.60%
Standard curve concentrations (ng/mL)	0.010 ng/mL to 10.198 ng/mL
QC concentrations (ng/mL)	LLQC : 0.010 ng/mL LQC : 0.030 ng/mL MQC: 3.099 ng/mL HQC: 7.231 ng/mL H1QC: 10.185 ng/mL
QC Intraday precision range (%)	LLQC: 5.77% LQC: 5.90% MQC: 1.65% HQC: 2.93% H1QC: 2.64%
QC Intraday accuracy range (%)	LLQC: 95.00% LQC: 92.22% MQC: 101.50% HQC: 94.58% H1QC: 97.23%
QC Interday precision range (%)	LLQC: 7.98% LQC: 6.12% MQC: 2.73% HQC: 2.96% H1QC: 2.44%
QC Interday accuracy range (%)	LLQC: 100.56% LQC: 93.33% MQC: 100.31% HQC: 92.15% H1QC: 96.26%
Bench-top stability (hrs)	22 hours @ room temperature
Stock stability (days)	21 hours at room temperature, 7 days @ 2ºC to 8ºC
Processed stability (hrs)	50 hours at 10°C
Freeze-thaw stability (cycles)	3 cycles and 5 cycles at -70ºC±10ºC
Long-term storage stability (days)	475 days at -70ºC±10ºC
Dilution integrity	Two times, five times and ten times

Selectivity	% Interference at the Rt and MRM in normal blank plasma with Heparin as an anticoagulant For Dextrorphan ≤ 14.80%, For Dextrorphan-d3 ≤ 2.85% % Interference at the Rt and MRM in Hemolysed plasma with Heparin as an anticoagulant For Dextrorphan ≤ 5.02%, For Dextrorphan-d3 ≤ 3.05% % Interference at the Rt and MRM in Lipimic plasma with Heparin as an anticoagulant For Dextrorphan≤ 11.47%, For Dextrorphan-d3 (IS) ≤ 2.52%

3.4.2 Partial Method Validation

Study ARL/10/408 & ARL/10/409

Information Requested	Data
Bioanalytical method validation report location	Module 5.3.1.4, Report No. ARL/REP/MI/019DMX/01, Amendment No: 02
Amendment Purpose	Check effect of concomitant drug such as Pseudoephedrine, Caffeine, Guaifenesin, Paracetamol and Ibuprofen by processing six replicates of LQC, MQC, HQC and H1QC spiked with all above drugs and Dextromethorphan and Dextrorphan.
Analyte	Dextromethorphan and Dextrorphan
Internal standard (IS)	Dextromethorphan-d3 and Dextrorphan-d3
Method description	Solid Phase Extraction, and HPLC-MS/MS
Limit of quantitation	For Dextromethorphan: 0.011 ng/mL For Dextrorphan: 0.011 ng/mL
Standard curve concentrations (ng/mL)	For Dextromethorphan: 0.011 ng/mL to 10.275 ng/mL For Dextrorphan: 0.011 ng/mL to 10.919 ng/mL
QC concentrations (ng/mL)	For Dextromethorphan: LQC : 0.030 ng/mL MQC : 3.095 ng/mL HQC : 7.222 ng/mL H1QC : 10.172 ng/mL For Dextrorphan: LQC : 0.032 ng/mL MQC : 3.286 ng/mL HQC : 7.667 ng/mL H1QC : 10.799 ng/mL

QC precision range with concomitant drugs (%)	For Dextromethorphan: LQC : 3.40% MQC : 1.79% HQC : 0.78% H1QC : 1.94% For Dextrorphan: LQC : 7.75% MQC : 2.02% HQC : 0.77% H1QC : 1.33%
QC accuracy range with concomitant drugs (%)	For Dextromethorphan: LQC : 101.11% MQC : 100.09% HQC : 97.30% H1QC : 98.04% For Dextrorphan: LQC : 104.17% MQC : 98.62% HQC : 98.63% H1QC : 100.09%
Conclusion	The concomitant drug effect for drugs such as Pseudoephedrine, Caffeine, Guaifenesin, Paracetamol and Ibuprofen to Dextromethorphan and Dextrorphan was found to be absent.

Study ARL/10/409

Information Requested	Data
Bioanalytical method validation report location	Module 5.3.1.4, Report No. ARL/REP/MI/019DMX/01, Amendment No: 03, 04
Amendment Purpose	1. Detection system changed from API 5500 (MI/01/020/0012) to Waters TQS (MI/03/020/0003) 2. Injection volume modified from 10.0 to 5.0 µL 3. Incorporated Cross selectivity, Processed sample stability (22 Hrs) and Haemolysis effect. 4. Incorporated Stock solution stability (40 days) and Whole Blood Stability (2 Hrs) 5. Incorporated Long Term Stability in Matrix at -70°C ±10°C for 475 days.
Analyte	Dextromethorphan and Dextrorphan
Internal standard (IS)	Dextromethorphan-d3 and Dextrorphan-d3
Method description	Solid Phase Extraction, and UPLC-MS/MS The firm noted: As Dextromethorphan and its metabolite Dextrorphan is light sensitive molecule, all activities like solution preparation, sample handling, sample transfer, sample processing and sample analysis was carried out under sodium vapour lamp.

Limit of quantitation	For Dextromethorphan: 0.010 ng/mL For Dextrorphan: 0.010 ng/mL
Standard curve concentrations (ng/mL)	For Dextromethorphan: 0.010 ng/mL to 10.151 ng/mL For Dextrorphan: 0.010 ng/mL to 10.178 ng/mL
QC concentrations (ng/mL)	For Dextromethorphan: LLQC : 0.010 ng/mL LQC : 0.030 ng/mL MQC : 3.069 ng/mL HQC : 7.130 ng/mL For Dextrorphan: LLQC : 0.010 ng/mL LQC : 0.030 ng/mL MQC : 3.079 ng/mL HQC : 7.154 ng/mL
QC precision range (%)	For Dextromethorphan: LLQC : 0.00% LQC : 1.82% MQC : 0.76% HQC : 1.12% For Dextrorphan: LLQC : 5.00% LQC : 1.37% MQC : 0.89% HQC : 1.57%
QC accuracy range (%)	For Dextromethorphan: LLQC : 100.00% LQC : 94.44% MQC : 99.04% HQC : 101.53% For Dextrorphan: LLQC : 103.33% LQC : 99.44% MQC : 100.70% HQC : 102.83%
Processed sample stability (hrs)	22 Hrs at room temperature
Stock solution stability (days)	40 days at 2ºC to 8ºC
Whole blood stability (hrs)	2 hours
Cross Selectivity	% Interference For Dextromethorphan : 5.90% For Dextrorphan: 1.36%

Long Term Stability in Matrix (-70°C ±10°C)	Results: For Dextromethorphan LQC: -3.11% HQC: -0.45% For Dextrorphan LQC: 13.86% HQC: -0.57% Acceptance Criteria: % Difference: NMT± 15% when compared with initial long term analysis respective QC data Conclusion: Long term stability in matrix is established for 475 days.

SOPs submitted	Yes
Does the duration of the each of the LTSS stability parameters support the sample preparation and assay dates	Yes

Comments on the Pre-Study Method Validation:

- The firm used a validated Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS method) to **simultaneously** measure plasma concentrations of dextromethorphan and dextrorphan for the fasting and fed BE studies. Dextromethorphan-d3 and dextrorphan-d3 were used as the internal standard.

- Sodium heparin was used as the anticoagulant for the preparation of the calibration curves and quality control (QC) samples in the validation study, which was the same anticoagulant used in subject sample collection of the BE studies.

- The solid phase extraction method was used to recover dextromethorphan and dextrorphan from human plasma. The mean percent recovery values of dextromethorphan and its internal standard dextromethorphan-d3 are 61.95% and 65.11%, respectively. The mean percent recovery values of dextrorphan and its internal standard dextrorphan-d3 are 31.28% and 32.03%, respectively. The recovery percentages of dextromethorphan and dextrorphan for all QC concentrations are comparable to their internal standards. The % CV is 6.98% for dextromethorphan and 3.48% for dextromethorphan-d3, respectively. The % CV is 5.79% for dextrorphan and 3.60% for dextrorphan-d3, respectively.

- Per firm's submission[7], there are four method validation report amendments, which are listed as below:

[7] DARRTS ANDA 203133 0000(1) 07/08/2011 ORIG-1/Multiple Categories/Subcategories, Module 5.3.1.4, Reports of Bioanalytical and Analytical Methods for Human Studies, arl-10-409-bioanalyt-methval, Method Validation Report-Amendment No. 04, pp 296 of 508

Amendment No.	Details of Amendment	Date of Amendment
01	Method transferred from API 5000 (MI/01/020/0009) to API 5500 (MI/01/020/0012)	08/02/10
02	Concomitant Drugs Effect exercise performed	12/02/10
03	1. Detection system changed from API 5500 (MI/01/020/0012) to Waters TQS (MI/03/020/0003) 2. Injection volume modified from 10.0 to 5.0 µL 3. Incorporated Cross selectivity, Processed sample stability (22 Hrs) and Haemolysis effect. 4. Incorporated Stock solution stability (40 days) and Whole Blood Stability (2 Hrs)	02/06/11
04	Incorporated Long Term Stability in Matrix at -70ºC ±10ºC for 475 days.	02/06/11

However, the firm only submitted the amendments No. 02, 03 and 04. The firm did not provide method validation report amendment No. 01, which contains details about method transfer from MS/MS model API 5000 to API 5500. The reviewer verified the in-study bioanalytical report. MS/MS model API 5000 was used in the fasting study sample analysis. Therefore, method validation report amendment No. 01 does not apply to current study.

- The firm submitted the long-term storage stability (LTSS) data of dextromethorphan and dextrorphan in human plasma with sodium heparin as the anticoagulant for 475 days under storage conditions at -70ºC±10ºC. Both LTSS data exceed the storage period for the sample of fasting (43 days) and fed (58 days) BE studies.

- The calibration curve range in the method validation was established from 0.01 ng/mL to 10.168 ng/mL for dextromethorphan. The firm provided dilution integrity study for dextromethorphan (dilution factors as 2, 5 and 10). The Dilution integrity data is adequate to cover the C_{max} concentrations in fasting and fed BE studies.

- The pre-study method validations for dextromethorphan and dextrorphan are **adequate**.

3.5 In Vivo Studies

Table 1. Summary of all in vivo Bioequivalence Studies

Dextromethorphan

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects No. (M/F) Type Age: mean (Range)	Mean Parameters (+/-SD)						Study Report Location
					C_{max} (ng/mL)	T_{max}* (hr)	AUC_{0-t} (ng*hr/mL)	AUC_{∞} (ng*hr/mL)	$T½$ (hr)	K_{el} (hr^{-1})	
ARL/10/408	The objective of this study is to demonstrate bioequivalence between the Test Product and the Reference Product[1]	Randomized, open label, balanced, two-treatment, two-period, two-sequence, single dose, crossover, (Fasting).	**Test Product (A):** Dextromethorphan Polistirex ER Suspension, EQ 30mg HBr/5ml (60 mg Dose), Batch No.: BB-ST-10012B	53 analyzed (44 Male / 9 Female) Healthy subjects	2.96 ± 3.01 (101.74)	5.50 (2.00-7.00)	48.52 ± 79.92 (164.72)	49.43 ± 82.68 (167.26)	9.38 ± 3.17 (33.78)	0.08 ± 0.03 (30.81)	Module 5.3.1.2
			Reference Product (B): Delsym® (Dextromethorphan Polistirex Extended Release Suspension), EQ 30mg HBr/5ml (60 mg Dose), Lot No.: 54554	28.64 ± 6.25 (19-41)	2.61 ± 2.56 (98.08)	5.50 (3.00-8.00)	42.92 ± 63.93 (148.93)	43.77 ± 66.21 (151.26)	9.43 ± 3.21 (34.02)	0.08 ± 0.02 (28.42)	
ARL/10/409	The objective of this study is to demonstrate bioequivalence between the Test Product and the Reference Product[2]	Randomized, open label, balanced, two-treatment, two-period, two-sequence, single dose, crossover, (Fed).	**Test Product (A):** Dextromethorphan Polistirex ER Suspension, EQ 30mg HBr/5ml (60 mg Dose), Batch No.: BB-ST-10012B	53 analyzed (43 Male/10 Female) Healthy subjects	3.85 ± 4.98 (129.41)	5.50 (1.50-12.00)	84.66 ± 199.77 (235.98)	93.04 ± 250.76 (269.51)	10.10 ± 5.60 (55.44)	0.08 ± 0.02 (27.23)	Module 5.3.1.2
			Reference Product (B): Delsym® (Dextromethorphan Polistirex Extended Release Suspension), EQ 30mg HBr/5ml (60 mg Dose), Lot No.: 54554	26.53 ± 5.01 (18-39)	3.34 ± 3.55 (106.32)	5.50 (2.75-11.00)	72.29 ± 160.01 (221.34)	78.78 ± 199.72 (253.52)	9.90 ± 5.12 (51.68)	0.08 ± 0.02 (28.19)	

Dextrorphan

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects No. (M/F) Type Age: mean (Range)	Mean Parameters (+/-SD)						Study Report Location
					C_{max} (ng/mL)	T_{max}* (hr)	AUC_{0-t} (ng*hr/mL)	AUC_{∞} (ng*hr/mL)	$T_{½}$ (hr)	K_{el} (hr^{-1})	
ARL/10/408	The objective of this study is to demonstrate bioequivalence between the Test Product and the Reference Product[1]	Randomized, open label, balanced, two-treatment, two-period, two-sequence, single dose, crossover, (Fasting).	**Test Product (A):** Dextromethorphan Polistirex ER Suspension, EQ 30mg HBr/5ml (60 mg Dose), Batch No.: BB-ST-10012B **Reference Product (B):** Delsym® (Dextromethorphan Polistirex Extended Release Suspension), EQ 30mg HBr/5ml (60 mg Dose), Lot No.: 54554	57 analyzed (48 Male / 9 Female) Healthy subjects 28.64 ± 6.25 (19-41)	1.45 ± 0.69 (47.76) 1.20 ± 0.53 (44.44)	5.00 (2.00-7.00) 5.00 (1.50-14.00)	13.14 ± 5.51 (41.93) 11.50 ± 4.84 (42.10)	13.40 ± 5.43 (40.53) 11.74 ± 4.77 (40.66)	10.30 ± 15.27 (148.25) 9.05 ± 8.68 (95.98)	0.11 ± 0.05 (43.00) 0.11 ± 0.04 (38.14)	Module 5.3.1.2
ARL/10/409	The objective of this study is to demonstrate bioequivalence between the Test Product and the Reference Product[2]	Randomized, open label, balanced, two-treatment, two-period, two-sequence, single dose, crossover, (Fed).	**Test Product (A):** Dextromethorphan Polistirex ER Suspension, EQ 30mg/5ml (60 mg Dose), Batch No.: BB-ST-10012B **Reference Product (B):** Delsym® (Dextromethorphan Polistirex Extended Release Suspension), EQ 30mg HBr/5ml (60 mg Dose), Lot No.: 54554	54 analyzed (44 Male/10 Female) Healthy subjects 26.53 ± 5.01 (18-39)	1.79 ± 0.84 (46.68) 1.70 ± 0.75 (43.78)	5.00 (1.50-11.00) 5.00 (1.50-11.00)	18.54 ± 8.17 (44.08) 17.33 ± 6.82 (39.35)	18.77 ± 8.10 (43.15) 17.55 ± 6.76 (38.55)	9.29 ± 12.26 (132.04) 8.75 ± 9.14 (104.44)	0.10 ± 0.04 (34.06) 0.11 ± 0.04 (35.05)	Module 5.3.1.2

Table 2. Reanalysis of Study Samples

Fasted-Dextromethorphan (Parent Drug)

Fasted Study, Study No. ARL/10/408 Additional information in Appendix 16.2.5.3 Section 7.8.1 and 7.8.2, Page 158 of 167 to 164 of 167								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used in reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic	00	00	0.00	0.00	00	00	0.00	0.00
Sample outside assay range	86	71	2.70	2.23	86	71	2.70	2.23
Inconsistent internal standard area response	00	00	0.00	0.00	00	00	0.00	0.00
Positive predose	04	05	0.13	0.16	04	05	0.13	0.16
Total	**90**	**76**	**2.83**	**2.39**	**90**	**76**	**2.83**	**2.39**

Note: Total number of samples analyzed for this study was three thousand one hundred and eighty seven (3187).

Fasted-Dextrorphan (Metabolite Drug)

Fasted Study, Study No. ARL/10/408 Additional information in Appendix 16.2.5.3 Section 7.8.3 and 7.8.4, Page 165 of 167								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used in reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic	00	00	0.00	0.00	00	00	0.00	0.00
Sample outside assay range	00	00	0.00	0.00	00	00	0.00	0.00
Inconsistent internal standard area response	02	00	0.06	0.00	02	00	0.06	0.00
Positive predose	01	00	0.03	0.00	01	00	0.03	0.00
Total	**03**	**00**	**0.09**	**0.00**	**03**	**00**	**0.09**	**0.00**

Note: Total number of samples analyzed for this study was three thousand one hundred and eighty seven (3187).

Fed-Dextromethorphan (Parent Drug)

Fed Study, Study No. ARL/10/409 Additional information in Appendix 16.2.5.3 Section 7.8.1 and 7.8.2, Page 153 of 165 to 160 of 165								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used in reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic	00	00	0.00	0.00	00	00	0.00	0.00
Sample outside assay range	88	46	2.91	1.52	88	46	2.91	1.52
Inconsistent internal standard area response	07	12	0.23	0.40	07	12	0.23	0.40
Positive predose	04	00	0.13	0.00	04	00	0.13	0.00
Batch Repeat (Acquisition batch of ARL_10_409_SUB_29)	28	28	0.93	0.93	28	28	0.93	0.93
Total	**127**	**86**	**4.20**	**2.85**	**127**	**86**	**4.20**	**2.85**

Note: Total number of samples analyzed for this study was three thousand and twenty (3020).

Fed-Dextrorphan (Metabolite Drug)

Fed Study, Study No. ARL/10/409 Additional information in Appendix 16.2.5.3 Section 7.8.3, Page 161 of 165 to 163 of 165								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used in reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic	00	00	0.00	0.00	00	00	0.00	0.00
Inconsistent internal standard area response	09	07	0.30	0.23	09	07	0.30	0.23
Batch Repeat (Acquisition batch of ARL_10_409_SUB_29)	28	28	0.93	0.93	28	28	0.93	0.93
Total	**37**	**35**	**1.23**	**1.16**	**37**	**35**	**1.23**	**1.16**

Note: Total number of samples analyzed for this study was three thousand and twenty (3020).

Table 3. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
(b) (4)		STANDARD OPERATING PROCEDURE FOR REPEAT SAMPLE ANALYSIS

Is there any other particular concern that should be investigated further?	No.

Comments from the Reviewer:

1. In the fasting study, a total of 166 samples (5.2%) were reanalyzed out of 3187 study samples for dextromethorphan. A total of 3 samples (0.1%) were reanalyzed out of 3187 study samples for metabolite dextrorphan. In the fed study, a total of 213 samples (5.2%) were reanalyzed out of 3020 study samples for dextromethorphan. A total of 72 samples (2.4%) were reanalyzed out of 3020 study samples for dextrorphan.

2. There were one hundred and fifty seven (157) samples in the fasting study and one hundred and thirty four (134) samples in the fed study that were reanalyzed for dextromethorphan under the reason of "sample outside assay range". The upper limit of calibration standard curve for dextromethorphan is 10.168 ng/mL. All reassy values after dilution and correction with the dilution factors (5 fold) were greater than 85% of 10.168 ng/mL. In addition, the firm had conducted acceptable pre-study dilution integrity study. The firm also submitted acceptable incurred sample reanalysis (ISR) data. However, the firm did not provide 100% analytical raw numerical data. The firm will be asked to provide this information for verification purpose.

3. There were nine (9) samples in the fasting study and four samples in the fed study that were reanalyzed for dextromethorphan under the reason of "positive pre-dose". The original values and repeat values are comparable. All values are slightly above LOQ (0.01 ng/mL) or BLQ. The reviewer deems those repeats are acceptable.

4. There were nineteen (19) samples in the fed study that were reanalyzed for dextromethorphan under the reason of "inconsistent internal standard area response". The SOP (b) (4) (Standard Operating Procedure for Repeat Sample Analysis; effective date (b) (4)) defines the inconsistent internal standard area response as the following: *the sample in the batch having internal standard response beyond ±50% of mean internal standard response in the batch including calibration curve and quality control samples (excluding system suitability and blank samples), and those samples will be repeated in singlet.* However, the firm did not provide the original analytical raw numerical data. The firm will be asked to provide this information for verification purpose.

5. There was one rejected batch in the fasting study (Run ID: ARL_10_408_SUB_07) for dextromethorphan and dextrorphan (simultaneous detection) due to autosampler error. Entire batch resubmitted as ARL_10_408_SUB_07_R after injecting system suitability. The rejection is in line with SOP # (b) (4) (Standard Operating Procedure for Batch Acceptance of Subject Sample Analysis; effective date (b) (4)).

6. There was one rejected batch in the fed study (Run ID: SUB_29) for dextromethorphan and dextrorphan (simultaneous detection) due to interference in CS0 at analyte retention time & multiple reaction monitoring (MRM) more than 20% of LLOQ area. The rejection is in line with SOP (b) (4) (Standard Operating Procedure for Batch Acceptance of Subject Sample Analysis; effective date (b) (4)), which states "*in blank matrix, response of the interfering peaks, if any, at the retention time and MRM of analyte(s) and internal standard should be ≤ 20% of the extracted CS-1 (LLOQ) response for analyte(s) and ≤ 5% of the extracted mean internal standard response, respectively*". However, the firm did not include the original data to support the reason for batch rejection. Therefore, the firm will be asked to submit the raw data for calibration standards, QC samples and study samples, such as peak area of analyte and internal standard, calculated concentration, etc. of the failed batch.

7. Overall, the reanalysis of study samples of the fasting and fed BE studies are **inadequate** per the above comments.

3.6 Waiver Request(s) For Modified Release Dosage Forms

N/A

3.7 Deficiency Comments

Deficiencies Related to the Bioequivalence Studies

1. The firm did not submit **ALL** analytical raw numerical data. The firm will be asked to provide complete (100%) raw numerical data including original and repeated analysis for all samples, including the data of peak area/height for the analyte, peak area/height for the internal standard, ratio of the peak area/height for the analyte to the peak area/height for the internal standard, dilution factor (if any), and the corresponding concentration for each assayed and reassayed sample of all samples, calibration standard concentration samples, and quality control samples for its fasting (#ARL/10/408) and fed (#ARL/10/409) BE studies..

2. The firm did not submit concentration and pharmacokinetic data of dextromethorphan in SAS transport files (.xpt) for fasting study subjects. Instead, the firm provided concentration and pharmacokinetic data of dextromethorphan in SAS transport files (.xpt) for fed study in duplicated. Therefore, the firm will be asked to submit dextromethorphan concentration and pharmacokinetic data for the fasting study in SAS transport format.

Deficiency Related to the Formulation

3. [redacted] (b) (4)

For Future Submissions

4. The firm used a non-standard high-fat vegetarian breakfast in the fed BE study (#ARL/10/409). Currently, there is no adequate data from which to conclude that a high-fat vegetarian breakfast served prior to dosing in BE studies under a fed state will have the same effect on drug absorption as the standard FDA high-fat breakfast using meat as the main protein source. Therefore, the DBIII does not encourage the use of vegetarian meals for breakfast in future fed BE study.

3.8 Recommendations

1. The Division of Bioequivalence III (DBIII) finds the fasting bioequivalence (BE) study (#ARL/10/408) **inadequate** due to the reason cited in the above deficiency comments. The Amneal Pharmaceuticals conducted the fasting study on its test product, Dextromethorphan Polistirex Extended Release Oral Suspension, EQ 30MG HBr/5mL, Batch # BB-ST-10012B, comparing it to RECKITT BENCKISER LLC's Delsym® (dextromethorphan polistirex) Extended Release Suspension, EQ 30MG HBr/5mL, Batch # 54554.

2. The DBIII finds the fed BE study (#ARL/10/409) **inadequate** due to the reason cited in the above deficiency comments. The Amneal Pharmaceuticals conducted the fed study on its test product, Dextromethorphan Polistirex Extended Release Oral Suspension, EQ 30MG HBr/5mL, Batch # BB-ST-10012B, comparing it to RECKITT BENCKISER LLC's Delsym® (dextromethorphan polistirex) Extended Release Suspension, EQ 30MG HBr/5mL, Batch # 54554.

3.9 Comments for Other OGD Disciplines

Discipline	Comment
None	

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Fasting Bioequivalence Study

4.1.1.1 Study Design

Table 4. Study Information

Study Number	ARL/10/408
Study Title	A randomized, open label, balanced, two-treatment, two-period, two-sequence, single dose, crossover, bioequivalence study of Dextromethorphan Polistirex Extended-Release Suspension 30mg/5ml Manufactured by Amneal Pharmaceuticals, USA with Delsym® (Dextromethorphan Polistirex Extended-Release Suspension) 30mg/5ml Distributed by Reckitt Benckiser Inc., Parsippany, NJ 07054-0224, in normal, healthy, adult, male and female human subjects under fasting conditions
Clinical Site (Name & Address)	Accutest Research Laboratories (I) Pvt. Ltd., A-31, M.I.D.C., T.T.C., Industrial Area, Khairane, Navi Mumbai-400 709, INDIA.
Principal Investigator	Dr. Suhas Khandave M.D. (Pharmacology)
Dosing Dates	Period I: 06/January/11 Period II: 13/January/11
Analytical Site (Name & Address)	(b) (4)
Analysis Dates	01/19/11 – 02/18/11
Analytical Director	(b) (4)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	43 days

Table 5. Product information

Product	**Test**	**Reference**
Treatment ID	**A**	**B**
Product Name	Dextromethorphan Polistirex ER Suspension	Delsym® (dextromethorphan polistirex) Extended Release Suspension
Manufacturer	Amneal Pharmaceuticals, USA	Reckitt Benckiser Inc.
Batch/Lot No.	BB-ST-10012B	54554
Manufacture Date	12/01/10	
Expiration Date		03/2013
Strength	EQ 30 mg HBr/5 mL Dextromethorphan HBr	EQ 30 mg HBr/5 mL Dextromethorphan HBr

Dosage Form	Suspension	Suspension
Bio-Batch Size	(b) (4)	
Production Batch Size		
Potency (Assay)	100.9%	99.2%
Content Uniformity (mean)	Top: 100.3% Middle: 100.3% Bottom: 100.2%	
Dose Administered	10 mL (EQ 60 mg Dextromethorphan HBr)	10 mL (EQ 60 mg Dextromethorphan HBr)
Route of Administration	Oral	Oral

Was the drug product administered per labeling?	Yes

Table 6. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	**Enrolled:** 58 **Dosed:**58 **Completed:** 57 **Samples Analyzed:** 57 **Data Analyzed:** 53
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization Scheme (Sequence of T and R)	**Yes,** **TR:** 2, 3, 5, 8, 9, 12, 14, 15, 17, 20, 22, 23, 25, 27, 29, 31, 33, 36, 38, 40, 42, 43, 46, 47, 49, 52, 53, 56 and 58 **RT:** 1, 4, 6, 7, 10, 11, 13, 16, 18, 19, 21, 24, 26, 28, 30, 32, 34, 35, 37, 39, 41, 44, 45, 48, 50, 51, 54, 55and 57
Blood Sampling Times	Pre-dose (collect within 1 hour prior to dosing), 1.00, 1.50, 2.00, 2.25, 2.50, 2.75, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 7.00, 8.00, 9.00, 10.00, 11.00, 12.00, 14.00, 17.00, 24.00, 30.00, 36.00, 48.00, 72.00, and 96.00 hours post-dose (72.00 and 96.00 hours samples were collected on ambulatory basis)
Blood Sample Processing & Storage (include storage temperature)	Blood samples were collected in sodium heparin vacutainer at desired sampling time point. Intravenous indwelling cannula was kept patent by injecting 0.2 mL of heparinized saline solution except for each ambulatory sample. Blood samples were collected after discarding the first 0.2 mL of heparinized blood from i.v. cannula. Centrifugation of the samples was done within 30 minutes after the last blood sample collection of respective time point. Blood samples were centrifuged at 5°C, at 3500 RPM for 10 minutes under refrigeration. Plasma was separated and placed in suitable labeled vials in two aliquots, one as analytical sample and the other as control sample. All the plasma samples were stored below -50°C until the analysis of the samples.

Comments on Study Design:

1. A total of 58 healthy adult subjects were enrolled in this study. 57 subjects completed the study. Data from 53 subjects were used in the dextromethorphan statistical analysis. Subject No. (b) (6) (period II) withdrew from the study due to adverse events including mild headache and moderate loose motion. Subjects No. (b) (6) were excluded from dextromethorphan analysis due to pre-dose concentrations exceed more than 5% of Cmax. However, those subjects were included in statistical analysis for metabolite dextrorphan. Therefore, the subjects included in the statistical analysis for dextromethorphan and dextrorphan are (b) (6) (b) (6), respectively.

2. Sodium heparin is used as anticoagulant in sample collection, which is consistent with pre-validated bioanalytical method.

3. The subjects were dosed with 10 ml Dextromethorphan Polistirex Extended Release Suspension EQ 30mg HBr/5ml (total EQ 60 mg Dextromethorphan HBr). The dose was selected based on the adult dosage in RLD labeling[8]. To ensure complete dosing of the oral suspension, the firm used a syringe which was held in upright position and was rotated 3-4 times in either direction to ensure thorough mixing prior to administration to the subjects' mouth. The syringe was then rinsed in a clean beaker with a part of water taken from the glass containing 240 ± 2 mL water. The rinsing solution and the remaining water were finally all administered to the subjects. The compliance for dosing was also assessed by a thorough check of the oral cavity by using a tongue depressor and torch immediately after dosing. The firm's study design and drug administration method are acceptable.

[8] Delsym® Label:
http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/018658Orig1s030lbl_replacement.pdf

4.1.1.2 Clinical Results

Table 7. Demographics Profile of Subjects Completing the Bioequivalence Study

Fasting Bioequivalence Study No. ARL/10/408			
		Treatment Groups	
		Test Product N = 53	Reference Product N = 53
Age (years)	Mean ± SD	28.64 ± 6.25	28.64 ± 6.25
	Range	19 - 41	19 - 41
Age Groups	< 18	Nil	Nil
	18 – 40	50 (94.34%)	50 (94.34%)
	41 – 64	03 (5.66%)	03 (5.66%)
	65 – 75	Nil	Nil
	> 75	Nil	Nil
Sex	Male	44 (83.02%)	44 (83.02%)
	Female	09 (16.98%)	09 (16.98%)
Race	Asian	53 (100%)	53 (100%)
	Black	Nil	Nil
	Caucasian	Nil	Nil
	Hispanic	Nil	Nil
	Other	Nil	Nil
BMI	Mean + SD	On protocol basis subjects were enrolled according to Life Insurance Corporation Chart*	On protocol basis subjects were enrolled according to Life Insurance Corporation Chart*
	Range		
Other Factors		Nil	Nil

Reviewer's Comment:

1. The demographic profile is listed for dextromethorphan. Subjects No. (b) (6) (b) (6) were excluded from dextromethorphan statistical analysis due to pre-dose concentrations exceed more than 5% of Cmax. However, those subjects were included in statistical analysis for dextrorphan.

2. The firm did not give detailed BMI mean and range, but noted "*On protocol basis subjects were enrolled according to Life Insurance Corporation Chart*". The reviewer checked the fasting study protocol (Study Code: ARL/10/408, Version: 03, Date: November 15, 2010), the firm used "*body weight within ± 15% of ideal weight as related to height and body frame according to Life Insurance Corporation (LIC) Chart"* (attached below) as the study inclusion criteria. The reviewer justifies that the

study subjects' body weight distributes in the normal weight range (BMI: 18.5 – 25) and won't impact the outcome of the study.

LIC Height-Weight Chart

Height –Weight Chart For Non Medical Cases For Men and Women

HEIGHT (CM)	AGE (YEARS)													
	18-22		23-27		28-32		33-37		38-42		43-45		46-50	
	WEIGHT (KGS)													
	MIN	MAX	MIN	MAX	MIN	MAX	MIN	MAX	MIN	MAX	MIN	MAX	MIN	MAX
140-145	41	52	41	53	43	53	43	57	43	59	43	60	44	60
146-150	43	54	43	56	44	59	45	60	45	60	45	61	46	62
151-155	45	56	46	58	46	62	47	64	47	64	47	64	48	65
156-160	48	59	48	61	48	65	50	67	50	67	50	68	51	69
161-165	51	62	51	65	51	69	53	71	53	71	53	72	54	73
166-170	54	66	54	69	55	73	56	75	56	75	56	76	57	77
171-175	58	71	58	73	58	76	60	80	60	80	60	81	61	82
176-180	61	75	62	78	62	83	64	88	64	88	64	87	65	88
181-185	65	80	65	83	66	88	68	92	68	92	68	93	69	94
186-190	69	85	69	89	70	94	72	97	72	97	72	98	73	99

Table 8. Dropout Information, Fasting Bioequivalence Study

Subject No.	Reason	Period	Replaced?
(b) (6)	Subject was withdrawn after 5.50 hours blood sample collection due to adverse event.	II	N/A

Table 9. Study Adverse Events, Fasting Bioequivalence Study

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Study No. ARL/10/408	
	Test	Reference
Body as a whole		
Headache	05 (8.62%)	00 (0.00%)
Dizziness	00 (0.00%)	01 (1.72%)
Gastrointestinal		
Nausea	02 (3.45%)	00 (00.00%)
Loose motion	01 (1.72%)	00 (00.00%)
Pain in epigastric region	00 (00.00%)	01 (1.72%)
Blood and Lymphatic system		
Low hemoglobin[a]	00 (00.00%)	00 (00.00%)
High eosinophil count[a]	00 (00.00%)	00 (00.00%)
High SGOT[a]	00 (00.00%)	00 (00.00%)
High SGPT[a]	00 (00.00%)	00 (00.00%)
Urinary Tract Infection[a]		
	00 (00.00%)	00 (00.00%)
Total	**08 (13.80%)**	**02 (3.45%)**

[a] The laboratory parameter was normal during screening, but was found to be abnormal in the post-study evaluation. As the subject had received both the treatments, it is difficult to attribute this adverse event to either of the treatments.

Subjects Experiencing Emesis

Subject Number	Test/Reference	Period	Time Post-Dose	Duration Between Dosing and Emesis (hrs)
N/A				

Was the adverse event profile observed during the fasting bioequivalence study comparable for the test and reference product? Please comment.

The total number of subjects who reported adverse events following the administration of test product is slightly greater than the total number of subjects who reported adverse events following the administration of the reference product. Eight (8) adverse events were observed in seven subjects following the administration of the test product and two (2) adverse events were observed in two subjects following the administration of the reference product. In addition, there are five (5) adverse events noted in four subjects during post-study evaluation, which cannot be attributed to either test or reference treatment.

Are there any serious adverse events or death? If so, are they reported to the OGD Safety Committee?

No serious adverse events (SAEs) were reported during the fasting BE study.

Are there any other safety concerns based on the adverse event profile?

No.

Table 10. Protocol Deviations, Fasting Bioequivalence Study

Type	Subject #s (Test)	Subject #s (Ref.)
Deviation in scheduled time in blood sample collection	(b) (6)	
Deviation in measurement of 24.00 hours post dose vitals sign in period I		
Deviation in housing criteria of at least 10.50 hours pre-dose in period I[a]		
Clinical laboratory investigations were to be done at in-house clinical laboratory, however; due to instrument break down (b) (4) samples were outsourced at (b) (4) for biochemical investigation.		

[a] As these deviations have occurred prior to any treatment being administered, their categorization with respect to the test or reference products cannot be done.

Comments on Dropouts/Adverse Events/Protocol Deviations:

- There was one (1) dropout throughout the study. Subject No. (b) (6) withdrew from the study after 5.50 hours blood sampling time in Period II due to adverse events (mild headache and moderate loose motion). The dropout was in accordance with the firm's protocol (Study Code: ARL/10/408, Version 03).

- All adverse events were mild in intensity, except the loose motion in Subject No. (b) (6) is in moderate intensity. The most common clinical adverse event caused by administration of test product or reference product is mild headache or dizziness, with the incidence of 8.62% and 1.72%, respectively. These adverse events are consistent with what has been reported in RLD[9], where drowsiness, dizziness, and fatigue can occur with therapeutic dosage and is believed to be drug-related.

- There were one hundred and fourteen (114) blood sampling deviations during the fasting BE study. As per the protocol, post-dose blood sample collection was to be done within 2 minutes of the scheduled time. Time point deviations were due to cannula blockage or poor blood flow or during ambulatory samples. Most time deviations for non-ambulatory samples are minor (within 10 minutes). Thus are considered to be insignificant by the reviewer. Ambulatory samples were collected in

[9] http://www.clinicalpharmacology-ip.com/Forms/Monograph/monograph.aspx?cpnum=179&sec=monadve&t=0

72.00 and 96.00 hours, thus the time deviations are in the elimination phase and won't impact the study outcome. The firm used actual sampling times for its pharmacokinetic (PK) calculations. Those time deviations should not change the bioequivalence study outcome.

- There were six (6) protocol deviations in measurement of 24.00 hours post-dose vitals sign in Period I. Per protocol, vital signs were to be measured within ± 30 minutes of scheduled time. However, for few subjects in Period I, 24:00 hrs vitals were recorded 10-20 minutes before scheduled time. These protocol deviations should not impact the bioequivalence study outcome.

- There were ten (10) protocol deviations in housing criteria. Per the protocol, all subjects were to be checked in the study at least 10.50 hours pre-dose. However, Subject Nos. (b) (6) (10 subjects) in Period I did not follow this criteria due to late availability of the pathology report. Since all these subjects were in the center and their restrictions, inclusion and exclusion criteria were well maintained, these deviations won't impact the bioequivalence study outcome.

- There was one (1) protocol deviation in the location of clinical laboratory investigation. Per protocol, clinical laboratory investigations were to be done at in-house clinical laboratory. However, due to instrument break down, samples were outsourced at (b) (4) for biochemical investigation. This protocol deviation should not impact the bioequivalence study outcome.

- The overall protocol deviations did not compromise the integrity of the study.

- The firm's handling of dropouts/adverse events/protocol deviations are acceptable.

- The clinical results are acceptable.

4.1.1.3 Bioanalytical Results

Table 11. Sample Analysis Calibration and Quality Control

Parent Drug: Dextromethorphan

Bioequivalence Study No. ARL/10/408 (Fasted Study) Analyte Name: Dextromethorphan									
Parameter	**Standard Curve Samples**								
Concentration (ng/mL)	0.011	0.021	0.051	0.253	1.012	4.046	6.069	8.092	10.095
Inter day Precision (%CV)	4.06	5.91	2.77	2.94	2.22	1.73	2.13	1.54	2.84
Inter day Accuracy (%Actual)	97.73	102.94	105.59	102.46	100.83	97.99	97.96	96.81	98.56
Linearity (Range of r)	0.9962 to 0.9998 (r > 0.9900)								

Linearity Range (ng/mL)	0.011 ng/mL to 10.095 ng/mL
Sensitivity/LOQ (ng/mL)	0.011 ng/mL

Bioequivalence Study No. ARL/10/408 (Fasted Study) Analyte Name: Dextromethorphan					
Parameter	**Quality Control Samples**				
	LQC	**L1QC**	**MQC**	**HQC**	**H1QC**
Concentration (ng/mL)	0.030	1.257	3.040	7.094	10.008
Inter day Precision (%CV)	6.60	2.87	3.13	2.88	3.34
Inter day Accuracy (%Actual)	102.89	99.52	100.67	97.06	98.69

Metabolite: Dextrorphan

Bioequivalence Study No. ARL/10/408 (Fasted Study) Analyte Name: Dextrorphan									
Parameter	**Standard Curve Samples**								
Concentration (ng/mL)	0.011	0.021	0.051	0.255	1.021	4.082	6.123	8.164	10.185
Inter day Precision (%CV)	3.92	5.41	3.48	2.45	2.39	2.24	2.80	2.25	3.19
Inter day Accuracy (%Actual)	98.43	101.31	105.54	104.75	102.51	98.02	97.82	96.20	95.87
Linearity (Range of r)	0.9962 to 0.9998 (r > 0.9900)								
Linearity Range (ng/mL)	0.011 ng/mL to 10.185 ng/mL								
Sensitivity/LOQ (ng/mL)	0.011 ng/mL								

Bioequivalence Study No. ARL/10/408 (Fasted Study) Analyte Name: Dextrorphan					
Parameter	**Quality Control Samples**				
	LQC	**L1QC**	**MQC**	**HQC**	**H1QC**
Concentration (ng/mL)	0.031	1.270	3.051	7.119	10.043
Inter day Precision (%CV)	6.29	3.50	3.52	3.42	3.34
Inter day Accuracy (%Actual)	100.54	101.17	101.72	96.64	96.98

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	Yes
Are there any concerns related to sample analysis (including reanalysis, run rejection, etc.)?	No

Were 20% of chromatograms included?*	Yes, Subject Nos. (b) (6)
Did the firm provide 100% numerical raw data (e.g. peak height, peak area, response count of IS and analyte) in run sequence order (i.e. Run log) in the instrument printout format?	**No**, the firm only submitted 20% of raw numerical data along with chromatograms.

*Subject No. (b) (6) was withdrawn from the study.

Table 12. SOP's Dealing with Sample Analysis

SOP No.	Effective Date of SOP	SOP Title
(b) (4)		STANDARD OPERATING PROCEDURE FOR REPEAT SAMPLE ANALYSIS

Comments:

1. There was one rejected batch (Run ID: 22/01/11 ARL_10_408_SUB_07) for dextromethorphan and dextrorphan (simultaneous detection) due to autosampler error. Entire batch resubmitted as ARL_10_408_SUB_07_R after injecting system suitability. The rejection is in line with SOP (b) (4) (Standard Operating Procedure for Batch Acceptance of Subject Sample Analysis; effective date (b) (4)).

2. The firm used 228 (7.2% of total 3187 sample analyzed) samples in its incurred sample reproducibility (ISR) testing for dextromethorphan and dextrorphan. ISR testing was performed as per SOP (b) (4) (Standard operating procedure incurred sample reanalysis, effective date (b) (4) The SOP acceptance criteria were set as at least 67% of the ISR samples should be within ±20% in terms of difference between repeat and initial values when compared with mean of initial and repeat values. A total of 226 out of 228 (99.1%) were found to be within ± 20% difference. Therefore, ISR for dextromethorphan and dextrorphan was found to be within acceptance criteria. The analytical methods are reproducible.

3. The firm only submitted 20% of raw numerical data along with chromatograms. The firm will be asked to provide complete (100%) raw numerical data including original and repeated analysis for all samples.

4. The firm's fasting study assay is **incomplete**.

4.1.1.4 Pharmacokinetic Results

Please note that the information below is obtained based on the assumption that the firm's repeated assays are acceptable. The PK parameters may change upon the DBIII receives additional information and re-evaluates the firm's repeated assays.

Firm Calculated

Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals

Dextromethorphan, N=53

Dextromethorphan Polistirex Extended Release Suspension, EQ 30 mg HBr/5 mL Dose (10 ml, EQ 60 mg Dextromethorphan HBr) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasted Bioequivalence Study (Study No. ARL/10/408), Dextromethorphan N=53 (Male = 44 and Female = 9)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (ng*hr/mL)	25.06	23.31	107.53	102.60-112.69
AUC0-inf (ng*hr/mL)	25.51	23.74	107.44	102.57-112.54
Cmax (ng/mL)	1.97	1.77	111.26	106.58-116.14

Dextrorphan, N=57 (supporting evidence)

Dextromethorphan Polistirex Extended Release Suspension, EQ 30 mg HBr/5 mL Dose (10 ml, EQ 60 mg Dextromethorphan HBr) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasted Bioequivalence Study (Study No. ARL/10/408), Dextrorphan N=57 (Male = 48 and Female = 9)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (ng*hr/mL)	11.81	10.27	115.0117	110.04-120.21
AUC0-inf (ng*hr/mL)	12.25	10.65	114.9933	110.27-119.92
Cmax (ng/mL)	1.20	1.00	120.0881	115.26-125.11

Arithmetic Mean Parameters and Ratios

Dextromethorphan, N=53

Formulations		C_{max} (ng/mL)	AUC_{0-t} (ng*hr/mL)	AUC_{0-inf} (ng*hr/mL)	T_{max} (hrs)	K_{el} (hrs^{-1})	$t_{1/2}$ (hrs)	AUC_{0-t}/ AUC_{0-inf} Ratio
Test Product A	Arithmetic Mean ± SD	2.96 ± 3.01	48.52 ± 79.92	49.43 ± 82.68	5.17 ± 1.24	0.08 ± 0.03	9.38 ± 3.17	98.26 ± 1.37
Reference Product B	Arithmetic Mean ± SD	2.61 ± 2.56	42.92 ± 63.93	43.77 ± 66.21	5.28 ± 0.99	0.08 ± 0.02	9.43 ± 3.21	98.19 ± 1.26
% Ratio (A/B)	Arithmetic Mean	113.49	113.03	112.93	-	-	-	-

Dextrorphan, N=57

Formulations		C_{max} (ng/mL)	AUC_{0-t} (ng*hr/mL)	AUC_{0-inf} (ng*hr/mL)	T_{max} (hrs)	K_{el} (hrs^{-1})	$t_{1/2}$ (hrs)	AUC_{0-t}/ AUC_{0-inf} Ratio
Test Product A	Arithmetic Mean ± SD	1.45 ± 0.69	13.14 ± 5.51	13.40 ± 5.43	4.56 ± 1.13	0.11 ± 0.05	10.30 ± 15.27	96.89 ± 8.28
Reference Product B	Arithmetic Mean ± SD	1.20 ± 0.53	11.50 ± 4.84	11.74 ± 4.77	4.65 ± 1.69	0.11 ± 0.04	9.05 ± 8.68	96.63 ± 6.74
% Ratio (A/B)	Arithmetic Mean	120.41	114.22	114.21	-	-	-	-

Is there a Tmax difference between T and R	No, T/R ratio: 1 (5.5 hrs vs. 5.5 hrs)
Are any CIs marginal?	No
Were the subjects dosed in groups?	No
Is the study design replicate and/or reference-scaled?	No
Is sampling time adequate?	Yes

Overall Comment:

- The firm excluded Subjects No. (b) (6) from statistical analysis for dextromethorphan due to pre-dose concentrations exceed more than 5% of Cmax. These subjects were kept in the statistical analysis for dextrorphan. The data exclusion and inclusion were in accordance with the firm's protocol (Study Code: ARL/10/408, Version 03).

- Based on the firm's calculation, the 90% confidence intervals (CIs) for the least squares geometric means of LnAUCt, LnAUCi and LnCmax of parent drug dextromethorphan meet the BE criteria of 80.00- 125.00%.

- However, the firm did not submit concentration and pharmacokinetic data of dextromethorphan in SAS transport files (.xpt) for fasting study subjects. Instead, the firm provided concentration and pharmacokinetic data of dextromethorphan in SAS transport files (.xpt) for fed study in duplicated. Therefore, the firm will be asked to submit dextromethorphan concentration and pharmacokinetic data for the fasting study in SAS transport format. .

- The PK parameters of the test and reference for the active metabolite dextrorphan were comparable. Therefore the metabolite data are supportive. The 90% CI for the least squares geometric mean of LnCmax for dextrorphan is 115.26-125.11%, which slightly falls out of the BE acceptance range of 80.00 - 125.00%. However, per draft product specific BE guidance of dextromethorphan polistirex[10], BE evaluation was made based on the data of the parent compound (dextromethorphan).

- However, the firm's *in vivo* BE study under fasted conditions is still **inadequate** due to the deficiencies specified in Section 3.7.

[10] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm085592.pdf

Table 16. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

(Firm-Submitted Data in Firm's Format)

Dextromethorphan

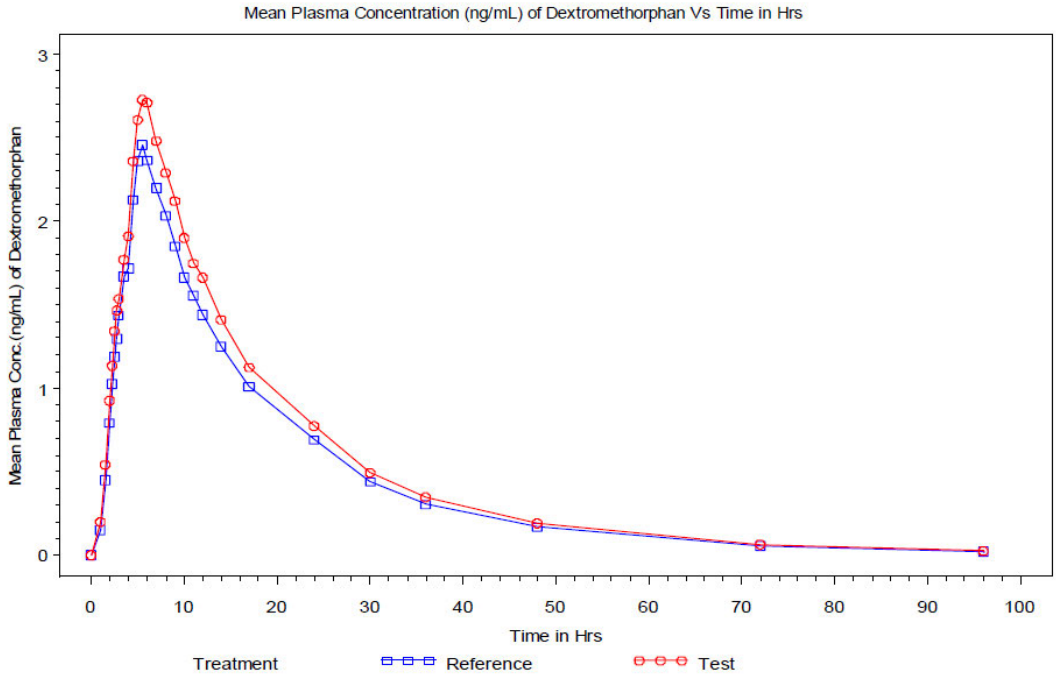
Sampling Hours	Test Product A			Reference Product B		
	Average	Std	CV %	Average	Std	CV %
0.00	0.001	0.008	525.69	0.003	0.016	628.73
1.00	0.200	0.303	151.24	0.150	0.143	95.37
1.50	0.542	0.757	139.85	0.451	0.517	114.78
2.00	0.926	1.138	123.00	0.792	0.847	107.06
2.25	1.135	1.263	111.29	1.027	1.108	107.92
2.50	1.343	1.524	113.44	1.191	1.349	113.24
2.75	1.466	1.598	109.04	1.299	1.433	110.28
3.00	1.535	1.657	107.95	1.436	1.619	112.71
3.50	1.770	1.964	110.96	1.670	1.891	113.23
4.00	1.910	2.142	112.16	1.719	1.933	112.47
4.50	2.359	2.446	103.68	2.128	2.254	105.93
5.00	2.606	2.631	100.96	2.360	2.320	98.32
5.50	2.727	2.751	100.88	2.456	2.401	97.73
6.00	2.710	2.798	103.22	2.365	2.366	100.02
7.00	2.481	2.732	110.13	2.197	2.332	106.15
8.00	2.290	2.709	118.30	2.034	2.334	114.75
9.00	2.121	2.572	121.26	1.849	2.184	118.09
10.00	1.900	2.488	130.92	1.663	1.995	119.94
11.00	1.748	2.365	135.34	1.554	1.930	124.15
12.00	1.663	2.309	138.83	1.439	1.810	125.84
14.00	1.410	2.162	153.32	1.250	1.658	132.70
17.00	1.125	1.883	167.35	1.009	1.442	142.93
24.00	0.774	1.489	192.48	0.690	1.152	167.02
30.00	0.495	1.141	230.23	0.440	0.836	190.08
36.00	0.348	0.896	257.62	0.304	0.659	216.71
48.00	0.193	0.586	304.39	0.169	0.443	263.13
72.00	0.065	0.249	381.85	0.057	0.198	344.38
96.00	0.026	0.111	420.52	0.021	0.088	416.99

Dextrorphan

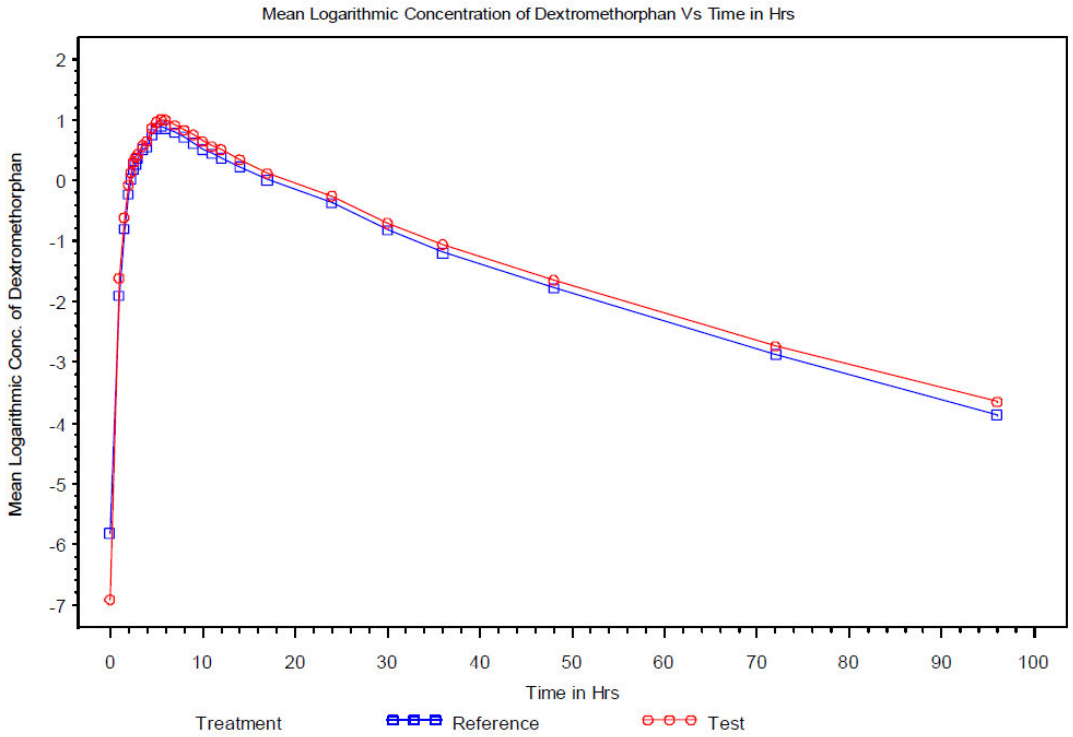
Sampling Hours	Test Product A			Reference Product B		
	Average	Std	CV %	Average	Std	CV %
0.00	0.000	0.000	-	0.000	0.000	-
1.00	0.263	0.291	110.52	0.201	0.185	92.08
1.50	0.524	0.479	91.30	0.425	0.361	85.00
2.00	0.754	0.559	74.09	0.621	0.466	75.12
2.25	0.858	0.582	67.83	0.714	0.515	72.11
2.50	0.944	0.598	63.31	0.759	0.516	67.94
2.75	0.994	0.596	60.00	0.805	0.540	67.01
3.00	1.036	0.595	57.47	0.826	0.523	63.31
3.50	1.071	0.552	51.55	0.880	0.501	56.96
4.00	1.094	0.538	49.18	0.887	0.476	53.60
4.50	1.293	0.618	47.80	1.075	0.522	48.51
5.00	1.296	0.623	48.07	1.084	0.491	45.34
5.50	1.210	0.564	46.63	1.031	0.446	43.31
6.00	1.148	0.535	46.58	0.965	0.419	43.46
7.00	0.928	0.435	46.90	0.807	0.357	44.27
8.00	0.796	0.383	48.15	0.686	0.302	44.01
9.00	0.679	0.321	47.26	0.595	0.277	46.58
10.00	0.570	0.282	49.43	0.506	0.223	44.17
11.00	0.510	0.252	49.37	0.455	0.207	45.49
12.00	0.440	0.221	50.19	0.399	0.184	46.11
14.00	0.341	0.187	54.67	0.322	0.151	46.74
17.00	0.207	0.114	55.29	0.205	0.106	51.89
24.00	0.099	0.063	63.83	0.101	0.058	57.50
30.00	0.051	0.040	79.27	0.051	0.039	76.16
36.00	0.031	0.036	116.51	0.030	0.027	91.27
48.00	0.013	0.019	153.42	0.011	0.015	141.09
72.00	0.003	0.010	286.95	0.002	0.007	303.27
96.00	0.001	0.005	376.08	0.001	0.003	532.85

Figure 1. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study (Firm-Submitted Plot)

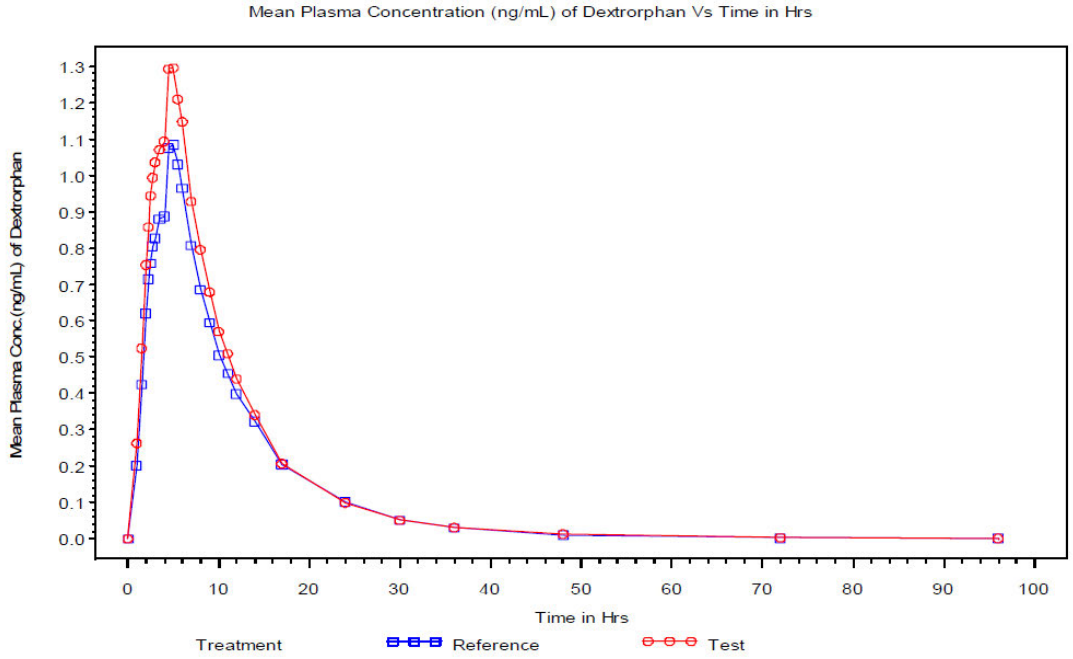
Dextromethorphan



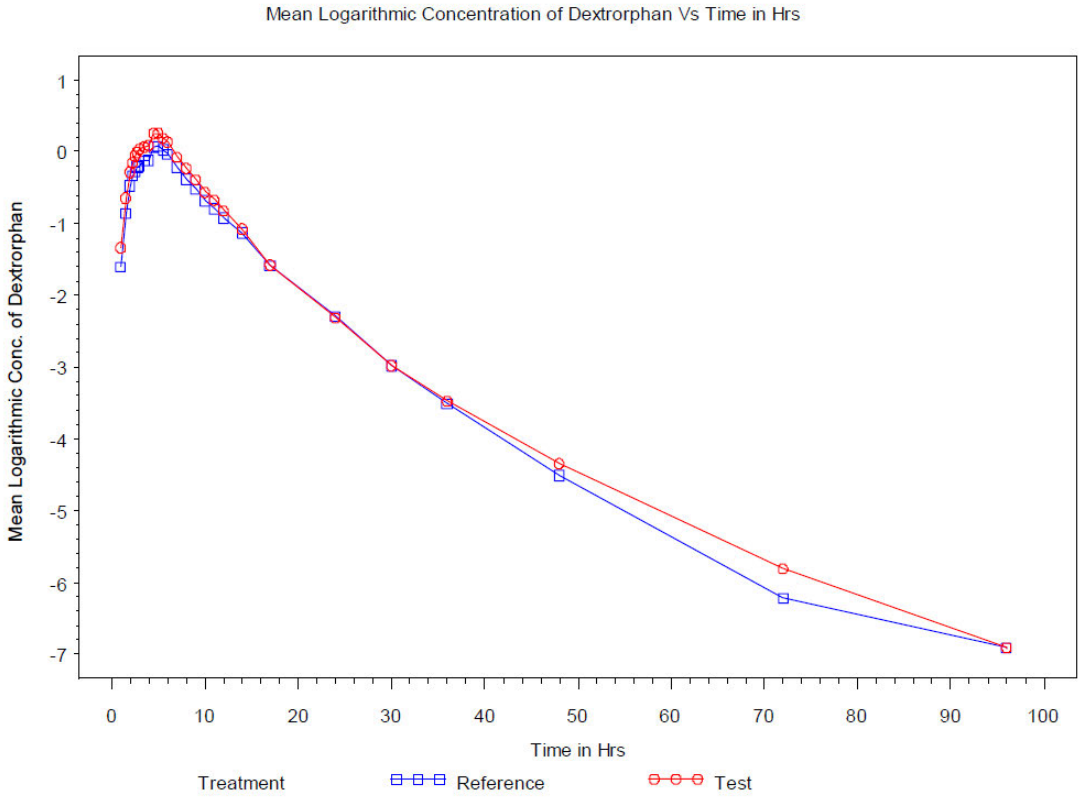
Semi Logarithmic Plot of Mean Plasma Concentraions Profile:



Dextrorphan



Semi Logarithmic Plot of Mean Plasma Concentraions Profile:



4.1.2 Single-dose Fed Bioequivalence Study

4.1.2.1 Study Design

Table 17. Study Information

Study Number	ARL/10/409
Study Title	A randomized, open label, balanced, two-treatment, two-period, two-sequence, single dose, crossover, bioequivalence study of Dextromethorphan Polistirex Extended-Release Suspension 30mg/5mL manufactured by Amneal Pharmaceuticals, USA with Delsym® (Dextromethorphan Polistirex Extended-Release Suspension) 30mg/5mL distributed by Reckitt Benckiser Inc., Parsippany, NJ 07054-0224, in normal, healthy, adult, male and female human subjects under fed conditions
Clinical Site (Name & Address)	Accutest Research Laboratories (I) Pvt. Ltd., A-31, M.I.D.C., T.T.C., Industrial Area, Khairane, Navi Mumbai-400 709, INDIA.
Principal Investigator	Dr. Suhas Khandave M.D. (Pharmacology)
Dosing Dates	Period I: 19/February/11 Period II: 28/February/11
Analytical Site (Name & Address)	(b) (4)
Analysis Dates	03/17/11 - 04/18/11
Analytical Director	(b) (4)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	58 days

Table 18. Product Information

Product	**Test**	**Reference**
Treatment ID	**A**	**B**
Product Name	Dextromethorphan Polistirex ER Suspension	Delsym® (dextromethorphan polistirex) Extended Release Suspension
Manufacturer	Amneal Pharmaceuticals, USA.	Reckitt Benckiser Inc., Parsippany, NJ 07054-0224
Batch/Lot No.	BB-ST-10012B	54554
Manufacture Date	12/01/10	
Expiration Date		03/2013
Strength	EQ 30 mg HBr/5 mL	EQ 30 mg HBr/5 mL
Dosage Form	Suspension	Suspension
Bio-Batch Size	(b) (4)	

Production Batch Size	(b) (4)	
Potency (Assay)	100.9%	99.2%
Content Uniformity (mean)	Top: 100.3% Middle: 100.3% Bottom: 100.2%	
Dose Administered	10 mL	10 mL
Route of Administration	Oral	Oral

Was the drug product administered per labeling?	Yes

Table 19. Study Design, Single-Dose Fed Bioequivalence Study

Number of Subjects	**Enrolled:** 58 **Dosed:** 56 **Completed:** 54 **Samples Analyzed:** 54 **Data Analyzed:** 53
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	9 days
Randomization Scheme (Sequence of T and R)	**Yes** **TR:** 1, 3, 5, 8, 9, 12, 14, 16, 18, 19, 21, 23, 26, 27, 29, 31, 33, 36, 38, 39, 41, 43, 45, 48, 50, 51, 54, 56 and 58 **RT:** 2, 4, 6, 7, 10, 11, 13, 15, 17, 20, 22, 24, 25, 28, 30, 32, 34, 35, 37, 40, 42, 44, 46, 47, 49, 52, 53, 55 and 57
Blood Sampling Times	Pre-dose (collect within 1 hour prior to dosing), 1.00, 1.50, 2.00, 2.25, 2.50, 2.75, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 7.00, 8.00, 9.00, 10.00, 11.00, 12.00, 14.00, 17.00, 24.00, 30.00, 36.00, 48.00, 72.00, and 96.00 hours post-dose (72.00 and 96.00 hours samples were collected on ambulatory basis)
Blood Sample Processing & Storage (include storage temperature)	Blood samples were collected in sodium heparin vacutainer at desired sampling time point. Intravenous indwelling cannula was kept patent by injecting 0.2 mL of heparinized saline solution except for each ambulatory sample. Blood samples were collected after discarding the first 0.2 mL of heparinized blood from i.v. cannula. Centrifugation of the samples was done within 30 minutes after the last blood sample collection of respective time point. Blood samples were centrifuged at 5°C, at 3500 RPM for 10 minutes under refrigeration. Plasma was separated and placed in suitable labeled vials in two aliquots, one as analytical sample and the other as control sample. All the plasma samples were stored below -50°C until the analysis of the samples.

Standard FDA Meal Used?	No. The details of the calories from fat, carbohydrate and protein for each individual component were provided. The test meal meets the high fat and high calorie recommendation.

Components of Non-standard FDA Meal Used in Fed Bioequivalence Study

Food-item	Amount	Ingredients	CHO (g)	Protein (g)	Fat (g)	Energy (calories)
HIGH FAT, HIGH CALORIE BREAKFAST						
01) Bread	2 small slices	Bread toast, (~35-40g)	15.0	3.0	0.5	80
		Butter, 10g	0.0	0.0	8.0	72
02) Paneer Bhurji	~ 150g	Paneer, 100g	7.9	13.4	23	292
		Onion, 50g	5.5	0.6	0	25
		Tomato, 20g	NA	NA	NA	NA
		Oil, 10ml/ 9g	0	0	10	90
03) Milk with almonds	1cup	Cow's milk, ~240ml	12	8	8	150
		Whole Almond, 15g	1.1	2.1	5.9	66
		Sugar, 10g	10	0	0	40
Total			**51.5**	**27.1**	**55.4**	**815**
Calories			**206**	**108**	**499**	
Percent			**25.3**	**13.3**	**61.4**	
LUNCH						

Comments on Study Design:

1. A total of 58 healthy adult subjects were enrolled in this study. 54 subjects completed the study. Data from 53 subjects were used in the dextromethorphan statistical analysis. Subject No. (b) (6) withdrew from the study due to non-compliance to fed condition in Period I (vomiting prior to dosing of Period I). Subject Nos. (b) (6) were withdrawn from the study due to adverse events (. Subject No. (b) (6) withdrew from the study due to onset of menses before dosing in Period I. Subjects No. (b) (6) was excluded from dextromethorphan statistical analysis r due to pre-dose concentration exceed more than 5% of Cmax. However, this subject was included in statistical analysis for dextrorphan. Therefore, the subjects included in the statistical analysis for dextromethorphan and dextrorphan are (b) (6) and (b) (6) respectively.

2. Sodium heparin is used as anticoagulant in sample collection, which is consistent with pre-validated bioanalytical method.

3. Guidance for Industry, Food-Effect Bioavailability and Fed Bioequivalence Studies (December 2002) states that "*A high-fat (approximately 50 percent of total caloric content of the meal) and high-calorie (approximately 800 to 1000 calories) meal is recommended as a test meal for food-effect BA and fed BE studies. This test meal should derive approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively*". The firm used vegetarian meals for their fed BE studies, maintaining a high-fat and high calorie meal.

4. There is no adequate data from which to conclude that vegetarian meals in bioequivalence studies will have the same effect on drug absorption as meals using meat as the main protein source. Therefore, the Division of Bioequivalence III does not encourage the use of vegetarian meals for fed bioequivalence studies.[11] The firm will be informed of the Agency's current recommendations as it pertains to fed meals.

5. The study design is **acceptable**.

[11] Control review of 71-559 (V:\FIRMSAM\COBALT\Controls\071559C1207.doc)

4.1.2.2 Clinical Results

Table 20. Demographics Profile of Subjects Completing the Bioequivalence Study

Fed Bioequivalence Study No. ARL/10/409			
		Treatment Groups	
		Test Product N = 53	Reference Product N = 53
Age (years)	Mean ± SD	26.53 ± 5.01	26.53 ± 5.01
	Range	18 - 39	18 - 39
Age Groups	< 18	Nil	Nil
	18 – 40	53 (100%)	53 (100%)
	41 – 64	Nil	Nil
	65 – 75	Nil	Nil
	> 75	Nil	Nil
Sex	Male	43 (81.13%)	43 (81.13%)
	Female	10 (18.87%)	10 (18.87%)
Race	Asian	53 (100%)	53 (100%)
	Black	Nil	Nil
	Caucasian	Nil	Nil
	Hispanic	Nil	Nil
	Other	Nil	Nil
BMI	Mean + SD	On Protocol basis Subjects were enrolled according to Life Insurance Corporation Chart	On Protocol basis Subjects were enrolled according to Life Insurance Corporation Chart
	Range		
Other Factors		Nil	Nil

Reviewer's Comment:

1. The demographic profile is listed for dextromethorphan. Subjects No. (b) (6) was excluded from dextromethorphan statistical analysis due to pre-dose concentration exceed more than 5% of Cmax. However, this subject was included in statistical analysis for dextrorphan.

2. The firm did not give detailed BMI mean and range, but noted "*On protocol basis subjects were enrolled according to Life Insurance Corporation Chart*". The reviewer checked the fed study protocol (Study Code: ARL/10/409, Version: 03, Date: November 15, 2010), the firm used "*body weight within ± 15% of ideal weight as related to height and body frame according to Life Insurance Corporation (LIC) Chart"* (attached in Section 4.1.1.2) as the study inclusion criteria. The reviewer

justifies that the study subjects' body weight distributes in the normal weight range (BMI: 18.5 – 25) and won't impact the outcome of the study.

Table 21. Dropout Information, Fed Bioequivalence Study

Subject No.	Reason	Period	Replaced?
(b) (6)	Subject was withdrawn due to non-compliance to fed condition	I	NA
	Subject was withdrawn due to adverse event after 72.00 hours post dose blood sample collection	I	NA
	Subject was withdrawn due to onset of menses in Period I before dosing	I	NA
	Subject was withdrawn due to adverse event after 09.00 hours post dose blood sample collection	II	NA

Table 22. Study Adverse Events, Fed Bioequivalence Study

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Study No. ARL/10/409	
	Test	Reference
Body as a whole		
Headache	01 (01.82%)	01 (01.79%)
Giddiness	01 (01.82%)	00 (00.00%)
Swelling over left cheek and periorbital region	00 (00.00%)	01 (01.79 %)
Fever	01 (01.82 %)	00 (00.00%)
Gastrointestinal		
Emesis	00 (00.00%)	01 (01.79 %)
Blood and Lymphatic system		
High eosinophil count[a]	00 (00.00%)	00 (00.00%)
High WBC count[a]	00 (00.00%)	00 (00.00%)
Urinary Tract Infection		
Abnormal urine analysis [a]	00 (00.00%)	00 (00.00%)
Total	**03 (05.45 %)**	**03 (05.36 %)**

[a] The laboratory parameter was normal during screening, but was found to be abnormal in the post-study evaluation. As the subject had received both the treatments, it is difficult to attribute this adverse event to either of the treatments.

Subjects Experiencing Emesis

Subject Number*	Test/Reference	Period	Time Post-Dose	Duration Between Dosing and Emesis (hrs)
(b) (6)	Reference	I	9.00	9.4 hours

Was the adverse event profile observed during the fasting bioequivalence study comparable for the test and reference product? Please comment.

Comparable. There is no strong evidence suggesting that the test drug caused substantially more serious adverse events comparing to the reference drug.

Are there any serious adverse events or death? If so, are they reported to the OGD Safety Committee?

No serious adverse events (SAEs) were reported during the fed BE study.

Are there any other safety concerns based on the adverse event profile?

No

Table 23. Protocol Deviations, Fed Bioequivalence Study

Type	Subject #s (Test)	Subject #s (Ref.)
Deviation in scheduled time in blood sample collection	(b) (6)	
Deviation in use of opened unused bottle of test and the reference investigational products for dispensing and dosing	--	--
Deviation in reporting of adverse event to IEC and sponsor within 14 calendar days	--	--
Deviation in measurement of 24.00 hours post dose vitals sign in Period II	(b) (6)	
Deviation in assigning the subject number serially as per the reporting time for the enrollment of Period I of the study[a]		

[a]As these deviations have occurred prior to any treatment being administered, their categorization with respect to the test or reference products cannot be done.

Comments on Dropouts/Adverse Events/Protocol Deviations:

- There were four (4) dropouts throughout the study. Subject No. (b) (6) withdrew from the study due to non-compliance to fed condition in Period I (vomi g prior to dosing of Period I). Subject No. (b) (6) was withdrawn from the study due to adverse event (moderate swelling over left cheek and periorbital region) after 72.00 hours post-dose blood sample collection in period I. Subject No. (b) (6) withdrew from the study due to onset of menses before dosing in period I. Subject No. (b) (6) was withdrawn from the study due to adverse event (moderate fever) after 9.00 hours post-dose blood sample collection in Period II. Those dropouts were in accordance with the firm's protocol (Study Code: ARL/10/409, Version 03).

- Subject No. (b) (6) experienced two mild adverse events including headache and emesis when received reference treatment in Period I, and experienced one moderate adverse event when received test treatment in Period II. The episode of vomiting for Subject No. (b) (6) with reference treatment is **within** 2 x the median of Tmax of dextr ethorphan (5.5 hrs). Subject No. (b) (6) was withdrawn from the study in Period II due to fever in moderate severity.

- All adverse events were mild in intensity, except the swelling over left cheek and periorbital region in Subject No. (b) (6) and fever in Subject No. (b) (6) were in moderate intensity. These adverse events are consistent with what has been reported in RLD[12], where drowsiness, dizziness, vomiting, rash, and fatigue have been reported.

- There were one hundred and eight (108) blood sampling deviations during the fed BE study. As per the protocol, post-dose blood sample collection was to be done within 2 minutes of the scheduled time. Time point deviations were due to cannula blockage or poor blood flow or during ambulatory samples. Most time deviations for non-ambulatory samples are minor (within 11 minutes). Thus are considered to be insignificant by the reviewer. Ambulatory samples were collected in 72.00 and 96.00 hours, thus the time deviations are in the elimination phase and won't impact the study outcome. The firm used actual sampling times for its pharmacokinetic (PK) calculations. Those time deviations should not change the bioequivalence study outcome.

- There were two (2) protocol deviations in measurement of 24.00 hours post-dose vitals sign in Period II. Per protocol, vital signs were to be measured within ± 30 minutes of scheduled time. However, 24.00 hours post dose vitals sign in Period II was erroneously taken 01 minute before the scheduled time of Subject No. (b) (6) minutes after the scheduled time of Subject No. (b) (6) These protocol deviations should not impact the bioequivalence study outcome.

- There were two (2) protocol deviations in assigning the subject number for the enrollment of Period I of the study. Per the protocol, all the volunteers were to be assigned serially the subject number as per their reporting time for the enrollment of Period I of the study. However check in for subject nos. (b) (6) (b) (6) was done after enrollment of subject no. (b) (6) as previously enrolled subject nos. (b) (6) (b) (6) went home due to personal reasons and hence were replaced with subject nos. (b) (6). This deviation should not impact the bioequivalence study outcome.

- There was one (1) protocol deviation in use of opened unused bottle of test and the reference investigational products for dispensing and dosing. Per protocol, the test and the reference investigational products (suspension) from opened unused bottle

[12] http://www.clinicalpharmacology-ip.com/Forms/Monograph/monograph.aspx?cpnum=179&sec=monadve&t=0

were to be destroyed at the end of the study period. However, in order to have sufficient quantity for retention purpose, this opened unused bottle was used for dispensing and dosing during subsequent study period. This protocol deviation should not impact the bioequivalence study outcome.

- There was one (1) protocol deviation in reporting of adverse event to IEC and sponsor. Per protocol, all adverse event and serious adverse event whether drug related or not were to be reported to the sponsor and IEC by the investigator within 14 calendar days. However, erroneously the reporting of adverse event to IEC and sponsor was delayed by 03 days. This protocol deviation should not impact the bioequivalence study outcome.

- There were four missing samples in the fed study. Missing sample values were labeled “MSV” in firm provided SAS transport dataset. These missing samples are in 72.00 hours or 96.00 hours ambulatory sampling time and are missing due to subjects not reported.

- The overall protocol deviations did not compromise the integrity of the study.

- The firm’s handling of dropouts/adverse events/protocol deviations are acceptable.

- The clinical results are **acceptable**.

4.1.2.3 Bioanalytical Results

Table 24. Sample Analysis Calibration and Quality Control

Dextromethorphan

Bioequivalence Study No. ARL/10/409 (Fed Study) Analyte Name: Dextromethorphan									
Parameter	**Standard Curve Samples**								
Concentration (ng/mL)	0.010	0.020	0.050	0.255	1.015	4.013	6.114	8.145	10.151
Inter day Precision (%CV)	3.25	5.59	3.39	2.31	1.68	1.73	2.11	1.59	1.79
Inter day Accuracy (%Actual)	101.21	96.55	93.34	97.59	103.25	101.79	101.42	101.03	101.33
Linearity (Range of r)	0.9981 to 0.9998 (r > 0.9900)								
Linearity Range (ng/mL)	0.010 ng/mL to 10.151 ng/mL								
Sensitivity/LOQ (ng/mL)	0.010 ng/mL								

Bioequivalence Study No. ARL/10/409 (Fed Study) Analyte Name: Dextromethorphan				
Parameter	**Quality Control Samples**			
	LQC	**MQC**	**HQC**	**M1QC**
Concentration (ng/mL)	0.030	3.069	7.130	1.501
Inter day Precision (%CV)	4.73	2.65	2.83	2.68
Inter day Accuracy (%Actual)	95.76	97.53	101.25	95.54

Dextrorphan

Bioequivalence Study No. ARL/10/409 (Fed Study) Analyte Name: Dextrorphan									
Parameter	**Standard Curve Samples**								
Concentration (ng/mL)	0.010	0.020	0.050	0.256	1.018	4.024	6.131	8.166	10.178
Inter day Precision (%CV)	1.87	3.74	2.92	1.85	2.17	1.84	2.35	1.68	1.72
Inter day Accuracy (%Actual)	100.36	98.48	94.07	98.40	104.16	101.69	100.92	100.48	99.94
Linearity (Range of r)	0.9974 to 0.9999 (r > 0.9900)								
Linearity Range (ng/mL)	0.010 ng/mL to 10.178 ng/mL								
Sensitivity/LOQ (ng/mL)	0.010 ng/mL								

Bioequivalence Study No. ARL/10/409 (Fed Study) Analyte Name: Dextrorphan				
Parameter	**Quality Control Samples**			
	LQC	**MQC**	**HQC**	**M1QC**
Concentration (ng/mL)	0.030	3.079	7.154	1.507
Inter day Precision (%CV)	4.58	2.75	3.23	3.65
Inter day Accuracy (%Actual)	96.23	97.81	100.59	95.10

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	Yes
Are there any concerns related to sample reanalysis or run rejection?	No

Were 20% of chromatograms included?	Yes, Subject Nos. (b) (6) (b) (6)
Did the firm provide numerical raw data (e.g. peak height, peak area, response count of IS and analyte) in run sequence order (i.e. Run log) in the instrument printout format?	**No**, the firm only submitted 20% of raw numerical data along with chromatograms.

Table 25. SOP's Dealing with Sample Analysis

SOP No.	Effective Date of SOP	SOP Title
(b) (4)		STANDARD OPERATING PROCEDURE FOR REPEAT SAMPLE ANALYSIS

Comments:

1. There was one rejected batch run (Run ID: SUB_29) for dextromethorphan and dextrorphan (simultaneous detection) due to interference in CS0 at analyte retention time & MRM more than 20% of LLOQ area. The rejection is in line with SOP # (b) (4) (Standard Operating Procedure for Batch Acceptance of Subject Sample Analysis; effective date (b) (4), which states "*in blank matrix, response of the interfering peaks, if any, at the retention time and MRM of analyte(s) and internal standard should be ≤ 20% of the extracted CS-1 (LLOQ) response for analyte(s) and ≤ 5% of the extracted mean internal standard response, respectively*". However, the firm did not provide raw numerical data to support its batch rejection. The firm will be asked to provide this information.

2. The firm used 208 (6.9 % of total 3020 sample analyzed) samples in its incurred sample reproducibility (ISR) testing for dextromethorphan and dextrorphan. ISR testing was performed as per SOP (b) (4) (Standard operating procedure incurred sample reanalysis (ISRA), effective date (b) (4)). The SOP acceptance criteria were set as at least 67% of the ISR samples should be within ±20% in terms of difference between repeat and initial values when compared with mean of initial and repeat values. A total of 208 out of 208 (100%) were found to be

within ±20% difference. Therefore, ISR for dextromethorphan and dextrorphan was found to be within acceptance criteria. The analytical methods are reproducible.

3. The firm only submitted 20% of raw numerical data along with chromatograms. The firm will be asked to provide complete (100%) raw numerical data including original and repeated analysis for all samples.

4. The firm's fed study assay is **incomplete** per the above comments.

4.1.2.4 Pharmacokinetic Results

Please note that the information below is obtained based on the assumption that the firm's repeated assays are acceptable. The PK parameters may change upon the DBIII receives additional information and re-evaluates the firm's repeated assays.

Firm Calculated

Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals

Dextromethorphan, N=53

Dextromethorphan Polistirex Extended Release Suspension, EQ 30 mg HBr/5 mL Dose (1 X 10 ml, EQ 60 mg Dextromethorphan HBr) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Bioequivalence Study (Study No. ARL/10/409), Dextromethorphan N=53 (Male = 43 and Female = 10)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (ng*hr/mL)	34.92	33.63	103.84	96.8629-111.3172
AUC0-inf (ng*hr/mL)	35.53	34.21	103.87	96.9404-111.2928
Cmax (ng/mL)	2.38	2.29	104.16	95.8039-113.2506

Dextrorphan, N=54 (supporting evidence)

Dextromethorphan Polistirex Extended Release Suspension, EQ 30 mg HBr/5 mL Dose (1 X 10 ml, EQ 60 mg Dextromethorphan HBr) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Bioequivalence Study (Study No. ARL/10/409), Dextrorphan N=54 (Male = 44 and Female = 10)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (ng*hr/mL)	16.63	15.89	104.63	98.2602-111.4193
AUC0-inf (ng*hr/mL)	17.04	16.25	104.85	98.5517-111.5501
Cmax (ng/mL)	1.51	1.45	104.48	96.0909-113.6073

Arithmetic Mean Parameters and Ratios

Dextromethorphan, N=53

Formulations		C_{max} (ng/mL)	AUC_{0-t} (ng*hr/mL)	AUC_{0-inf} (ng*hr/mL)	T_{max} (hrs)	K_{el} (hrs^{-1})	$t_{1/2}$ (hrs)	AUC_{0-t}/ AUC_{0-inf} Ratio
Test Product A (N=53)	Arithmetic Mean ± SD	3.85 ± 4.98	84.66 ± 199.77	93.04 ± 250.76	5.70 ± 1.24	0.08 ± 0.02	10.10 ± 5.60	98.37 ± 3.16
Reference Product B (N=53)	Arithmetic Mean ± SD	3.34 ± 3.55	72.29 ± 160.01	78.78 ± 199.72	5.96 ± 1.61	0.08 ± 0.02	9.90 ± 5.12	98.38 ± 3.00
% Ratio (A/B)	Arithmetic Mean	115.22	117.11	118.11	-	-	-	-

Dextrorphan, N=54

Formulations		C_{max} (ng/mL)	AUC_{0-t} (ng*hr/mL)	AUC_{0-inf} (ng*hr/mL)	T_{max} (hrs)	K_{el} (hrs^{-1})	$t_{1/2}$ (hrs)	AUC_{0-t}/ AUC_{0-inf} Ratio
Test Product A (N=54)	Arithmetic Mean ± SD	1.79 ± 0.84	18.54 ± 8.17	18.77 ± 8.10	4.81 ± 1.40	0.10 ± 0.04	9.29 ± 12.26	97.97 ± 6.17
Reference Product B (N=54)	Arithmetic Mean ± SD	1.70 ± 0.75	17.33 ± 6.82	17.55 ± 6.77	5.22 ± 1.86	0.11 ± 0.04	8.75 ± 9.14	98.04 ± 4.94
% Ratio (A/B)	Arithmetic Mean	105.05	106.95	106.93	-	-	-	-

Is there a Tmax difference between T and R	No , T/R ratio: 1 (5.5 hr vs. 5.5 hrs)
Are any CIs marginal?	No
Were the subjects dosed in groups?	No
Is the study design replicate and/or reference-scaled?	No
Is sampling time adequate?	Yes

Overall Comment:

- The firm excluded Subjects No. (b) (6) from dextromethorphan statistical analysis due to pre-dose concentrations exceed m re than 5% of Cmax. This subject was included in the statistical analysis for dextrorphan. The data exclusion and inclusion were in accordance with the firm's protocol (Study Code: ARL/10/409, Version 03).

- Per the RLD labeling, no food effect is specified for Delsym® (Dextromethorphan Polistirex Extended Release Suspension), EQ 30MG HBR/5ML. In the current application, the Cmax concentration of dextromethorphan was increased by 20.8% and 29.4% for test and reference products, respectively. The AUCt of dextromethorphan was increased by 39.3% and 44.3% for test and reference products, respectively. The Cmax concentration of dextrorphan was increased by 25.8% and 45.0% for test and reference products, respectively. The AUCt of dextrorphan was increased by 40.8% and 54.7% for test and reference products, respectively.

- Based on the firm's calculation, the 90% CIs for the least squares geometric means of LnAUCt, LnAUCi and LnCmax of dextromethorphan meet the BE criteria of 80.00-125.00%.

- The PK parameters of the test and reference for the active metabolite dextrorphan were comparable. Therefore the metabolite data are supportive.

- However, the firm's *in vivo* BE study under fed conditions is still **inadequate** due to the deficiencies specified in Section 3.7.

Table 28. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study (Firm-submitted Data in Firm's Format)

Dextromethorphan

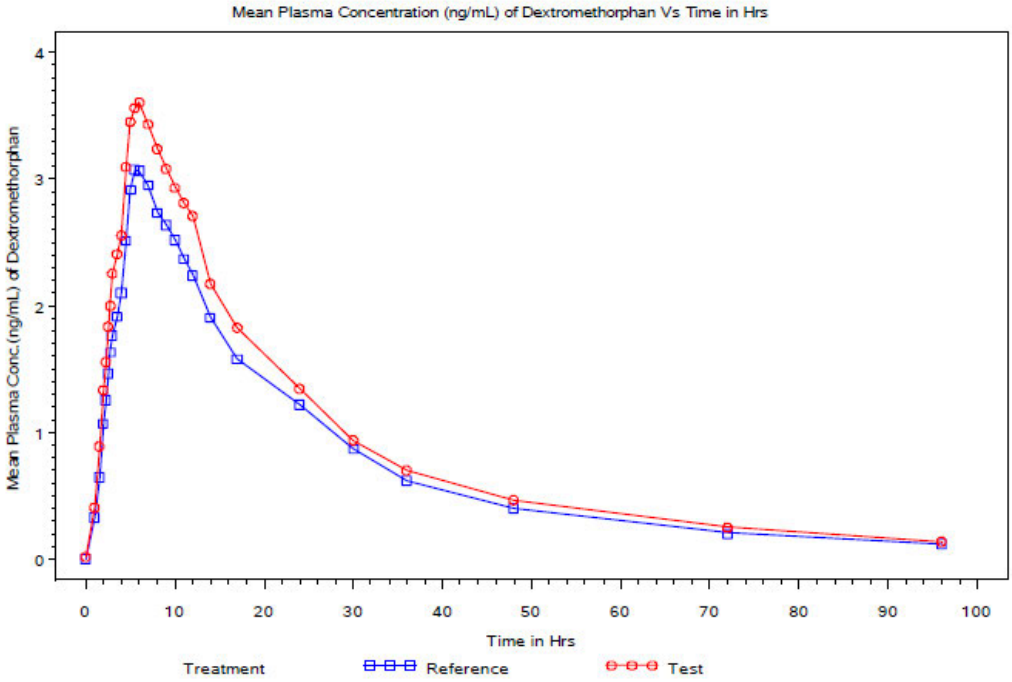
Sampling Hours	Test Product A			Reference Product B		
	Average	Std	CV %	Average	Std	CV %
0.00	0.018	0.120	675.03	0.000	0.000	-
1.00	0.407	0.453	111.27	0.329	0.282	85.96
1.50	0.892	0.769	86.23	0.647	0.463	71.65
2.00	1.335	1.183	88.58	1.072	0.839	78.28
2.25	1.557	1.500	96.28	1.259	0.969	76.98
2.50	1.838	1.917	104.30	1.466	1.154	78.68
2.75	2.001	2.169	108.40	1.635	1.359	83.07
3.00	2.257	2.651	117.47	1.766	1.530	86.65
3.50	2.410	2.879	119.45	1.915	1.737	90.67
4.00	2.558	3.240	126.66	2.101	1.997	95.07
4.50	3.098	3.946	127.36	2.517	2.482	98.62
5.00	3.455	4.288	124.11	2.919	2.925	100.22
5.50	3.565	4.345	121.90	3.075	3.250	105.69
6.00	3.607	4.500	124.78	3.068	3.223	105.05
7.00	3.435	4.454	129.67	2.955	3.320	112.34
8.00	3.241	4.515	139.30	2.737	3.233	118.13
9.00	3.084	4.501	145.96	2.639	3.278	124.20
10.00	2.934	4.517	153.94	2.520	3.297	130.85
11.00	2.814	4.643	165.00	2.371	3.308	139.54
12.00	2.711	4.780	176.28	2.242	3.243	144.65
14.00	2.175	3.966	182.33	1.906	3.075	161.37
17.00	1.829	3.593	196.37	1.580	2.821	178.58
24.00	1.346	3.147	233.79	1.222	2.718	222.38
30.00	0.940	2.587	275.09	0.869	2.402	276.34
36.00	0.702	2.252	320.79	0.621	2.032	327.24
48.00	0.467	1.862	398.36	0.401	1.638	408.65
72.00	0.250	1.341	536.76	0.204	1.093	537.01
96.00	0.138	0.844	609.69	0.117	0.725	618.89

Dextrorphan

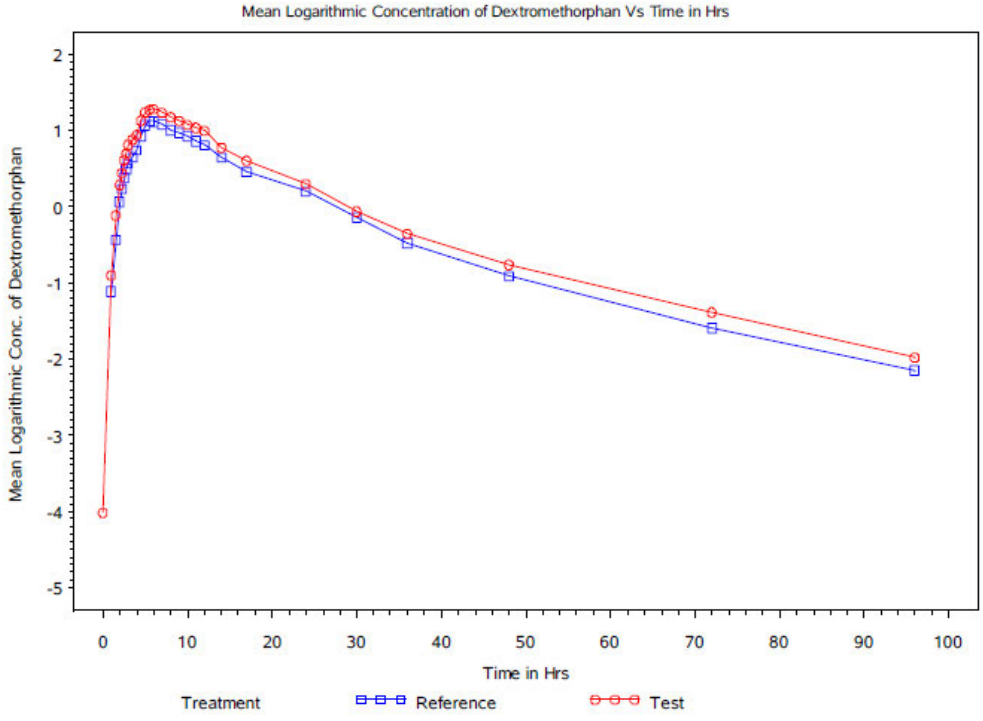
Sampling Hours	Test Product A			Reference Product B		
	Average	Std	CV %	Average	Std	CV %
0.00	0.000	0.000	-	0.000	0.000	-
1.00	0.458	0.432	94.26	0.397	0.350	88.12
1.50	0.836	0.622	74.42	0.685	0.490	71.59
2.00	1.080	0.706	65.30	0.940	0.579	61.61
2.25	1.170	0.744	63.63	1.049	0.622	59.28
2.50	1.232	0.767	62.24	1.121	0.624	55.68
2.75	1.282	0.765	59.68	1.186	0.657	55.43
3.00	1.350	0.818	60.61	1.226	0.664	54.15
3.50	1.359	0.748	55.02	1.247	0.622	49.85
4.00	1.376	0.743	54.01	1.281	0.602	47.04
4.50	1.616	0.789	48.83	1.544	0.703	45.52
5.00	1.704	0.814	47.76	1.607	0.724	45.04
5.50	1.597	0.736	46.11	1.467	0.647	44.09
6.00	1.503	0.675	44.89	1.383	0.576	41.63
7.00	1.263	0.541	42.84	1.181	0.476	40.33
8.00	1.097	0.473	43.12	1.029	0.420	40.81
9.00	0.982	0.437	44.45	0.901	0.362	40.17
10.00	0.914	0.442	48.34	0.865	0.388	44.88
11.00	0.814	0.401	49.24	0.781	0.380	48.62
12.00	0.673	0.337	50.04	0.645	0.305	47.37
14.00	0.493	0.265	53.84	0.473	0.230	48.66
17.00	0.315	0.173	54.85	0.304	0.167	54.77
24.00	0.154	0.084	54.62	0.146	0.088	60.24
30.00	0.074	0.047	63.41	0.072	0.051	70.95
36.00	0.043	0.035	81.91	0.041	0.033	80.57
48.00	0.018	0.020	114.26	0.016	0.018	113.72
72.00	0.004	0.009	261.22	0.003	0.008	274.14
96.00	0.001	0.005	364.81	0.001	0.004	363.74

Figure 2. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study (Firm-submitted Plot)

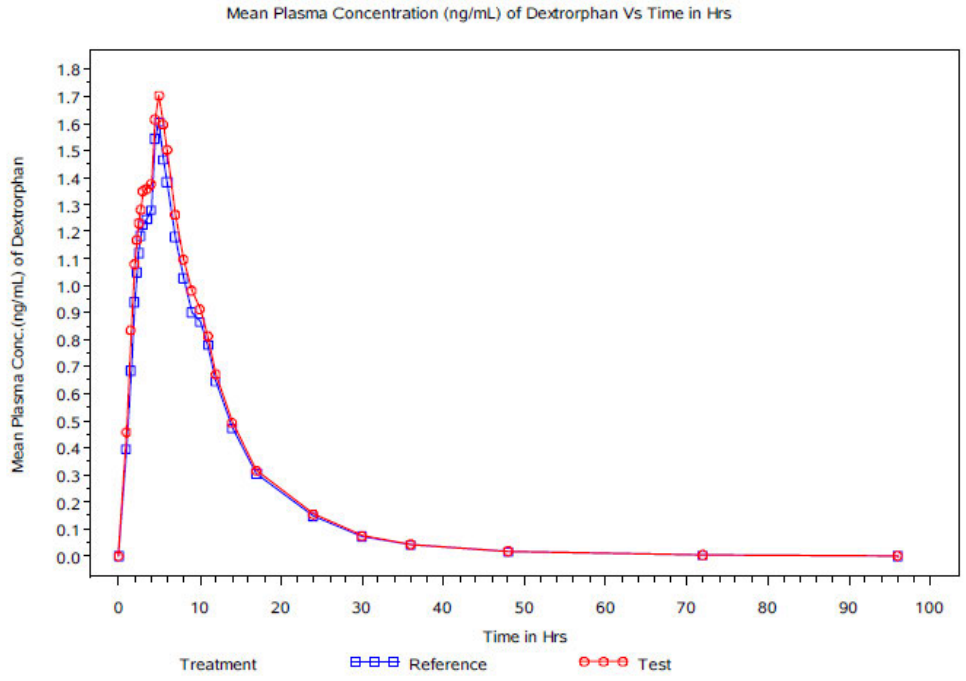
Dextromethorphan



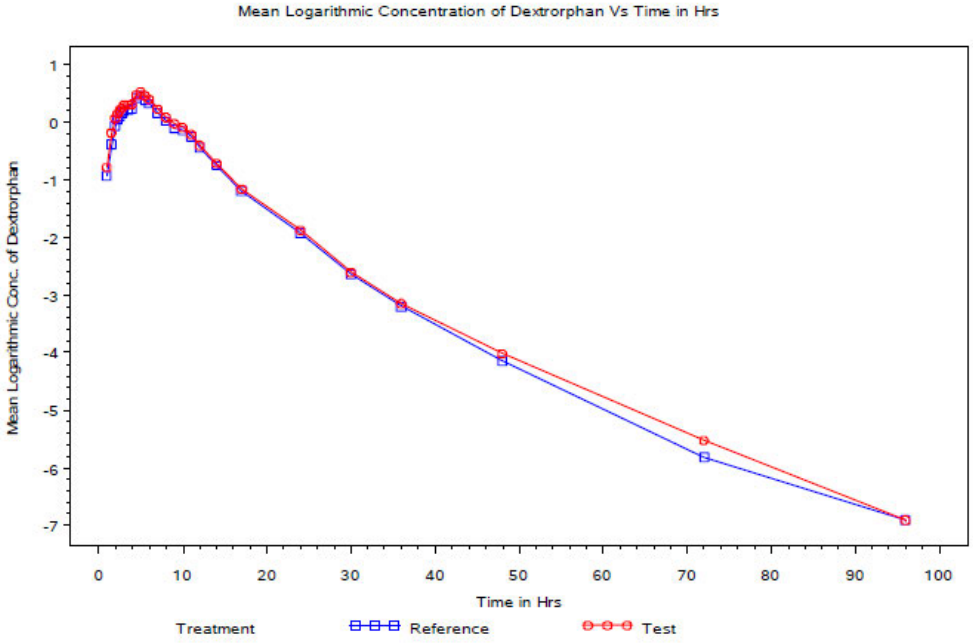
Semi Logarithmic Plot of Mean Plasma Concentraions Profile:



Dextrorphan



Semi Logarithmic Plot of Mean Plasma Concentraions Profile:



4.2 Formulation Data

Test Product: Dextromethorphan Polistirex ER Suspension, EQ 30 mg HBr/5 mL

Ingredients	Quantity in mg/ 5 mL	mg per dose (Dose: 10 mL)	Quantity in %w/v	Quantity in %w/w[1]
Dextromethorphan Hydroboromide	30.00	60.00		
Sodium Polystyrene Sulfonate, USP (b) (4)				
Polyethylene Glycol 3350 (b) (4) NF				
Ethylcellulose, NF (b) (4)				
Corn Oil, NF				
Tragacanth (b) (4) NF				
Xanthan Gum, NF				
Propylene Glycol, USP				
Methylparaben, NF				
Propylparaben, NF				
Sucrose, NF				
Edetate Disodium, USP				
(b) (4) Citric Acid, USP				
Polysorbate-80 (b) (4) NF				
FD & C Yellow # 6				
(b) (4) Flavor (b) (4)				
HCl , NF (b) (4) OR NaOH (b) (4) NF				
Purified Water, USP				
Total			**100**	**100**

(b) (4)

[13] DARRTS ANDA 203133, 0001(2) 08/25/2011 ORIG-1/Quality/Response to Information Request, ORIG-1/Quality/Quality Information, Module 1.2 Cover Letters

Are the amounts of all inactive ingredients based on Maximum Daily Dose (MDD) within IIG (per unit) limits?	No, the firm has conducted a number of toxicity studies to justify the amounts of sodium polystyrene sulfonate used in the test formulation.
If no, are they all above/within IIG (per day) limits?	No, Please see comments
Are all color additives and elemental iron within limits specified by CFR (if applicable) or less than 0.1% of the total unit weight (w/w)?	N/A.
Are all strengths of the test product proportionally similar per the BA/BE guidance criteria?	N/A

Comments:

1. Per RLD labeling, the maximum daily dose (MDD) for Dextromethorphan Polistirex ER Suspension, EQ 30 mg HBr/5 mL for adults, elderly and adolescents (age ≥12 years) is 120 mg/day [14].

2. The RLD formulation is listed as below:

[14] http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021449s020lbl.pdf

Delsym® (Dextromethorphan Polistirex Extended Release Suspension), EQ 30MG HBr/5mL (N018658)[15]

Current approved and marketed Delsym® Orange Suspension		
INGREDIENTS	**Spec. No.**	**mg/5 mL**
(b) (4) **FD&C Yellow # 6** (b) (4)		(b) (4)
Citric Acid, (b) (4)		
(b) (4)		
Sucrose, NF		
High Fructose Corn Syrup (b) (4)		
Propylene Glycol		
Methylparaben		
Propylparaben		
Xanthan Gum*		
(b) (4) Tragacanth*		
Polysorbate 80		
Dextromethorphan Polistirex**		
(b) (4)		
Flavor (b) (4) (b) (4)		
Water, Purified		

(b) (4)

[15] DARRTS, NDA 018658, REV-CLINPHARM-01 (General Review), Partha Roy, Review Completed: 05/11/2007

Ingredient	Quantity at Maximum Daily Dose*	CDER's IIG Limits by Oral route[18] Amount (mg)	Test formulation Below or Exceed FDA IIG
Sodium Polystyrene Sulfonate, USP (b) (4) (b) (4)			(b) (4)
Polyethylene Glycol 3350 (b) (4) NF			
Ethylcellulose, NF (b) (4)			
Corn Oil, NF			
Tragacanth (b) (4) NF			
Xanthan Gum, NF			
Propylene Glycol, USP			
Methylparaben, NF			
Propylparaben, NF			
Sucrose, NF			
Edetate Disodium, USP			
(b) (4) Citric Acid, USP			
Polysorbate-80 (b) (4) NF			
FD & C Yellow # 6			
(b) (4) Flavor (b) (4)			

* Maximum recommended daily dose is EQ 120 mg HBr.

(b) (4)

(b) (4)

2 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

6. (b) (4)

7. Therefore, the formulation of the test product is **inadequate.**

4.3 Office of Study Integrity and Surveillance (OSIS) Inspection

(b) (4)

Summary OSI Inspection History for the Clinical and Analytical Sites:

1. NDA 205040 (Clinical Site): The OSI inspection was requested in 10/10/2013[32]. The clinical study was conducted between 07/13/2011 – 07/24/2011[33], which is within ± 3.5 years from the study dates of the current ANDA. The OSI inspection outcome for the clinical site was VAI (Voluntary Action Indicated).

   OSI finding #1: An investigation was not conducted in accordance with the signed statement of investigator and investigational plan. Specifically, your Clinical Investigator is responsible for ensuring that an investigation is conducted per signed Form FDA-1572 and the study protocol. However, review of records of the Study Protocols ARL/11/227 and ARL/11/228 revealed the following deviations:

   A) Your Clinical Investigator failed to delegate the responsibilities in writing for ensuring that all associates and employees assisting in these investigations are informed about their obligation in meeting the above commitments. Instead, he signed one document dated 07/11/11 and 07/11/11 for documenting his discussion with a Sub/Co-Investigator regarding the details of Study Protocols ARL/11/227 and ARL/11/228, respectively.

   B) Your Clinical Investigator did not review or countersign any documents of the study subjects which include informed consent forms (ICF), Screening, including their blood tests/ECG reports required for their enrollment in the study, randomization and drug dosing, other case report forms (CRF), protocol deviation, adverse event reports and post study blood tests. Instead, he countersigned a coversheet each of all CRFs dated 08/01/11 and 08/02/11 of the aforesaid of Study Protocols ARL/11/227 and ARL/11/228, respectively.

   OSI evaluation: The clinical investigator should have delegated authorities to Sub/Co-Investigator and associates in writing for their responsibilities for studies ARL/11/227 and ARL/11/228. Also, the investigator himself should have reviewed

[32] DARRTS NDA 205040 ARAOJO, DAVID E, 10/10/2013 N/A 10/10/2013 FRM-CONSULT-09 (Biopharmaceutical Inspections Request)
[33] NDA 205040 reference BE studies submitted (b) (4)
(b) (4)

informed consent forms (ICF), screening, drug dosing, protocol deviation, adverse event reports and post study blood tests. However, the observation may not have impact on results of the clinical studies. This review cannot ascertain whether human subject safety was affected. The clinical data from studies ARL/11/227 and ARL/11/228 are acceptable for review.

Reviewer's Comments for OSI Finding #1: In current application, the clinical investigator has countersigned the documents of the study subjects such as informed consent forms (ICF), randomization and drug dosing, other case report forms (CRF), protocol deviation, and adverse event reports. Therefore, the reviewer has determined that that the above OSI finding #1 **does not have an** impact on the current ANDA.

2. (b) (4)

4.4 ATTACHMENT

Justification not to issue ECD/IR for ANDA 203133

From: Chen, Alicia Sent: Mon 2/23/2015 9:47 AM
To: Ren, Ke; Wang, Yun (OGD/DB3)
Cc:
Subject: FW: ECD/IR for ANDA 203133

Hello Ke and Yun,

The RPM replied that her recommendation is to hold off on our ECD/IR and to issue a CR. This is because Chemistry has major deficiencies and labeling has deficiencies as well. Please let me know what you think and what you'd like to do, and I will reply back to the RPM with our decision.

Thanks!,
Alicia

[34] DARRTS NDA 205425 ZEBALLOS, MONICA I, 07/24/2013 N/A 07/24/2013 FRM-CONSULT-09 (Biopharmaceutical Inspections Request)
[35] DARRTS NDA 205425 0002 (3) 07/02/2013 ORIG-1/Multiple Categories/Subcategories Module 5.3.1.2 Comparative BA and BE Study Reports

BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 203133

APPLICANT: Amneal Pharmaceuticals

DRUG PRODUCT: Dextromethorphan Polistirex Extended Release Suspension, EQ 30 mg HBr/5 mL

The Division of Bioequivalence III (DBIII) has completed its review and has identified the following deficiencies:

Deficiencies Related to the Bioequivalence (BE) Studies

1. You did not submit **ALL** analytical raw numerical data. Please provide complete (100%) raw numerical data, in the instrument printout format, including original and repeated analysis for all samples, including the data of peak area/height for the analyte, peak area/height for the internal standard, ratio of the peak area/height for the analyte to the peak area/height for the internal standard, dilution factor (if any), and the corresponding concentration for each assayed and reassayed sample of all samples, calibration standard concentration samples, and quality control samples for your fasting (#ARL/10/408) and fed (#ARL/10/409) BE studies.

2. You did not submit concentration and pharmacokinetic data of dextromethorphan in SAS transport files (.xpt) for fasting (#ARL/10/408) study subjects. Instead, you provided concentration and pharmacokinetic data of dextromethorphan in SAS transport files (.xpt) for fed (#ARL/10/409) study in duplicated. Therefore, please submit dextromethorphan concentration and pharmacokinetic data for the fasting study in SAS transport format.

Deficiency Related to the Formulation

3. (b) (4)

For Future Submissions

4. You used a non-standard high-fat vegetarian breakfast in the fed BE study (#ARL/10/409). Currently, there is no adequate data from which to conclude that a high-fat vegetarian breakfast served prior to dosing in BE studies under a fed state will have the same effect on drug absorption as the standard FDA high-fat breakfast

using meat as the main protein source. Therefore, the DBIII does not encourage the use of vegetarian meals for breakfast in future fed BE study.

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Hoainhon N. Caramenico, M.S., M.S.
Acting Director, Division of Bioequivalence III
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

4.5 Outcome Page

ANDA: 203133

COMPLETED ASSIGNMENT FOR 203133 ID: 25348

Reviewer: Yun, Wang **Date Completed:**

Verifier: , **Date Verified:**

Division: Division of Bioequivalence

Description: Dextromethorphan Polistirex ER Suspension, EQ 30 mg HBr/5 mL, Amneal Pharmaceuticals

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Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
25348	7/8/2011	Bioequivalence Study (REGULAR)	Fasting Study	1	1
25348	7/8/2011	Bioequivalence Study (REGULAR)	Fed Study	1	1
25348	7/8/2011	Quality Assessment	Quality	4	4
				Total:	6

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	203133		
Drug Product Name	Dextromethorphan Polistirex Extended-Release Suspension		
Strength (s)	30 mg/5 mL		
Applicant Name	Amneal Pharmaceuticals		
Applicant Address	85 Adams Avenue, Hauppauge, New York: 11788		
US Agent Name and the mailing address	Alpesh Patel, Vice President, Global Regulatory Affairs 85 Adams Avenue, Hauppauge, NY 11788		
US Agent's Telephone Number	631-952-0214 Ext. 183		
US Agent's Fax Number	631-299-3995		
Original Submission Date(s)	(07/07/2011, and amendments 04/24/2012 and 06/14/2012)		
Submission Date(s) of Amendment(s) Under Review	01/04/2013 (supporting document #12)		
First Generic	No		
Reviewer	Z.Z. Wahba, Ph.D.		
Study Number (s)	ARL/10/408	ARL/10/409	
Study Type (s)	Fasting	Fasting	
Strength(s)	10 ml suspension, oral	10 ml suspension, oral	
Clinical Site	Accutest Research Laboratories		
Clinical Site Address	Accutest Research Laboratories (I) Pvt. Ltd., A-31, M.I.D.C., T.T.C., Industrial Area, Khairane, Navi Mumbai-400 709, INDIA.		
Analytical Site	(b) (4)		
Analytical Address			

OVERALL REVIEW DISSOLUTION RESULT	**ADEQUATE**

BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	STUDY/TEST TYPE	STRENGTH	REVIEW RESULT
1	Fasting	30 mg/5 mL	**PENDING**
1	Fed	30 mg/5 mL	**PENDING**
1	Dissolution	30 mg/5 mL	**ADEQUATE**

REVIEW OF A DISSOLUTION AMENDMENT

I. EXECUTIVE SUMMARY

This is a bioequivalence (BE) amendment (01/04/2013) for Amneal's Dextromethorphan Polistirex Extended Release Oral Suspension, 30 mg/5 mL. In this amendment the firm acknowledged its acceptance of the FDA recommended dissolution method and specifications (communicated on 05/16/2012), as follows:

Dissolution Medium:	500 mL of 0.1N HCl at 37ºC + 0.5ºC for 1 hour followed with addition of 400 mL of phosphate buffer (final pH 6.8) containing 0.25 M Sodium chloride after 1 hr sampling.
USP Apparatus:	II (Paddle)
RPM:	50
Temperature:	37°C± 0.5°C
Specifications	Acid Stage: 1 hr (b) (4) Buffer Stage: 30 min: (b) (4); 60 min: (b) (4); 360 min (6 hrs) NLT (b) (4)

Note: Individual dissolution data are provided in the Attachment section.

Brief Background:
The original dissolution review [DARRTS ANDA 203133 REV-BIOEQ-02(Dissolution Review), 02/27/2012] was found incomplete. The submitted dissolution results indicated that the FDA-recommended method [500 mL of 0.1 N HCl, paddle at 50 rpm] is not appropriate for this drug due to slow release (b) (4) at 180 minutes. In addition, the firm only collected samples up to 180 minutes. The dissolution testing was found incomplete.

On 04/24/2012, the firm submitted amendment providing additional dissolution testing as requested by the Division of Bioequivalence I (DB I). Based on the comparative dissolution data obtained in different dissolution media [DARRTS ANDA 203133 REV-BIOEQ-02(Dissolution Review), 05/08/2012], the DB I recommended the above dissolution method and specifications as the most appropriate and discriminating method for the test product. The firm was asked to acknowledge the following dissolution method and specifications.

On 06/14/2012 and 08/08/2012, the firm submitted two amendments [DARRTS ANDA 203133 REV-BIOEQ-02(Dissolution Review), 07/20/2012 and 09/12/2012]. In these amendments, the firm accepted the FDA recommended dissolution method; however, the firm proposed different specifications (see below):

The firm's proposed specifications		
	Time Points	% Dissolution
Acid Stage	1 hour	(b) (4)
Buffer Stage	30 minutes	
	60 minutes	
	360 minutes (6 hrs)	

To justify its request of change, the firm provided the results of dissolution data from three lots two of which were stored lots for 17 and 18 months [DARRTS ANDA 203133 REV-BIOEQ-02(Dissolution Review), 07/20/2012]. The DB did not accept the dissolution specifications on the basis of the dissolution testing data on the stored lots. Therefore, in the latest DBI letter to the firm, dated 09/12/2012, for supporting the firm's newly proposed specifications, the DBI requested that the firm submit dissolution data using 12 units of the newly manufactured test lot, comparing it with 12 units of an unexpired lot of the reference listed drug product. In addition, the firm was asked to provide documents to show that the new lot is manufactured, controlled and tested under the same conditions as the test biolot used in the original bioequivalence studies.

In the current amendment responding to the DBI's 09/12/2012 letter, instead of providing the data requested, the firm acknowledged its acceptance of the original FDA recommended dissolution method and specifications. The dissolution portion of this ANDA is now adequate. The BE will review the fasted and fed BE studies at a later date.

II. TABLE OF CONTENTS

III. BACKGROUND ON THE DISSOLUTION SECTION OF THIS APPLICATION:

See the original dissolution review [DARRTS ANDA 203133 REV-BIOEQ-02(Dissolution Review), 02/27/2012, and 05/08/2012].

IV. RESPONSES TO DEFICIENCY COMMENTS:

Deficiency comments are as stated in the DB dissolution review of the original submission [DARRTS ANDA 203133 REV-BIOEQ-02(Dissolution Review), 09/12/2012].

DB's Deficiency Comment

Your submitted dissolution data for a newly manufactured test lot, for only 6 units, to support your proposed change in the FDA-recommended specifications for your drug product, Dextromethorphan Polistirex Extended-Release Suspension, 30 mg/5 mL, are incomplete. Please submit dissolution data for 12 units of the newly manufactured test lot, comparing it with 12 units of an unexpired lot of the reference listed drug product.

Please be informed of the following:

(1) In the submission of your dissolution study amendment, please include a statement confirming that the new lot was manufactured, controlled and tested under the same conditions as the biobatch (Lot #BB-ST-10012B) used in the original bioequivalence studies, in terms of i) formulation, ii) manufacturing process, iii) in-process controls, iv) specifications, v) site, vi) equipment, etc.

(2) Please inform the Division of Chemistry (DC), Office of Generic Drugs, of the manufacturing of the new batch of the test product, and submit to the Division of Chemistry the complete Chemistry Manufacturing and Controls (CMC) data and documentation of the new test lot for evaluation by the DC.

(3) Please submit to the DBI the Certificates of Analysis (COA) for the new test lot and the unexpired reference lot used in the additional request dissolution testing. Please clearly indicate the dissolution testing date.

Firm's Response to the Deficiency Comment

After evaluating the dissolution data of all the batches (R&D Batches and ANDA submission batch), Amneal acknowledges the agency's recommended dissolution method and specifications recommended in the bioequivalence deficiency letter dated May 16, 2012 (see blow).

Dissolution Medium:	500 mL of 0.1N HCl at 37 °C ± 0.5 °C for 1 hour followed with addition of 400 mL of phosphate buffer (final pH 6.8) containing 0.25 M Sodium chloride after 1 hr sampling.
USP Apparatus:	II (Paddle)
RPM :	50
Temperature:	37 º C ± 0.5 º C
Specifications	Acid Stage: 1 hr (b) (4) Buffer Stage: 30 min: (b) (4) 60 min: (b) (4) 360 min (6 hrs) NLT (b) (4)

Accordingly, Amneal has revised the drug product specifications and analytical method to include the FDA recommended specifications and dissolution testing parameters. Please refer Module 3.2.P.5.1 for the revised drug product specifications and Module 3.2.P.5.2 for the revised dissolution test method. The revised dissolution test method was validated as per ICH guidance in the actual lab conditions and the validation report is provided in Module 3.2.P.5.3 of this amendment.

DB's Comment on the Firm's Response to the Deficiency Comment

The firm's response is acceptable. The firm acknowledged its acceptance of the following FDA-recommended dissolution method and specifications:

Dissolution Medium:	500 mL of 0.1N HCl at 37ºC ± 0.5ºC for 1 hour followed with addition of 400 mL of phosphate buffer (final pH 6.8) containing 0.25 M Sodium chloride after 1hr sampling.
USP Apparatus:	II (Paddle)
RPM:	50
Temperature:	37°C± 0.5°C
Specifications	Acid Stage: 1 hr (b) (4) Buffer Stage: 30 min: (b) (4) 60 min: (b) (4); 360 min (6 hrs) NLT (b) (4)

IV. DEFICIENCY COMMENTS:

None

V. RECOMMENDATIONS:

The in vitro dissolution testing conducted by Amneal Pharmaceuticals on its Dextromethorphan Polistirex Extended Release Oral Suspension, 30 mg/5 mL, is acceptable. The DB I acknowledges that the firm will performed the following recommended dissolution method and specifications.

Dissolution Medium:	500 mL of 0.1N HCl at 37ºC ± 0.5ºC for 1 hour followed with addition of 400 mL of phosphate buffer (final pH 6.8) containing 0.25 M Sodium chloride after 1hr sampling.
USP Apparatus:	II (Paddle)
RPM:	50
Temperature:	37°C± 0.5°C
Specifications	Acid Stage: 1 hr (b) (4) Buffer Stage: 30 min: (b) (4); 60 min: (b) (4) 360 min (6 hrs) NLT (b) (4)

VI. ATTACHMENTS:

Results of Dissolution Method
(Note: This method is recommended by DB)

Dissolution Medium:	500 mL of 0.1N HCl at 37°C ± 0.5°C for 1 hour, followed with addition of 400 mL of phosphate buffer (final pH 6.8) with **0.25 M NaCl**
Apparatus:	USP Apparatus II
RPM:	50
Temperature:	37°C ± 0.5°C
Time Points:	1 hour in acid followed by 30 minutes, 1, 1.5, 3, 6, 9, 12, 18 and 24 hours in buffer

Table 15. Results for Amneal's product as per FDA with 0.25 M NaCl									
Sample#	Acid Medium	Basic Medium							
	1 hour	30 minutes	60 minutes	90 minutes	3 hours	6 hours	9 hours	18 hours	24 hours
1	(b) (4)								
2									
3									
4									
5									
6									
7									
8									
9									
10									
11									
12									
Minimum									
Maximum									
Mean	**26**	**48**	**65**	**72**	**81**	**92**	**93**	**94**	**93**
% RSD	10.6	9.5	7.0	6.5	6.5	6.2	6.5	6.6	6.5

Table 16. Results for RLD as per FDA with 0.25 M NaCl									
Sample#	Acid Medium	Basic Medium							
	1 hour	30 minutes	60 minutes	90 minutes	3 hours	6 hours	9 hours	18 hours	24 hours
1	(b) (4)								
2									
3									
4									
5									
6									
7									
8									
9									
10									
11									
12									
Minimum									
Maximum									
Mean	26	38	51	58	69	84	90	93	94
% RSD	5.7	4.1	4.4	4.5	5.0	6.1	6.4	6.7	6.3

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:	203133
APPLICANT:	Amneal Pharmaceuticals
DRUG PRODUCT:	Dextromethorphan Polistirex Extended-Release Suspension, 30 mg/5 mL

The Division of Bioequivalence I (DB I) has completed its review of the dissolution testing portion of your submission(s) acknowledged on the cover sheet. The review of the bioequivalence (BE) studies will be conducted later.

We acknowledge you will conduct dissolution testing for your test product using the following FDA-recommended dissolution method and specifications:

Dissolution Medium:	500 mL of 0.1N HCl at 37°C ± 0.5°C for 1 hour followed with addition of 400 mL of phosphate buffer (final pH 6.8) containing 0.25 M Sodium chloride after 1hr sampling.
USP Apparatus:	II (Paddle)
RPM:	50
Temperature:	37°C± 0.5°C
Specifications	Acid Stage: 1 hr (b) (4) Buffer Stage: 30 min: (b) (4); 60 min: (b) (4) (b) (4) 360 min (6 hrs) NLT (b) (4)

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

VII. OUTCOME

ANDA 203133

Completed Assignment for 203133 ID: 18841

Reviewer: Wahba, Zakaria Date Completed:
Verifier: , Date Verified:
Division: Division of Bioequivalence
Description:

Productivity:

ID	Letter Date	Productivity Category	Sub Category	Productivity	Subtotal
18841	1/4/2013	Dissolution Data (REGULAR)	Dissolution Amendment	0	0
				Total:	0

DIVISION OF BIOEQUIVALENCE 2 REVIEW COMPLEXITY SUMMARY
ANDA: 203133

Dissolution Study	
Dissolution Study	1
TOTAL:	***1***

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

/s/

ZAKARIA Z WAHBA
01/16/2013

MOHEB H MAKARY
01/16/2013

HOAINHON N CARAMENICO on behalf of DALE P CONNER
01/16/2013

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	203133		
Drug Product Name	Dextromethorphan Polistirex Extended-Release Suspension		
Strength (s)	30 mg/5 mL		
Applicant Name	Amneal Pharmaceuticals		
Applicant Address	85 Adams Avenue, Hauppauge, New York 11788		
US Agent Name and the mailing address	Alpesh Patel, Vice President, Global Regulatory Affairs 85 Adams Avenue, Hauppauge, NY 11788		
US Agent's Telephone Number	631-952-0214 Ext. 183		
US Agent's Fax Number	631-299-3995		
Original Submission Date(s)	(07/07/2011, and amendments dated 04/24/2012 and 06/14/2012)		
Submission Date(s) of Amendment(s) Under Review	08/08/2012		
First Generic	No		
Reviewer	Z.Z. Wahba, Ph.D.		
Study Number (s)	ARL/10/408	ARL/10/409	
Study Type (s)	Fasting	Fasting	
Strength(s)	10 ml suspension, oral	10 ml suspension, oral	
Clinical Site	Accutest Research Laboratories		
Clinical Site Address	Accutest Research Laboratories (I) Pvt. Ltd., A-31, M.I.D.C., T.T.C., Industrial Area, Khairane, Navi Mumbai-400 709, INDIA.		
Analytical Site	(b) (4)		
Analytical Address			

OVERALL REVIEW DISSOLUTION RESULT	**INADEQUATE**

BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	STUDY/TEST TYPE	STRENGTH	REVIEW RESULT
1	Fasting	30 mg/5 mL	**PENDING**
1	Fed	30 mg/5 mL	**PENDING**
1	Dissolution	30 mg/5 mL	**INADEQUATE**

REVIEW OF A DISSOLUTION AMENDMENT

I. EXECUTIVE SUMMARY

In the previous dissolution amendment [DARRTS 203133, REV-BIOEQ-02(Dissolution Review), 07/20/2012], the firm submitted acceptable dissolution data according to the FDA-recommended dissolution method (table, provided below). Based on the submitted dissolution data [DARRTS 203133, REV-BIOEQ-02(Dissolution Review), 05/08/2012], the Division of Bioequivalence (DB) has recommended the following specifications:

The FDA recommended dissolution method and specifications	
Dissolution Medium:	500 mL of 0.1N HCl at 37ºC ± 0.5ºC for 1 hour followed with addition of 400 mL of phosphate buffer (final pH 6.8) containing 0.25 M Sodium chloride after 1hr sampling.
USP Apparatus:	II (Paddle)
RPM:	50
Temperature:	37°C± 0.5°C
Specifications	**Acid Stage:** 1 hr (b) (4) **Buffer Stage:** 30 min: (b) (4) 60 min: 360 min (6 hrs) NLT (b) (4)

In this amendment (08/08/2012), the firm accepted the FDA recommended dissolution method; however, the firm proposed the following different specifications:

The firm's proposed specifications		
	Time Points	**% Dissolution**
Acid Stage	1 hour	(b) (4)
Buffer Stage	30 minutes	
	60 minutes	
	360 minutes (6 hrs)	

To justify its proposed specifications, the firm compared dissolution data obtained from a fresh lot (6 units) to the bio-lot (12 units) stored for 17 months, details are provided below (section III of this review).

From the DBI point of view, the firm's response to the above deficiency (letter dated: 05/15/2012) is still incomplete. The firm is requested to submit dissolution data using 12 units of the newly manufactured test lot, comparing it with 12 units of an unexpired lot of the reference listed drug product. In addition, the firm should provide documents to show that the new lot is manufactured, controlled and tested under the same conditions as the test biolot used in the original bioequivalence studies.

The dissolution part of this application is incomplete pending firm's response to the deficiency cited above.

The DBI will review the fasted and fed BE studies at a later date.

II. TABLE OF CONTENTS

III. BACKGROUND ON THE DISSOLUTION SECTION OF THIS APPLICATION:

See the original dissolution review [DARRTS ANDA 203133 REV-BIOEQ-02(Dissolution Review), 02/27/2012, 05/08/2012 and 07/20/2012].

IV. RESPONSES TO DEFICIENCY COMMENTS:

Deficiency comments are as stated in the DB dissolution review of the original submission [DARRTS ANDA 203133 REV-BIOEQ-02(Dissolution Review), 07/20/2012].

DB's Deficiency Comment

Your proposal to change the FDA-recommended specifications for your test product, Dextromethorphan Polistirex Extended-Release Suspension, 30 mg/5 mL, is not acceptable based on unacceptable supportive data. (b) (4) The DB observed that the results showed the opposite direction of change. By comparing the dissolution results of the biostudy test lot # BB-ST-10012B (manufactured in December 2010), provided in the original submission, with the dissolution results of the same lot at 17 months old, the data indicated that the dissolution mean value (b) (4) at the 6-hour time point.

The dissolution specifications are generally established based on the dissolution data on 12 units of the fresh biostudy test lot (not stored lot) that has been shown bioequivalent in bioequivalence studies. Therefore, the dissolution testing data on the stored lots, as submitted by you in the current amendment, are not acceptable for supporting your proposed change in specifications. The dissolution data for batch # BB-ST-10012B manufactured in December 2010, and for the Process Engineering (PE) Batch # BB-PE-10-012 manufactured in November 2010 were obtained when they were at least 17 and 18 month old, respectively.

You may submit additional dissolution data of at least three ***fresh*** production lots to support your proposed revision of the dissolution specifications.

Alternatively, please acknowledge your acceptance of the following FDA-recommended dissolution method and specifications:

Dissolution Medium:	500 mL of 0.1N HCl at 37ºC ± 0.5ºC for 1 hour followed with addition of 400 mL of phosphate buffer (final pH 6.8) containing 0.25 M Sodium chloride after 1hr sampling.
USP Apparatus:	II (Paddle)
RPM:	50
Temperature:	37°C± 0.5°C
Specifications	Acid Stage: 1 hr (b) (4) Buffer Stage: 30 min: (b) (4) 60 min: (b) (4) 360 min (6 hrs) NLT (b) (4)

Firm's Response to the Deficiency Comment

Based on the communication between Teresa Ramson, Regulatory Manager, OGD, DBE and Srinivas Kone from Analytical R&D of Amneal Pharmaceuticals on August 07, 2012, Amneal hereby submits this Amendment. This Amendment is in reference to the Amneal's reply (ANDA # 203133; Sequence # 0007 dated on June 14, 2012) of Amneal's proposal to slightly change the FDA recommended specifications for our drug product, Dextromethorphan Polistirex Extended Release Suspension, eq. to 30 mg/5 mL of Dextromethorphan Hydrobromide. In the Bioequivalence Deficiency Letter dated 07/25/2012, the Division of Bioequivalence stated that the (b) (4) Further, it is mentioned in the deficiency letter that the DB observed that the results showed the opposite direction of change. By comparing the dissolution results of the bio study test lot # BB-ST-10012B (manufactured in December 2010), provided in the original submission, with the dissolution results of the same lot at l7 months old, the data indicated that the dissolution mean value (b) (4) at the 6-hour time point.

In view of the above observation made by the Division of Bioequivalence, Amneal would like to clarify to the agency that the dissolution results of the bio study test lot # BB-ST-10012B (manufactured in December 2010) provided in the original submission ((b) (4) at 6 hours) was as per our in-house dissolution test method where as the dissolution results of the same lot BB-ST-10012B (17 months old) provided in the Bioequivalence amendment ((b) (4) at 6 hours) dated June 14, 2012 (Sequence# 0007) was as per the dissolution test method recommended by the Division of Bioequivalence in the deficiency letter dated May 16, 2012.

In order to compare the dissolution data of the 17 months old lot # BB-ST-10012B with that of the initial dissolution results; Amneal has manufactured a fresh representative R&D batch (# RD1590-176) and conducted dissolution test using the DB recommended dissolution method to obtain initial dissolution profiles. Obtained results are compared in below table. The dissolution results in the following table shows that the % dissolved in 6 hours for the freshly manufactured batch (initial) is (b) (4) as compared to the 17 months old batch, i.e. (b) (4) using DB recommended Dissolution method.

Table 1. Dissolution Summary					
Batch #	Sample # (No. of Units)	Acid stage	Buffer stage		
		1 hour	30 minutes	1 hour	6 hours
BB-ST-10012B (Mfg Date# 12/2010)	1	(b) (4)			
	2				
	3				
	4				
	5				
	6				
	7				
	8				
	9				
	10				
	11				
	12				
Average	NA	26	55	65	86
RD1590-176 (Mfg Date# 05/2012)	1	(b) (4)			
	2				
	3				
	4				
	5				
	6				
Average	NA	25	51	60	79

We respectfully request the agency to review our dissolution data and accept our proposed dissolution specifications as mentioned below for this product.

Amneal Proposed Dissolution Specifications:

	Time Points	% Dissolution
Acid Stage	1 hour	(b) (4)
Buffer Stage	30 minutes	
	60 minutes	
	360 minutes (6 hrs)	

DB's Comment on the Firm's Response to the Deficiency Comment

The dissolution testing is incomplete (for details, see the deficiency comment section, below).
Results of f_2 calculation for the above submitted dissolution data is 65.72

The firm's response to the above deficiency is incomplete.

IV. DEFICIENCY COMMENTS:

The dissolution testing is incomplete. The firm is requested to submit dissolution data using 12 units of the newly manufactured test lot, comparing it with 12 units of the unexpired lot of the reference product. Since the firm is planning to use a newly manufactured test lot for setting the dissolution specifications for its test drug product, the firm will be asked to (1) indicate to the DBI that the new lot is manufactured, controlled and tested under the same conditions as the biolot used in the original bioequivalence study, in terms of i) formulation, ii) manufacturing process, iii) in-process controls, iv) specifications, v) site, vi) equipment, etc. (2) to inform the Division of Chemistry, Office of Generic Drugs, of the manufacturing of the new batch of the test product, and submit to this review division (DBI) the complete CMC data and documentation of the new lot for evaluation by the division, and (3) to submit to the DBI the Certificates of Analysis (COA) for the new test lot.

V. RECOMMENDATIONS:

The dissolution testing conducted by Amneal Pharmaceuticals on its Dextromethorphan Polistirex Extended Release Oral Suspension, 30 mg/5 mL, is incomplete due to the deficiency cited in the deficiency section.

BIOEQUIVALENCE DEFICIENCIES

ANDA:	203133
APPLICANT:	Amneal Pharmaceuticals
DRUG PRODUCT:	Dextromethorphan Polistirex Extended-Release Suspension, 30 mg/5 mL

The Division of Bioequivalence I (DBI) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence (BE) studies will be conducted later. The following deficiency has been identified:

Your submitted dissolution data for a newly manufactured test lot, for only 6 units, to support your proposed change in the FDA-recommended specifications for your drug product, Dextromethorphan Polistirex Extended-Release Suspension, 30 mg/5 mL, are incomplete. Please submit dissolution data for 12 units of the newly manufactured test lot, comparing it with 12 units of an unexpired lot of the reference listed drug product.

Please be informed of the following:

(1) In the submission of your dissolution study amendment, please include a statement confirming that the new lot was manufactured, controlled and tested under the same conditions as the biobatch (Lot #BB-ST-10012B) used in the original bioequivalence studies, in terms of i) formulation, ii) manufacturing process, iii) in-process controls, iv) specifications, v) site, vi) equipment, etc.

(2) Please inform the Division of Chemistry (DC), Office of Generic Drugs, of the manufacturing of the new batch of the test product, and submit to the Division of Chemistry the complete Chemistry Manufacturing and Controls (CMC) data and documentation of the new test lot for evaluation by the DC.

(3) Please submit to the DBI the Certificates of Analysis (COA) for the new test lot and the unexpired reference lot used in the additional request dissolution testing. Please clearly indicate the dissolution testing date.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

VI. OUTCOME

ANDA 203133

Completed Assignment for 203133 ID: 17839

Reviewer: Wahba, Zakaria Date Completed:
Verifier: , Date Verified:
Division: Division of Bioequivalence
Description: Dextromethorphan Polistirex Extended-Release Suspension

Productivity:

ID	Letter Date	Productivity Category	Sub Category	Productivity	Subtotal
17839	8/8/2012	Dissolution Data (REGULAR)	Dissolution Amendment	1	1
				Total:	1

DIVISION OF BIOEQUIVALENCE 2 REVIEW COMPLEXITY SUMMARY
ANDA: 203133

Dissolution Study	
Dissolution Study	1
TOTAL:	1.0

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

/s/

ZAKARIA Z WAHBA
09/12/2012

MOHEB H MAKARY
09/12/2012

HOAINHON N CARAMENICO on behalf of DALE P CONNER
09/12/2012

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	203133		
Drug Product Name	Dextromethorphan Polistirex Extended-Release Suspension		
Strength (s)	30 mg/5 mL		
Applicant Name	Amneal Pharmaceuticals		
Applicant Address	85 Adams Avenue, Hauppauge, New York: 11788		
US Agent Name and the mailing address	Alpesh Patel, Vice President, Global Regulatory Affairs 85 Adams Avenue, Hauppauge, NY 11788		
US Agent's Telephone Number	631-952-0214 Ext. 183		
US Agent's Fax Number	631-299-3995		
Original Submission Date(s)	(07/07/2011, and amendment dated 04/24/2012)		
Submission Date(s) of Amendment(s) Under Review	06/14/2012		
First Generic	No		
Reviewer	Z.Z. Wahba, Ph.D.		
Study Number (s)	ARL/10/408	ARL/10/409	
Study Type (s)	Fasting	Fasting	
Strength(s)	10 ml suspension, oral	10 ml suspension, oral	
Clinical Site	Accutest Research Laboratories		
Clinical Site Address	Accutest Research Laboratories (I) Pvt. Ltd., A-31, M.I.D.C., T.T.C., Industrial Area, Khairane, Navi Mumbai-400 709, INDIA.		
Analytical Site	(b) (4)		
Analytical Address			
OVERALL REVIEW DISSOLUTION RESULT	**INADEQUATE**		

BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	STUDY/TEST TYPE	STRENGTH	REVIEW RESULT
1	Fasting	30 mg/5 mL	**PENDING**
1	Fed	30 mg/5 mL	**PENDING**
1	Dissolution	30 mg/5 mL	**INADEQUATE**

REVIEW OF A DISSOLUTION AMENDMENT

I. EXECUTIVE SUMMARY

In the previous dissolution amendment [DARRTS 203133, REV-BIOEQ-02(Dissolution Review), 05/08/2012], the firm submitted acceptable dissolution data according to the FDA-recommended dissolution method (table, provided below). Based on the submitted dissolution data (individual data provided in the Attachment section of this report), the Division of Bioequivalence (DB) has recommended the following specifications:

The FDA recommended dissolution method and specifications	
Dissolution Medium:	500 mL of 0.1N HCl at 37ºC ± 0.5ºC for 1 hour followed with addition of 400 mL of phosphate buffer (final pH 6.8) containing 0.25 M Sodium chloride after 1hr sampling.
USP Apparatus:	II (Paddle)
RPM:	50
Temperature:	37°C± 0.5°C
Specifications	**Acid Stage:** 1 hr (b) (4) **Buffer Stage:** 30 min: (b) (4) 60 min: 360 min (6 hrs) NLT (b) (4)

In this amendment (06/14/2012), the firm accepted the FDA recommended dissolution method; however, the firm proposed the following different specifications:

The firm's proposed specifications		
	Time Points	**% Dissolution**
Acid Stage	1 hour	(b) (4)
Buffer Stage	30 minutes	
	60 minutes	
	360 minutes (6 hrs)	

To justify its request of change, the firm provided the results of dissolution data from three lots which two of them are stored lots for 17 and 18 months (details in the section IV of this review).

The firm's justification is not acceptable. The DB also does not agree with the firm's statement, (b) (4) However, the fact is that the results show the opposite. By comparing the dissolution results of the biolot (No. BB-ST-10012B manufactured in December 2010) provided in the original submission vs. the same lot 17 month old, the data indicate that the dissolution mean value (b) (4) at 6 hour time point (for details see the Attachment section).

From the DB point of view, the firm's proposed dissolution specifications are not acceptable. The DB's recommended dissolution specifications are established based on the submitted dissolution data for the biolot (fresh) that has been used in bioequivalence studies. The DB does not accept the dissolution specifications on the basis of the dissolution testing data on the stored lots.

In order to justify its proposed specifications, the firm may submit additional dissolution data of ***three fresh production lots of the test product***, to determine if a revision of the dissolution specification is warranted. Alternatively, the firm is requested to acknowledge the DB recommended specifications.

Therefore, the previously communicated (05/15/2012) DB - recommended dissolution method and specifications remain unchanged as provided in the table above.

The dissolution part of this application is incomplete pending firm's acceptance of the DB recommended dissolution method and specifications.

The DB will review the fasted and fed BE studies at a later date.

II. TABLE OF CONTENTS

III. BACKGROUND ON THE DISSOLUTION SECTION OF THIS APPLICATION:

See the original dissolution review [DARRTS ANDA 203133 REV-BIOEQ-02(Dissolution Review), 02/27/2012, and 05/08/2012].

IV. RESPONSES TO DEFICIENCY COMMENTS:

Deficiency comments are as stated in the DB dissolution review of the original submission [DARRTS ANDA 203133 REV-BIOEQ-02(Dissolution Review), 05/08/2012].

DB's Deficiency Comment

Your dissolution testing is acceptable. Based on the submitted dissolution data, the DB recommends the dissolution method and specifications below. Please acknowledge the following FDA-recommended dissolution method and specifications.

Dissolution Medium:	500 mL of 0.1N HCl at 37ºC ± 0.5ºC for 1 hour followed with addition of 400 mL of phosphate buffer (final pH 6.8) containing 0.25 M Sodium chloride after 1hr sampling.
USP Apparatus:	II (Paddle)
RPM:	50
Temperature:	37°C± 0.5°C
Specifications	Acid Stage: 1 hr (b) (4) Buffer Stage: 30 min: (b) (4) 60 min: (b) (4) 360 min (6 hrs) NLT (b) (4)

Firm's Response to the Deficiency Comment

Based on the Agency's recommendation on specifications for dissolution of Dextromethorphan Polistirex Extended-Release oral Suspension Equivalent to 30 mg/5 mL of Dextromethorphan Hydrobromide, Amneal has performed dissolution testing on the ANDA submission batch (Batch # BB-ST-10012B) manufactured in December 2010, the Process Engineering (PE) Batch (Batch # BB-PE-10-012) manufactured in November 2010 and on the freshly prepared representative R&D Batch (Batch # RD1590-176) manufactured in May 2012 to verify the compliance with the FDA recommended dissolution specifications.
The observed dissolution testing results are summarized in below table:

Table 1. Dissolution Summary					
Batch #	Sample # (No. of Units)	Acid stage	Buffer stage		
		1 hour	30 minutes	1 hour	6 hours
BB-ST-10012B (Mfg Date# 12/2010)	1	[redacted] (b) (4)			
	2				
	3				
	4				
	5				
	6				
	7				
	8				
	9				
	10				
	11				
	12				
BB-PE-10-012 (Mfg Date# 11/2010)	1				
	2				
	3				
	4				
	5				
	6				
RD1590-176 (Mfg Date# 05/2012)	1				
	2				
	3				
	4				
	5				
	6				
Min (%)					
Max (%)					
Mean (%)		25	54	63	84
% RSD		10.7	7.6	6.7	4.5

It is apparent from the dissolution data that the release profiles of ANDA submission batch and PE batch (**18 Month old**) are comparable to the freshly prepared R&D batch. [redacted] (b) (4) . Therefore, the initial release of the batch at 6 hour becomes critical where % dissolved is at or just below [redacted] (b) (4) Therefore, based on these results, it is our assessment that the specification for this Extended Release suspension at 6 hour should be NLT [redacted] (b) (4) instead of NLT [redacted] (b) (4) However, this change in the specification does not alter the quality of the drug product from a release perspective and allows some space for batch to batch uniformity.

For the reason stated above, Amneal would like to have following specification for % dissolved at each time point with slight modifications from the Agency's recommended method and seeking for the Agency's acceptance.

Amneal Proposed Dissolution Specifications:

	Time Points	% Dissolution
Acid Stage	1 hour	(b) (4)
Buffer Stage	30 minutes	
	60 minutes	
	360 minutes (6 hrs)	

DB's Comment on the Firm's Response to the Deficiency Comment

The firm's justification is not acceptable. The DB does not agree with the firm's statement, (b) (4) . However, the fact is that the results show the opposite. By comparing the dissolution results of the biolot (# BB-ST-10012B manufactured in December 2010), provided in the original submission vs. the same lot 17 month old, the data indicate that the dissolution mean value (b) (4) at 6 hour time point (for details see the Attachment section).

Therefore, the firm's proposal to change the DB's recommended specifications for its test product Dextromethorphan Polistirex Extended-Release Suspension, 30 mg/5 mL is not acceptable. As per the DB practice, the dissolution specifications are established based on the dissolution data on **12 units** of the biolot (fresh, not stored) that has been used in bioequivalence studies. The DB does not accept the dissolution specifications on the basis of the dissolution testing data on stored lots. Therefore, the DB does not agree with the firm's proposed revision of the dissolution specifications.

The firm may submit dissolution data of at least three fresh (not stored) production lots, to determine if a revision of the dissolution specifications is warranted. It should be pointed out that the dissolution data submitted in this amendment [batch # BB-ST-10012B manufactured in December 2010, and the Process Engineering (PE) Batch # BB-PE-10-012 manufactured in November 2010] are based on stored lots (17 and 18 month old, respectively).

Alternatively, the firm is requested to acknowledge its acceptance of the following FDA-recommended dissolution method and specifications:

Dissolution Medium:	500 mL of 0.1N HCl at 37ºC ± 0.5ºC for 1 hour followed with addition of 400 mL of phosphate buffer (final pH 6.8) containing 0.25 M Sodium chloride after 1hr sampling.
USP Apparatus:	II (Paddle)
RPM:	50
Temperature:	37°C± 0.5°C
Specifications	Acid Stage: 1 hr (b) (4) Buffer Stage: 30 min: (b) (4); 60 min (b) (4) 360 min (6 hrs) NLT (b) (4)

IV. DEFICIENCY COMMENTS:

The dissolution testing is incomplete. The firm may submit dissolution data of at least three fresh (not stored) production lots, to determine if a revision of the dissolution specifications is warranted.
Alternatively, the firm is requested to acknowledge its acceptance of the following FDA-recommended dissolution method and specifications:

Dissolution Medium:	500 mL of 0.1N HCl at 37ºC ± 0.5ºC for 1 hour followed with addition of 400 mL of phosphate buffer (final pH 6.8) containing 0.25 M Sodium chloride after 1hr sampling.
USP Apparatus:	II (Paddle)
RPM:	50
Temperature:	37°C± 0.5°C
Specifications	Acid Stage: 1 hr (b) (4) Buffer Stage: 30 min: (b) (4) 60 min: (b) (4) 360 min (6 hrs) NLT (b) (4)

V. RECOMMENDATIONS:

The dissolution testing conducted by Amneal Pharmaceuticals on its Dextromethorphan Polistirex Extended Release Oral Suspension, 30 mg/5 mL, is incomplete due to the deficiency cited in the deficiency section.

VI. ATTACHMENTS:

Results of Dissolution Method
(Note: This method is recommended by DB)

Dissolution Medium:	500 mL of 0.1N HCl at 37°C ± 0.5°C for 1 hour, followed with addition of 400 mL of phosphate buffer (final pH 6.8) with **0.25 M NaCl**
Apparatus:	USP Apparatus II
RPM:	50
Temperature:	37°C ± 0.5°C
Time Points:	1 hour in acid followed by 30 minutes, 1, 1.5, 3, 6, 9, 12, 18 and 24 hours in buffer

Table 15. Results for Amneal's product as per FDA with 0.25 M NaCl									
Sample#	Acid Medium	Basic Medium							
	1 hour	30 minutes	60 minutes	90 minutes	3 hours	6 hours	9 hours	18 hours	24 hours
1	(b) (4)								
2									
3									
4									
5									
6									
7									
8									
9									
10									
11									
12									
Minimum									
Maximum									
Mean	**26**	**48**	**65**	**72**	**81**	**92**	**93**	**94**	**93**
% RSD	10.6	9.5	7.0	6.5	6.5	6.2	6.5	6.6	6.5

Table 16. Results for RLD as per FDA with 0.25 M NaCl									
Sample#	Acid Medium	Basic Medium							
	1 hour	30 minutes	60 minutes	90 minutes	3 hours	6 hours	9 hours	18 hours	24 hours
1	(b) (4)								
2									
3									
4									
5									
6									
7									
8									
9									
10									
11									
12									
Minimum									
Maximum									
Mean	26	38	51	58	69	84	90	93	94
% RSD	5.7	4.1	4.4	4.5	5.0	6.1	6.4	6.7	6.3

Summary of the Dissolution data of the biolot provide in the original submission (fresh, not stored)

Batch #	Sample # (No. of Units)	Acid stage 1 hour	Buffer stage 30 minutes	Buffer stage 1 hour	Buffer stage 6 hours
BB-ST-10012B (Mfg Date# 12/2010)	Min (%)	(b) (4)			
	Max (%)				
	Mean (%)	26	48	65.00	92.00
	% RSD	10.60	9.50	7.00	6.20

Dissolution Performance of the Biolot after 17 months storage.

Batch #	Sample # (No. of Units)	Acid stage 1 hour	Buffer stage 30 minutes	Buffer stage 1 hour	Buffer stage 6 hours
BB-ST-10012B	1	(b) (4)			
(Mfg Date# 12/2010)	2				
	3				
	4				
	5				
	6				
	7				
	8				
	9				
	10				
	11				
	12				
	Min (%)				
	Max (%)				
	Mean (%)	26	55.25	65.08	86.08
	% RSD	3.52	5.21	4.68	2.97

For information only lot #BB-PE-10-012 (stored for 18 months) and lot # RD1590-176 (fresh lot)

Batch #	Sample # (No. of Units)	Acide Stage 1 hr	Buffer Stage 30 min	Buffer Stage 1 hr	Buffer Stage 6 hrs
BB-PE-10-012	1	(b) (4)			
(Mfg Date# 11/2010)	2				
	3				
	4				
	5				
	6				
	Min (%)				
	Max (%)				
	Mean (%)	24.75	54.38	63.83	84.50
	% RSD	2.25	2.13	2.86	2.93
RD1590-176	1	(b) (4)			
(Mfg Date# 05/2012)	2				
	3				
	4				
	5				
	6				
	Min (%)				
	Max (%)				
	Mean (%)	25.13	51.00	59.50	79.00
	% RSD	1.36	1.67	2.51	0.63

BIOEQUIVALENCE DEFICIENCIES

ANDA:	203133
APPLICANT:	Amneal Pharmaceuticals
DRUG PRODUCT:	Dextromethorphan Polistirex Extended-Release Suspension, 30 mg/5 mL

The Division of Bioequivalence (DB) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence (BE) studies will be conducted later. The following deficiency has been identified:

Your proposal to change the FDA-recommended specifications for your test product, Dextromethorphan Polistirex Extended-Release Suspension, 30 mg/5 mL, is not acceptable based on unacceptable supportive data. The DB does not agree with your statement that (b) (4) The DB observed that the results showed the opposite direction of change. By comparing the dissolution results of the biostudy test lot # BB-ST-10012B (manufactured in December 2010), provided in the original submission, with the dissolution results of the same lot at 17 months old, the data indicated that the dissolution mean value (b) (4) at the 6-hour time point.

The dissolution specifications are generally established based on the dissolution data on **12 units** of the fresh biostudy test lot (not stored lot) that has been shown bioequivalent in bioequivalence studies. Therefore, the dissolution testing data on the stored lots, as submitted by you in the current amendment, are not acceptable for supporting your proposed change in specifications. The dissolution data for batch # BB-ST-10012B manufactured in December 2010, and for the Process Engineering (PE) Batch # BB-PE-10-012 manufactured in November 2010 were obtained when they were at least 17 and 18 month old, respectively.

You may submit additional dissolution data of at least three ***fresh*** production lots to support your proposed revision of the dissolution specifications.

Alternatively, please acknowledge your acceptance of the following FDA-recommended dissolution method and specifications:

Dissolution Medium:	500 mL of 0.1N HCl at 37°C ± 0.5°C for 1 hour followed with addition of 400 mL of phosphate buffer (final pH 6.8) containing 0.25 M Sodium chloride after 1hr sampling.
USP Apparatus:	II (Paddle)
RPM:	50
Temperature:	37°C± 0.5°C
Specifications	Acid Stage: 1 hr (b) (4) Buffer Stage: 30 min: (b) (4); 60 min: (b) (4) (b) (4) 360 min (6 hrs) NLT (b) (4)

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

VII. OUTCOME

ANDA 203133

Completed Assignment for 203133 ID: 17386

Reviewer: Wahba, Zakaria Date Completed:
Verifier: , Date Verified:
Division: Division of Bioequivalence
Description:

Productivity:

ID	Letter Date	Productivity Category	Sub Category	Productivity	Subtotal
17386	6/14/2012	Dissolution Data (REGULAR)	Dissolution Amendment	1	1
				Total:	1

DIVISION OF BIOEQUIVALENCE 2 REVIEW COMPLEXITY SUMMARY
ANDA: 203133

Dissolution Study	
Dissolution Study	1
TOTAL:	***1.0***

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

/s/

ZAKARIA Z WAHBA
07/19/2012

MOHEB H MAKARY
07/19/2012

HOAINHON N CARAMENICO on behalf of DALE P CONNER
07/20/2012

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	203133		
Drug Product Name	Dextromethorphan Polistirex Extended-Release Suspension		
Strength (s)	30 mg/5 mL		
Applicant Name	Amneal Pharmaceuticals		
Applicant Address	85 Adams Avenue, Hauppauge, New York: 11788		
US Agent Name and the mailing address	Alpesh Patel, Vice President, Global Regulatory Affairs 85 Adams Avenue, Hauppauge, NY 11788		
US Agent's Telephone Number	631-952-0214 Ext. 183		
US Agent's Fax Number	631-299-3995		
Original Submission Date(s)	07/07/2011		
Submission Date(s) of Amendment(s) Under Review	04/24/2012 –supporting document #8		
First Generic	No		
Reviewer	Z.Z. Wahba, Ph.D.		
Study Number (s)	ARL/10/408	ARL/10/409	
Study Type (s)	Fasting	Fasting	
Strength(s)	10 ml suspension, oral	10 ml suspension, oral	
Clinical Site	Accutest Research Laboratories		
Clinical Site Address	Accutest Research Laboratories (I) Pvt. Ltd., A-31, M.I.D.C., T.T.C., Industrial Area, Khairane, Navi Mumbai-400 709, INDIA.		
Analytical Site	(b) (4)		
Analytical Address			

OVERALL REVIEW DISSOLUTION RESULT	**INADEQUATE**

BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	STUDY/TEST TYPE	STRENGTH	REVIEW RESULT
1	Fasting	30 mg/5 mL	**PENDING**
1	Fed	30 mg/5 mL	**PENDING**
1	Dissolution	30 mg/5 mL	**INADEQUATE**

REVIEW OF A DISSOLUTION AMENDMENT

I. EXECUTIVE SUMMARY

The original dissolution review [DARRTS ANDA 203133 REV-BIOEQ-02(Dissolution Review), 02/27/2012] was found incomplete. The submitted dissolution results indicated that the FDA-recommended method [500 mL of 0.1 N HCl, paddle at 50 rpm] is not appropriate for this drug due to slow release (b) (4) at 180 minutes. In addition, the firm only collected samples up to 180 minutes.

In this amendment, the firm provided additional dissolution testing as requested by Division of Bioequivalence I (DB I). Based on the comparative dissolution data obtained in different dissolution media (data are provided in the Attachment section), DB I recommends the following dissolution method and specifications as the most appropriate and discriminating method for the test product, Dextromethorphan Polistirex Extended Release Oral Suspension, 30 mg/5 mL.

Dissolution Medium:	500 mL of 0.1N HCl at 37ºC + 0.5ºC for 1 hour followed with addition of 400 mL of phosphate buffer (final pH 6.8) containing 0.25 M Sodium chloride after 1 hr sampling.
USP Apparatus:	II (Paddle)
RPM:	50
Temperature:	37°C± 0.5°C
Specifications	Acid Stage: 1 hr (b) (4) Buffer Stage: 30 min: (b) (4); 60 min: (b) (4); 360 min (6 hrs) NLT (b) (4)

The firm should acknowledge the above mentioned dissolution method and specifications.

The DB I will review the fasted and fed BE studies at a later date.

II. TABLE OF CONTENTS

III. BACKGROUND ON THE DISSOLUTION SECTION OF THIS APPLICATION:

See the original dissolution review [DARRTS ANDA 203133 REV-BIOEQ-02(Dissolution Review), 02/27/2012].

IV. RESPONSES TO DEFICIENCY COMMENTS:

Deficiency comments are as stated in the DBE dissolution review of the original submission [DARRTS ANDA 203133 REV-BIOEQ-02(Dissolution Review), 02/27/2012].

Deficiency Comment #1

You have conducted dissolution testing using the dissolution method recommended in the FDA dissolution method website, as well as your proposed dissolution method. The dissolution was shown to be incomplete at the last sampling time point of 3 hours, based on the FDA-recommended method (with a mean of (b) (4) *and* (b) (4) *for the test and reference product, respectively). On the other hand, the dissolution relatively quickly reached a mean of* (b) (4) *for the test product at 4 hours, based on your proposed method which uses* (b) (4) (b) (4) *In order to fully and properly evaluate all available methods, and determine the most appropriate method and specifications for your test product, we recommend that you conduct additional dissolution testing using the following method which uses no surfactant: The testing should be done in 500 mL of 0.1N HCl at 37ºC + 0.5ºC for 1 hour, followed with addition of 400 mL of phosphate buffer (final pH 6.8), at 37ºC + 0.5ºC, after 1 hr sampling, using USP apparatus II (Paddle) at 50 rpm. The recommended sampling times are 30, 60, 90, and 180 minutes and until at least* (b) (4) *of the labeled amount of the drug is dissolved.*

Firm's Response to the Deficiency Comment #1

As recommended by the agency in the Bioequivalence deficiency letter dated March 07, 2012, Amneal has performed dissolution testing on RLD and Amneal' product in following dissolution medium and conditions without surfactant:

Dissolution Medium:	500 mL of 0.1N HCl for 1 hour followed with addition of 400 mL of phosphate buffer (final pH 6.8) after 1 hr sampling.
USP Apparatus:	II (Paddle)
RPM:	50
Temperature:	37°C± 0.5°C

Time Point:	1 Hour (Acid Stage) 30, 60, 90 and 180 minutes and until at least (b) (4) of the labeled amount of the drug is dissolved.

From the dissolution results, about (b) (4) of drug release at 6 hours with a stagnant value from 6 hours to 24 hours was observed for RLD. Similarly for Amneal's product, about (b) (4) release obtained at 6 hours with a stagnant value up to 24 hours is observed. The drug did not released beyond (b) (4) till 24 hours time point. The individual dosage unit data as well as the mean, range (min and max) and RSD of 12 units of Amneal's drug product and RLD are summarized in following tables.

Dissolution Parameters:

Dissolution Medium: **500 mL of 0.1N HCl at 37°C ± 0.5°C for 1 hour, followed with addition of 400 mL of phosphate buffer (final pH 6.8)**

Apparatus: USP Apparatus II

RPM: 50

Temperature: 37°C ± 0.5°C

Time Points: 1 hour in acid followed by 30 minutes, 1, 1.5, 3, 6, 9, 12, 18 and 24 hours in buffer

Table 1. Dissolution Results for Amneal's product (Batch # BB-ST-10012B)

Sample#	Acid Medium	Basic Medium							
	1 hour	30 minutes	60 minutes	90 minutes	3 hours	6 hours	9 hours	18 hours	24 hours
1	(b) (4)								
2									
3									
4									
5									
6									
7									
8									
9									
10									
11									
12									
Minimum									
Maximum									
Mean	26	43	56	63	71	82	84	84	84
% RSD	7.2	7.1	7.7	7.6	5.7	6.5	5.0	3.9	3.4
Reference: Notebook # 3862 and Page # 126, 133									

Table 2. Dissolution Results for RLD (Delsym® Lot # 54554, Exp: 03/2013)									
Sample#	Acid Medium	Basic Medium							
	1 hour	30 minutes	60 minutes	90 minutes	3 hours	6 hours	9 hours	18 hours	24 hours
1	(b) (4)								
2									
3									
4									
5									
6									
7									
8									
9									
10									
11									
12									
Minimum									
Maximum									
Mean	26	34	46	53	62	75	80	82	84
% RSD	2.7	4.3	3.8	4.2	4.2	3.6	3.8	3.6	3.2
Reference: Notebook # 3862 and Page # 126, 133									

Since the Dextromethorphan Polistirex Extended Release oral Suspension is pertaining to a resin complex, a possible cause of these results could be less availability of cations in order to exchange the drug for release. Hence, Amneal had contacted the Division of Bioequivalence on March 23, 2012 to discuss these results and recommended to allow the addition of cations (NaCl) in the dissolution medium to obtain the desired drug release.

Based on the communication between DB I (Teresa Ramson, Regulatory Manager, OGD, DBI) and Amneal Pharmaceuticals (Srinivas Kone from Analytical R&D) on March 28, 2012, Amneal has performed additional dissolution testing to evaluate the effect of Sodium chloride at different concentration levels (b) (4) 0.25M) on the release of drug from the drug product. ***Details of the results are provided in the Attachment section of this review (below).***

The following table summarizes the results:

Table 17. Comparative dissolution results with different NaCl concentration		
Time	(b) (4)	0.25 M NaCl
0		0
1		(b) (4)
1.5		
2		
2.5		
4		
7		
10		
19		
25		

Graphical presentation to evaluate the effect of NaCl

(b) (4)

Firm's comments on the dissolution results:
The comparative dissolution results indicated that the release of Dextromethorphan Hydrobromide increases with the increase in the Sodium Chloride concentration. The optimum level of Sodium chloride is 0.25 M.

Based on the dissolution data, it seems that the dissolution testing performed with 500 mL 0.1N HCl (Acid Stage) followed by addition of 400 mL Phosphate buffer (pH 6.8) containing 0.25 M Sodium chloride gives best suitable results.

DB's Comment on Deficiency Comment #1:

Based on the comparison dissolution data in different dissolution media, DB I recommends the following dissolution method and specifications (see below) as the most appropriate and discriminating method for the test product, Dextromethorphan Polistirex Extended Release Oral Suspension, 30 mg/5 mL. The recommended method is the same as that used in the Experiment III shown below.

Dissolution Medium:	500 mL of 0.1N HCl at 37ºC + 0.5ºC for 1 hour followed with addition of 400 mL of phosphate buffer (final pH 6.8) containing 0.25 M Sodium chloride after 1 hr sampling.
USP Apparatus:	II (Paddle)
RPM:	50
Temperature:	37°C± 0.5°C
Specifications	Acid Stage: 1 hr (b) (4) Buffer Stage: 30 min: (b) (4); 60 min: (b) (4); 360 NLT (b) (4)

V. DEFICIENCY COMMENTS:

The dissolution testing is incomplete. Based on the submitted dissolution data, the firm should acknowledge the following FDA-recommended dissolution method and specifications.

Dissolution Medium:	500 mL of 0.1N HCl at 37ºC + 0.5ºC for 1 hour followed with addition of 400 mL of phosphate buffer (final pH 6.8) containing 0.25 M Sodium chloride after 1 hr sampling.
USP Apparatus:	II (Paddle)
RPM:	50
Temperature:	37°C± 0.5°C
Specifications	Acid Stage: 1 hr (b) (4) Buffer Stage: 30 min: (b) (4); 60 min: (b) (4) 360 NLT (b) (4)

VI. RECOMMENDATIONS:

The dissolution testing conducted by Amneal Pharmaceuticals on its Dextromethorphan Polistirex Extended Release Oral Suspension, 30 mg/5 mL, is incomplete due to the deficiency cited in the deficiency section.

VII. ATTACHMENTS:

Dissolution using Phosphate Buffer 6.8 with addition of Sodium Chloride

Since the Dextromethorphan Hydrobromide Extended Release Suspension pertains a resin complex, a possible cause of these results could be less availability of cations in order to exchange the drug for release.

Therefore, Amneal contacted the Division of Bioequivalence to discuss about the results. Based on the controlled correspondence with Division of Bioequivalence, Amneal added different molality of Sodium Chloride in the phosphate buffer pH 6.8 to establish the proper concentration of Sodium Chloride as Sodium Chloride adds more cations irrespective of any pH change.

Based on these following dissolution media were evaluated

1. (b) (4)
2.
3. 500 mL of 0.1N HCl for 1 hour and followed by addition of 400mL of phosphate buffer to pH 6.8 containing 0.25 M NaCl

Experiment III
(Note: This method is recommended by DB I)

Dissolution Medium: 500 mL of 0.1N HCl at 37°C ± 0.5°C for 1 hour, followed with addition of 400 mL of phosphate buffer (final pH 6.8) with **0.25 M NaCl**

Apparatus: USP Apparatus II

RPM: 50

Temperature: 37°C ± 0.5°C

Time Points: 1 hour in acid followed by 30 minutes, 1, 1.5, 3, 6, 9, 12, 18 and 24 hours in buffer

Table 15. Results for Amneal's product as per FDA with 0.25 M NaCl

Sample#	Acid Medium	Basic Medium							
	1 hour	30 minutes	60 minutes	90 minutes	3 hours	6 hours	9 hours	18 hours	24 hours
1	(b) (4)								
2									
3									
4									
5									
6									
7									
8									
9									
10									
11									
12									
Minimum									
Maximum									
Mean	**26**	**48**	**65**	**72**	**81**	**92**	**93**	**94**	**93**
% RSD	10.6	9.5	7.0	6.5	6.5	6.2	6.5	6.6	6.5

Table 16. Results for RLD as per FDA with 0.25 M NaCl									
Sample#	Acid Medium	Basic Medium							
	1 hour	30 minutes	60 minutes	90 minutes	3 hours	6 hours	9 hours	18 hours	24 hours
1	(b) (4)								
2									
3									
4									
5									
6									
7									
8									
9									
10									
11									
12									
Minimum									
Maximum									
Mean	26	38	51	58	69	84	90	93	94
% RSD	5.7	4.1	4.4	4.5	5.0	6.1	6.4	6.7	6.3

Summary of the dissolution stated above with different dissolution medium (effect of NaCl)

Table 17. Comparative dissolution results with different NaCl concentration		
Time	(b) (4)	0.25 M NaCl
0		0
1		(b) (4)
1.5		
2		
2.5		
4		
7		
10		
19		
25		

BIOEQUIVALENCE DEFICIENCIES

ANDA:	203133
APPLICANT:	Amneal Pharmaceuticals
DRUG PRODUCT:	Dextromethorphan Polistirex Extended-Release Suspension, 30 mg/5 mL

The Division of Bioequivalence I (DBI) has completed its review of the dissolution portion of the submission acknowledged on the cover sheet. The review of the bioequivalence studies will be conducted later. The following deficiency has been identified:

Your dissolution testing is acceptable. Based on the submitted dissolution data, the DBI recommends the dissolution method and specifications below. Please acknowledge the following FDA-recommended dissolution method and specifications.

Dissolution Medium:	500 mL of 0.1N HCl at 37°C ± 0.5°C for 1 hour followed with addition of 400 mL of phosphate buffer (final pH 6.8) containing 0.25 M Sodium chloride after 1hr sampling.
USP Apparatus:	II (Paddle)
RPM:	50
Temperature:	37°C± 0.5°C
Specifications	Acid Stage: 1 hr (b) (4) Buffer Stage: 30 min: (b) (4) 60 min: (b) (4); 360 min (6 hrs) NLT (b) (4)

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

VIII. OUTCOME

ANDA 203133

Completed Assignment for 203133 ID: 16753

Reviewer: Wahba, Zakaria Date Completed:
Verifier: , Date Verified:
Division: Division of Bioequivalence
Description:

Productivity:

ID	Letter Date	Productivity Category	Sub Category	Productivity	Subtotal
16753	4/24/2012	Other	Dissolution Amendment	1	1
				Total:	1

DIVISION OF BIOEQUIVALENCE 2 REVIEW COMPLEXITY SUMMARY
ANDA: 203133

Dissolution Study	
Dissolution Study	1
TOTAL:	***1.0***

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

/s/

ZAKARIA Z WAHBA
05/07/2012

MOHEB H MAKARY
05/08/2012

HOAINHON N CARAMENICO on behalf of DALE P CONNER
05/08/2012

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	203133		
Drug Product Name	Dextromethorphan Polistirex Extended-Release Suspension		
Strength (s)	30 mg/5 mL		
Applicant Name	Amneal Pharmaceuticals		
Applicant Address	85 Adams Avenue, Hauppauge, New York: 11788		
US Agent Name and the mailing address	Alpesh Patel, Vice President, Global Regulatory Affairs 85 Adams Avenue, Hauppauge, NY 11788		
US Agent's Telephone Number	631-952-0214 Ext. 183		
US Agent's Fax Number	631-299-3995		
Original Submission Date(s)	07/07/2011		
Submission Date(s) of Amendment(s) Under Review	-		
First Generic	No		
Reviewer	Z.Z. Wahba, Ph.D.		
Study Number (s)	ARL/10/408	ARL/10/409	
Study Type (s)	Fasting	Fasting	
Strength(s)	10 ml suspension, oral	10 ml suspension, oral	
Clinical Site	Accutest Research Laboratories		
Clinical Site Address	Accutest Research Laboratories (I) Pvt. Ltd., A-31, M.I.D.C., T.T.C., Industrial Area, Khairane, Navi Mumbai-400 709, INDIA.		
Analytical Site	(b) (4)		
Analytical Address			
OVERALL REVIEW DISSOLUTION RESULT	**INADEQUATE**		

BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	STUDY/TEST TYPE	STRENGTH	REVIEW RESULT
1	Fasting	30 mg/5 mL	**PENDING**
1	Fed	30 mg/5 mL	**PENDING**
1	Dissolution	30 mg/5 mL	**INADEQUATE**

I. EXECUTIVE SUMMARY

This is a review of the dissolution testing data only.

There is no USP method for this product but there is an FDA-recommended method. The firm conducted the dissolution testing using the FDA-recommended method as well as three other media (all media used 500 mL buffer, paddle, 50 rpm) as follows:

1. 0.1N Hydrochloric Acid (**FDA-recommended method**)
2. (b) (4)
3.
4.

The submitted dissolution results indicate that the FDA-recommended method [500 mL of 0.1 N HCl, paddle at 50 rpm] is not appropriate for this drug due to slow release (b) (4) at 180 minutes. In addition, the firm only collected samples up to 180 minutes. The other three methods show relatively fast release by the first hour ((b) (4) release).

Based on the submitted dissolution data and consultation with DB I dissolution focal point (see the Attachments section for details), the firm is requested to conduct additional dissolution testing in 500 mL of 0.1N HCl at 37ºC $\pm$ 0.5ºC, with addition of 400 mL of Phosphate Buffer (final pH 6.8), at 37ºC $\pm$ 0.5ºC, after 1 hr sampling, using USP apparatus II (Paddle) at 50 rpm. The recommended sampling times are 30, 60, 90, and 180 minutes or until at least (b) (4) of the labeled amount of the drug is dissolved.

The submitted dissolution testing is incomplete.

The DB I will review the fasted and fed BE studies at a later date.

Table 1 - A: SUBMISSION CONTENT CHECKLIST

Information			YES	NO	N/A
Is there an FDA-recommended dissolution method?			☒	☐	☐
Did the firm use the FDA-recommended dissolution method?			☒	☐	☐
Is there a USP dissolution method?			☐	☒	☐
Did the firm use the USP dissolution method?			☐	☐	☒
Did the firm use 12 units of both test and reference in dissolution testing			☒	☐	☐
Did the firm provide complete dissolution data (all raw data, range, mean, % CV, dates of dissolution testing)			☒	☐	☐
Did the firm conduct dissolution testing with its own proposed method			☐	☒	☐
Is FDA method in the public dissolution database (on the web)			☐	☒	☐
SAS datasets submitted to the electronic document room (edr)	Fasting BE study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Fed BE study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Other study	BE parameters	☐	☐	☒
		Individual data	☐	☐	☒
Are these datasets appropriately submitted? (e.g., are they blank, readable, duplicated, etc.?)			☐	☐	☒
Are the DBE Summary Tables present an in either PDF and/or MS Word Format?			☒	☐	☐
If any of the tables are missing or incomplete please indicate that in the comments and request the firm to provide the complete DBE Summary Tables 1-16.					
Is the Long Term Storage Stability (LTSS) sufficient to cover the maximum storage time of the study samples?			☒	☐	☐
If the LTSS is NOT sufficient please request the firm to provide the necessary data.					

FDA's External Dissolution Database

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)	Date Updated
Dextromethorphan Polistirex	Suspension (Extended Release)	II (Paddle)	50	0.1N HCl	500	30, 60, 90 and 180	10/06/2008

Table 2: SUMMARY OF IN VITRO DISSOLUTION DATA

The following tables are the dissolution data for all strengths (test and reference).

Dissolution Conditions	Apparatus:	USP Type II (Paddle)	Medium:	**0.1N Hydrochloric Acid**	
	Speed of Rotation:	50 rpm	Volume:	500 mL	
	Temperature:	37°C ± 0.5°C	Tolerance:	90 minutes: NMT (b) (4) (Q)	
Firm's Proposed Specifications	Refer to 3.2.P.5.1 for Finished Product Specification (**No specificity was provided for this drug**)				
Dissolution Testing Site (Name, Address)	Amneal Pharmaceuticals, 131 Chambers Brook Road, Branchburg, NJ 08776				

Analysis Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Active Ingredient Name	No. of Dosage Units	Parameters	Sample Collection Times % Dissolution			
					30 min	60 min	90 min	180 min
05/31/2011	Dextromethorphan Polistirex Extended-Release Suspension 30 mg/5 mL Batch No.: BB-ST-10012 Mfg Date: 12/01/2010	Dextromethorphan Hydrobromide	12	Mean	21	28	32	36
				Min.	(b) (4)			
				Max				
				RSD	9.2	8.4	8.5	6.2
05/31/2011	Delsym® (Dextromethorphan Polistirex Extended-Release Suspension) 30 mg/5 mL Batch No.: 54554 Exp Date: 03/2013		12	Mean	23	25	26	30
				Min.	(b) (4)			
				Max				
				RSD	3.9	3.0	3.4	10.1

(b) (4)

Over all comments on the dissolution data:

Are individual dissolution data submitted?	Yes
Are the dissolution data pooled?	No
Is the Dissolution SOP provided in Module 3?	Yes
Is the Assay SOP submitted?	Yes
Is the Validation Report for the Assay Method submitted?	Yes

II. COMMENTS:

1. There is no USP method for this product but there is an FDA-recommended method. The firm conducted the dissolution testing using the FDA-recommended method as well as three other media (all media used 500 mL buffer, paddle, 50 rpm) as follows:

   i. 0.1N Hydrochloric Acid (**FDA-recommended method**)
   ii. (b) (4)
   iii.
   vi.

   The submitted dissolution results indicate that the FDA recommended method [500 mL of 0.1N HCl, paddle at 50 rpm] is not appropriate for this drug due to slow release (b) (4) at 180 minutes. In addition, the firm only collected samples up to 180 minutes. The other three methods show relatively fast release by the first hour (b) (4) Therefore, the submitted dissolution testing is incomplete.

   Based on the submitted dissolution data and consultation with DB I dissolution focal point (see the Attachments section for details), the firm is requested to conduct additional dissolution testing in 500 mL of 0.1N HCl at 37ºC ± 0.5ºC, with addition of 400 mL of Phosphate Buffer (final pH 6.8), at 37ºC ± 0.5ºC, after 1 hr sampling, using USP apparatus II (Paddle) at 50 rpm. The recommended sampling times are 30, 60, 90, and 180 minutes or until at least (b) (4) of the labeled amount of the drug is dissolved.

2. The DB I will review the fasting and fed BE studies at a later date.

III. DEFICIENCY COMMENTS:

1. The firm's submitted dissolution testing is incomplete. The firm is requested to conduct additional dissolution testing in 500 mL of 0.1N HCl at 37ºC ± 0.5ºC, with addition of 400 mL of Phosphate Buffer (final pH 6.8), at 37ºC ± 0.5ºC, after 1 hr sampling, using USP apparatus II (Paddle) at 50 rpm. The recommended sampling times are 30, 60, 90, and 180 minutes or until at least (b) (4) of the labeled amount of the drug is dissolved.

IV. RECOMMENDATIONS:

The dissolution testing conducted by Amneal Pharmaceuticals on its Dextromethorphan Polistirex Extended Release Oral Suspension, 30 mg/5 mL is incomplete due to the deficiency cited in the deficiency section.

V. ATTACHMENTS:

From: Dehaven, Wayne
Sent: Wednesday, February 22, 2012 1:50 PM
To: Wahba, Zakaria Z
Subject: RE: A request for dissolution consult - ANDA 203133 (Dextromethorphan Polistirex ER Suspension, 30 mg/5 mL)

Hi Zak:

Here are my thoughts on your question:

1. The FDA-recommended method (i.e. the NDA method) does not dissolve to completion, and as such, probably is not the best dissolution method for release specification for generic versions of this product. Please note that the specifications for the NDA are (b) (4) at 0.5 hours; (b) (4) at 1 hour; and (b) (4) in 3 hours; and at 24 hours, only approximately (b) (4) is dissolved [see in DARRTS for NDA #018658 11/08/2004 REV-CLINPHARM-01(General Review)]. According to Guidance for Industry: Extended Release Oral Dosage Forms - Development, Evaluation, and Application of In Vitro / In Vivo Correlations: *the last time point should be the time point where at least 80% of the drug has dissolved. If the maximum amount dissolved is less than 80%, the last time point should be the time when the plateau of the dissolution profile has been reached.* Based on the submitted data for ANDA #203133, the dissolution has NOT reached plateau at 3 hours (180 minutes). According to data on NDA, dissolution hasn't really reached a clear plateau even at 24 hours [see in DARRTS for NDA #018658 11/08/2004 REV-CLINPHARM-01(General Review)]. Based on these observations, I think the FDA-method is not appropriate for this product.

2. As you pointed out, the firm's proposed method (b) (4) is less discriminatory than the method used in ANDA # 091135 [500 mL of 0.1 N HCl at 37°C ± 0.5°C, with addition of 400 mL of Phosphate Buffer **(final pH = 6.8)**, at 37°C ± 0.5°C, after 1 hr sampling, using USP apparatus II (Paddle) at 50 rpm]. In addition, the firm's proposed method uses (b) (4) and is a method which uses a single buffer media for dissolution method.

3. In my opinion, I would recommend the firm conduct comparative dissolution testing using the method from ANDA #091135 [500 mL of 0.1 N HCl at 37°C ± 0.5°C, with addition of 400 mL of Phosphate Buffer **(final pH = 6.8)**, at 37°C ± 0.5°C, after 1 hr sampling, using USP apparatus II (Paddle) at 50 rpm].

4. After the firm submits the new dissolution testing results, then a decision on the most appropriate dissolution method (i.e. their proposed method or the method recommended from ANDA #091135) and specifications for this product can be made.

If you have any further questions, please let me know. Please remember that this is just my opinion, and consult with your TL for further input.

Thanks,

Wayne

From: Wahba, Zakaria Z
Sent: Friday, February 10, 2012 3:38 PM
To: Munshi, Utpal; Dehaven, Wayne
Cc: Wahba, Zakaria Z
Subject: A request for dissolution consult - ANDA 203133 (Dextromethorphan Polistirex ER Suspension, 30 mg/5 mL)

Hi Wayne and Utpal,
The firm conducted its dissolution testing in 4 different media (all 500 mL, paddle, 50 rpm) as follows:

1. 0.1 N Hydrochloric Acid **(FDA-recommended method)**
2. (b) (4)
3.
4.

The submitted results indicate that the FDA recommended method (method 1) is not appropriate for this drug (slow release: (b) (4) in 180 min). In addition, the firm only collected its samples up to 180 min. The other three methods show relatively fast release by the first hour ((b) (4) release).

In house data (DARRTS) for ANDA 09135: The initial dissolution reviewer for ANDA 091135 considered the dissolution testing was inadequate. In the full review of ANDA 09135 [DARRTS ANDA 091135 REV-BIOEQ-01(General Review), 07/28/2011, reviewer: W. DeHaven, Ph.D.], the dissolution was accepted and the following comment was communicated to the firm:

The DBE acknowledges that you will continue to conduct dissolution testing in 500 mL of 0.1 N HCl at 37ºC + 0.5ºC, with addition of 400 mL of Phosphate Buffer, at 37ºC + 0.5ºC, after 1 hr sampling, using USP apparatus II (Paddle) at 50 rpm.
The test product should meet the following specifications:
1 hr: NMT (b) (4)
3 hrs: (b) (4)
6 hrs:
12 hrs: NLT (b) (4)

Please provide me with your dissolution consult on this ANDA.
Thanks,
Zak

Note: Attached is the needed dissolution data for this ANDA

<< File: 203133D0711-dissolution data.doc >> << File: 203133D0711-individual dissolution data.doc >>

BIOEQUIVALENCE DEFICIENCY

ANDA:	203133
APPLICANT:	Amneal Pharmaceuticals
DRUG PRODUCT:	Dextromethorphan Polistirex Extended-Release Suspension, 30 mg/5 mL

The Division of Bioequivalence has completed its review of the dissolution portion of the submission acknowledged on the cover sheet. The review of the bioequivalence studies will be conducted later. The following deficiency has been identified:

You have conducted dissolution testing using the dissolution method recommended in the FDA dissolution method website, as well as your proposed dissolution method. The dissolution was shown to be incomplete at the last sampling time point of 3 hours, based on the FDA-recommended method (with a mean of 36% and 30% for the test and reference product, respectively). On the other hand, the dissolution relatively quickly reached a mean of (b) (4) for the test product at 4 hours based on your proposed method which uses (b) (4). In order to fully and properly evaluate all available methods, and determine the most appropriate method and specifications for your test product, we recommend that you conduct additional dissolution testing using the following method which uses no surfactant: The testing should be done in 500 mL of 0.1N HCl at 37°C ± 0.5°C for 1 hour, followed with addition of 400 mL of phosphate buffer (final pH 6.8), at 37°C ± 0.5°C, after 1 hr sampling, using USP apparatus II (Paddle) at 50 rpm. The recommended sampling times are 30, 60, 90, and 180 minutes and until at least (b) (4) of the labeled amount of the drug is dissolved.

Comparative dissolution profiles of all additional dissolution testing should include individual dosage unit data as well as the mean, range, and relative standard error (%RSD) at each time point for twelve dosage units of each lot tested. Please also provide summary tables for the dissolution testing data in eCTD table format.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

VI. OUTCOME

ANDA: 203133

Completed Assignment for 203133 ID: 16179

Reviewer: Wahba, Zakaria Date Completed:
Verifier: , Date Verified:
Division: Division of Bioequivalence
Description: Dextromethorphan Polistirex ER Suspension

Productivity:

ID	Letter Date	Productivity Category	Sub Category	Productivity	Subtotal
16179	7/7/2011	Dissolution Data	Dissolution Review	1	1
				Bean Total:	1

DBII Complexity Points
ANDA: 203133

Dissolution Study	
Dissolution Study	1
TOTAL:	***1.0***

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

/s/

ZAKARIA Z WAHBA
02/24/2012

MOHEB H MAKARY
02/25/2012

HOAINHON N CARAMENICO on behalf of DALE P CONNER
02/27/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 203133

OTHER REVIEWS

MEMORANDUM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Research and Evaluation
Office of Drug Evaluation IV
Division of Nonprescription Clinical Evaluation (DNCE); HFD-560

Date:	December 14, 2011
To:	Trang Tan, Ph.D., OGD Product Quality Consult Coordinator, Office of Generic Products
From:	Wafa Harrouk, Ph.D., Senior Pharmacologist/Toxicologist, DNCE
Via:	Andrea Leonard-Segal, M.D., Division Director, DNCE Paul Brown, Associate Director for Pharmacology/Toxicology, Immediate Office, Office of New Drugs
Re:	Generics Consult #2011-0554; ANDA#: 203133
Subject:	Pharmacology/Toxicology review of the (b) (4) (b) (4) USP (b) (4) in Dextromethorphan Polistyrex Extended Release Oral Suspension

---

BACKGROUND

The Office of Generics is requesting a Pharmacology/Toxicology review of (b) (4) (b) (4), an inactive ingredient listed under ANDA 203133 for Dextromethorphan Polistyrex Extended Release Oral Suspension (with an equivalent of 30 mg/5 ml of Dextromethorphan Hydrobromide (Dex HBr). This over-the-counter drug is used to temporarily relieve cough due to minor throat and bronchial irritation as may occur with the common cold or inhaled irritants and can be dosed up to 4 times daily (representing 120 mg Dex HBr/day or up to 2 mg/kg/day for an average person of 60 kg body weight). The sponsor, Amneal Pharmaceuticals, (b) (4) /including a 28-day and a 90-day oral toxicity study conducted in the rat, both of which show a favorable toxicity profile. Further justification given by the sponsor included the absence of post-marketing adverse experience for (b) (4) as well as the long history of use of (b) (4) as an active and inactive ingredient in the following products: 1) (b) (4)

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

/s/

WAFA HARROUK
01/03/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 203133

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 203133

INFORMATION REQUEST

AMNEAL PHARMACEUTICALS
Attention: Pavan Kumar
Director, Regulatory Affairs
50 HORSEBLOCK RD
BROOKHAVEN, NY 11719

Dear Pavan Kumar:

Please refer to your Abbreviated New Drug Application (ANDA) dated July 7, 2011, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) for DEXTROMETHORPHAN POLISTIREX SUSPENSION, EXTENDED RELEASE, 30MG/5ML (OTC).

We also refer to your submission dated April 24, 2017.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response, no later than July 6, 2017, in order to continue our evaluation of your ANDA.

Drug Product Deficiencies:

If you do not submit a complete response by July 6, 2017, the review will be closed and the listed deficiencies will be incorporated in a COMPLETE RESPONSE correspondence.

Please note, submitting unsolicited information in your response to this Information Request may have an impact on your Target Action Date.

All items listed on this Information Request shall be addressed in its entirety, any partial or incomplete response will not be reviewed and the same deficiency list will be issued to you again as part of the Complete Response Letter issued by OGD. Please note that a commitment to address an item in the future is not considered satisfying the Information Request.

Send your submission through the Electronic Submission Gateway http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm. Prominently

identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
Drug Product

If you have any questions, please contact me, Regulatory Business Process Manager, at (240) 402-6958.

Sincerely,

{See appended electronic signature page}

Camille Smith, MS, PharmD, RAC
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 06/06/2017 01:48:22 PM
To: pkumar@amneal.com
CC: camille.smith@fda.hhs.gov
BCC:
Subject: INFORMATION REQUEST ANDA 203133 (Response requested by June 9, 2017)

Please refer to the attached document. Thank you and kind regards.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 203133

INFORMATION REQUEST

AMNEAL PHARMACEUTICALS LLC
Attention: Pavan Kumar
Director, Regulatory Affairs
50 HORSEBLOCK RD
BROOKHAVEN, NY 11719

Dear Pavan Kumar:

Please refer to your Abbreviated New Drug Application (ANDA) dated July 7, 2011, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) for DEXTROMETHORPHAN POLISTIREX SUSPENSION, EXTENDED RELEASE, 30MG/5ML (OTC).

We also refer to your submission dated April 24, 2017.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response, no later than June 9, 2017, in order to continue our evaluation of your ANDA.

1. In the 'current' view of the electronic submission, we note the following:

    a. Section 32P1 contains two documents 'description and composition' which appear redundant, and the Sequence 0017 document is the most recent. Please explain your reason for not replacing the Sequence 0014 version of this document, or delete it now if it was replaced with the Sequence 0017 document.

    b. [redacted] (b) (4)

2. Please acknowledge your awareness that USP <231> will be obsolete and replaced by USP <232/233> as of January 1, 2018. We expect you to comply with USP <232/233> as of January 1, 2018.

If you do not submit a complete response by June 9, 2017, the review will be closed and the listed deficiencies will be incorporated in a COMPLETE RESPONSE correspondence.

Please note, submitting unsolicited information in your response to this Information Request may have an impact on your Target Action Date.

All items listed on this Information Request shall be addressed in its entirety, any partial or incomplete response will not be reviewed and the same deficiency list will be issued to you again as part of the Complete Response Letter issued by OGD. Please note that a commitment to address an item in the future is not considered satisfying the Information Request.

Send your submission through the Electronic Submission Gateway http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
Drug Product

If you have any questions, please contact me, Regulatory Business Process Manager, at (240) 402-6958.

Sincerely,

Camille Smith, MS, PharmD, RAC
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 03/22/2017 04:32:46 PM
To: alpesh@amneal.com
CC: camille.smith@fda.hhs.gov
BCC:
Subject: INFORMATION REQUEST ANDA 203133

Please refer to the attached document. Thank you and kind regards.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 203133

INFORMATION REQUEST

Amneal Pharmaceuticals LLC
Attention: Alpesh Patel
Vice President, Global Regulatory Affairs
50 Horseblack Road
Brookhaven, NY 11719
alpesh@amneal.com

Dear Alpesh Patel:

Please refer to your Abbreviated New Drug Application (ANDA) dated July 7, 2011, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) for Dextromethorphan Polistirex Extended Release Oral Suspension equivalent to 30 mg/5 mL of Dextromethorphan Hydrobromide.

We also refer to your July 14, 2016 and February 6, 2017 submissions.

We are reviewing the chemistry section of your submission and have the following comments and information requests. We request a prompt written response, no later than 30 days, (Note for ANDA products: in general the requested date should not exceed 30 days per (b) (4) Process for Issuing Deficiencies and Information Requests for Generic Drug Chemistry Review) in order to continue our evaluation of your ANDA.

List of the deficiencies:

Chemistry deficiencies:

(b) (4)

[redacted]

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3. (b) (4)

4.

5.

If you do not submit a complete response by April 24, 2017, the review will be closed and the listed deficiencies will be incorporated in a COMPLETE RESPONSE correspondence.

All items listed on this Information Request shall be addressed in its entirety, any partial or incomplete response will not be reviewed and the same deficiency list will be issued to you again as part of the Complete Response Letter issued by OGD. Please note that a commitment to address an item in the future is not considered satisfying the Information Request.

Send your submission through the Electronic Submission Gateway http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
Chemistry

If you have any questions, please contact Camille Smith, Regulatory Business Process Manager, at (240) 402-6958.

Sincerely,

Camille M. Smith -A

Digitally signed by Camille M. Smith -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001821738, cn=Camille M. Smith -A
Date: 2017.03.22 16:25:07 -04'00'

Camille Smith, MS, PharmD, RAC
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 12/06/2016 02:12:13 PM
To: alpesh@amneal.com
CC: camille.smith@fda.hhs.gov
BCC:
Subject: INFORMATION REQUEST ANDA 203133

Please refer to attached document. Thank you and kind regards.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 203133

INFORMATION REQUEST

Amneal Pharmaceuticals
Attention: Alpesh Patel
Vice President, Global Regulatory Affairs
50 Horseblock Road
Brookhaven, NY 11719
alpesh@amneal.com

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) dated July 7, 2011, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) for Dextromethorphan Polistirex Extended Release Oral Suspension equivalent to 30 mg/5 mL of Dextromethorphan Hydrobromide.

We also refer to your July 14, 2016 submission.

We are reviewing the chemistry section of your submission and have the following comments and information requests. We request a prompt written response, no later than 30 days, (Note for ANDA products: in general the requested date should not exceed 30 days per (b) (4): Process for Issuing Deficiencies and Information Requests for Generic Drug Chemistry Review) in order to continue our evaluation of your ANDA.

List of the deficiencies:

Chemistry deficiencies:

(b) (4)

3 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

If you do not submit a complete response by January 6, 2017, the review will be closed and the listed deficiencies will be incorporated in a COMPLETE RESPONSE correspondence.

All items listed on this Information Request shall be addressed in its entirety, any partial or incomplete response will not be reviewed and the same deficiency list will be issued to you again as part of the Complete Response Letter issued by OGD. Please note that a commitment to address an item in the future is not considered satisfying the Information Request.

Send your submission through the Electronic Submission Gateway http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
Chemistry

If you have any questions, please contact Camille Smith, Regulatory Business Process Manager, at (240) 402-6958.

Sincerely,

Camille M. Smith -A

Dig tally signed by Cam lle M Smith A
DN c=US o=U S Government ou=HHS ou=FDA ou=People 0 9 2342 19200300 100 1 1=2001821738 cn=Camil e M Smith A
Date 2016 12 06 14 01 30 05'00'

Camille Smith, M.S., Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory OperationsOffice of Pharmaceutical Quality
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 11/08/2016 01:19:25 PM
To: alpesh@amneal.com
CC:
BCC: linda.park1@fda.hhs.gov
Subject: Easily Correctible Deficiency for ANDA 203133

ANDA 203133

Amneal Pharmaceuticals
85 Adams Avenue
Hauppauge, NY 11788
Attention: Alpesh Patel

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) submitted on July 8, 2011 under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Dextromethorphan Polistirex Extended Release Oral Suspension, EQ 30 mg dextromethorphan hydrobromide (HBr)/5 mL.

The following Easily Correctable Deficiency has been identified:

In the amendment submission date July 14, 2016, you only submitted the complete (100%) raw numerical data for the fasting BE study (#ARL/10/408) and sample list report for two repeated batches for the fed BE study (#ARL/10/409), but did not submit ALL analytical raw numerical data for your fed BE study (#ARL/10/409). Please provide complete (100%) raw numerical data, in the instrument printout format, including original and repeated analysis for all samples, including the data of peak area/height for the analyte, peak area/height for the internal standard, ratio of the peak area/height for the analyte to the peak area/height for the internal standard, dilution factor (if any), and the corresponding concentration for each assayed and reassayed sample of all samples, calibration standard concentration samples, and quality control samples for your fed (#ARL/10/409) BE study.

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Provide a complete response to these deficiencies by November 18, 2016. We will not process or review a partial response. Facsimile or e-mail responses will not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

EASILY CORRECTABLE DEFICIENCY
BIOEQUIVALENCE
REFERENCE #11213491

If FDA does not receive a complete response by November 18, 2016, the review will be closed and the listed deficiencies will be incorporated in a COMPLETE RESPONSE correspondence. For more information, please refer to the guidance for industry, ANDA Submissions – Amendments and Easily Correctable Deficiencies under GDUFA, available on FDA's website.

If you have any questions, contact Linda Park, Office of Bioequivalence Project Manager at 240-402-5120.

**Please acknowledge receipt of this communication by sending an email to linda.park1@fda.hhs.gov

Sincerely,

Linda Park
OFFICE OF GENERIC DRUGS
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 07/18/2016 07:59:12 AM
To: alpesh@amneal.com
CC:
BCC: vikas.arora@fda.hhs.gov
Subject: TARGET ACTION DATE NOTIFICATION on ANDA 203133

ANDA 203133

NOTIFICATION -- TARGET ACTION DATE

AMNEAL PHARMACEUTICALS
85 ADAMS AVE
HAUPPAUGE, NEW YORK 11788 UNITED STATES
Attention: Alpesh Patel

Dear Sir,

Please refer to your Abbreviated New Drug Application (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Dextromethorphan Polistirex Extended-release Oral Suspension, 30 mg/5 mL (OTC).

We acknowledge your response to the Complete Response letter dated July 14, 2016.

The Office of Generic Drugs (OGD), Center for Drug Evaluation and Research, Food and Drug Administration (FDA), is notifying you of our new internal, administrative TARGET ACTION DATE for the above indicated ANDA.

The Target Action Date is the date by which FDA will strive to provide a communication on this ANDA. A TAD will be considered met if the applicant receives an Approval, Tentative Approval, Complete Response (CR) or a complete set of Informational Requests (IRs) by the action date. A complete set of IRs means that each pending discipline communicated its comments to the applicant. In that case, the TAD will be met if the last discipline communicates its IR by the action date.

We note that FDA is not required to inform applicants of Target Action Dates, but is providing Target Action Dates at this time as a courtesy to help applicants ascertain when communications may occur for their applications as we implement the Generic Drug User Fee Amendments of 2012 (GDUFA). Notification of a Target Action Date does not constitute a commitment or guarantee that we will take action on your application by the Target Action Date. Any amendments submitted after this notification will affect whether FDA will provide a communication on the application by the Target Action Date.

GDUFA establishes goal dates for the review of ANDAs submitted beginning October 1, 2014. Target Action Dates are not GDUFA goal dates.

The Target Action Date for this ANDA is December 14, 2016.

Please contact your Regulatory Project Manager, Vikas Arora at (240) 402-8884 for an additional status update of your application.

Sincerely,

Vikas Arora
OFFICE OF GENERIC DRUGS
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Complete Response Letter Checklists

Complete Response Letter (**not cGMP**)

Yes	No	If any statement is checked NO, STOP and DO NOT issue letter
☒	☐	All relevant discipline reviews are complete and finalized in DARRTS
☒	☐	DMF first cycle review(s) complete
☒	☐	DMF Deficiency letter(s) issued to DMF holder(s) prior to ANDA CR issuance OR DMF is adequate
☒	☐	Status of the DMF(s) cited in the Product Quality and Microbiology (if applicable) sections is/are current →if needed, update DMF deficiencies to reflect current status per DMF Status and ANDA CR Chart
☒	☐	All amendments have been addressed (reviewed or deferred per IQP 4025.02)
☒	☐	There are no pending consults
NA	☐	Received clearance from REMS Coordinator (if applicable)
☒	☐	ANDA is not on hold for "other" reasons (e.g. safety, tamper resistance, abuse deterrent)
☒	☐	Chemistry (Product Quality) deficiencies have been accurately added to CR letter OR Chemistry is adequate
☒	☐	Bioequivalence deficiencies have been accurately added to the CR letter OR Bioequivalence is adequate
X	☐	Dissolution deficiencies have been accurately added to the CR letter OR Dissolution is adequate
NA	☐	Microbiology deficiencies have been accurately added to the CR letter OR Microbiology is adequate (if applicable)
NA	☐	Clinical deficiencies have been accurately added to the CR letter OR Clinical is adequate (if applicable)
☒	☐	Labeling deficiencies have been accurately added to the CR letter OR Labeling is adequate
☒	☐	EES is acceptable or withheld (if withheld EES provided approval of selected CR template language) OR RPM received concurrence from Team Leader that ANDA is a priority and CR letter should be issued
☒	☐	OSI is not pending/is not required OR RPM received concurrence from Team Leader that ANDA is a priority and CR letter should be issued

cGMP Complete Response Letter

Yes	No	If any statement is checked NO, STOP and DO NOT issue letter
☐	☐	All relevant discipline reviews are ADEQUATE and finalized DARRTS (including REMS)
☐	☐	There are no open amendments
☐	☐	There are no pending consults
☐	☐	OSI is adequate/is not pending
☐	☐	Received written confirmation from EES staff authorizing issuance of the cGMP CR letter referencing the withheld facility and approving the selected template language

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 203133

INFORMATION REQUEST

Amneal Pharmaceuticals
Attention: Alpesh Patel
Vice President, Global Regulatory Affairs
85 Adams Avenue
Hauppauge, NY 11788

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) dated July 8, 2011, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) for Dextomethorphan Polistirex Extended Release Oral Suspension, Equivalent to 30 mg Dextromethorphan HBR per 5 mL.

We are reviewing the Product Quality section of your submission and have the following comments and information requests. We request a prompt written response, no later than **May 18, 2015**, in order to continue our evaluation of your ANDA.

A. Deficiencies

(b) (4)

[redacted]

10 Page(s) have been Withheld in Full as b4 (CCI/TS) immediatley following this page

(b) (4)

Send your submission through the Electronic Submission Gateway http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
CHEMISTRY
REFERENCE # 101621

Please note, if information or data submitted exceeds the data requested in the Information Request this may result in conversion to a Tier 2 Unsolicited Amendment (i.e., an amendment with information not requested by FDA). If the submitted data is determined to be a Tier 2 unsolicited amendment, this may affect the goal date.

If you have any questions, please contact Brijet Burton, Regulatory Business Project Manager, at (240) 402-4878.

Sincerely,

Brijet N. Burton Coachman -S

Digitally signed by Brijet N Burton Coachman -S
DN: c=US, o=U.S. Government, ou=HHS, ou=CMS, ou=People, 0.9.2342.19200300.100.1.1=2000028104, cn=Brijet N Burton Coachman -S
Date: 2015.04.17 17:30:33 -04'00'

Brijet Burton, MS, MPP, PA-C
Regulatory Business Project Manager
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

BIOEQUIVALENCE AMENDMENT

ANDA 203133

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Pl.
Rockville, MD 20855-2810

APPLICANT: Amneal Pharmaceuticals TEL: (b) (6)

ATTN: Alpesh Patel FAX: 631-299-3995

FROM: Teresa Ramson FDA CONTACT PHONE: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on July 7, 2011, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Dextromethorphan Polistirex Extended-Release Suspension, 30 mg/5 mL.

Reference is also made to your amendment submitted on August 08, 2012.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached ____ page(s). This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review.** Your cover letter should clearly indicate:

Bioequivalence Response to Information Request

If applicable, please clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this **communication with your response.**
Please submit a copy of your amendment in an archival (blue) jacket and unless submitted electronically through the gateway, a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents is:*

Office of Generic Drugs
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855-2810

ANDAs will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

Please submit your response in electronic format. This will improve document availability to review staff.

ANDA:	203133
APPLICANT:	Amneal Pharmaceuticals
DRUG PRODUCT:	Dextromethorphan Polistirex Extended-Release Suspension, 30 mg/5 mL

The Division of Bioequivalence I (DBI) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence (BE) studies will be conducted later. The following deficiency has been identified:

Your submitted dissolution data for a newly manufactured test lot, for only 6 units, to support your proposed change in the FDA-recommended specifications for your drug product, Dextromethorphan Polistirex Extended-Release Suspension, 30 mg/5 mL, are incomplete. Please submit dissolution data for 12 units of the newly manufactured test lot, comparing it with 12 units of an unexpired lot of the reference listed drug product.

Please be informed of the following:

(1) In the submission of your dissolution study amendment, please include a statement confirming that the new lot was manufactured, controlled and tested under the same conditions as the biobatch (Lot #BB-ST-10012B) used in the original bioequivalence studies, in terms of i) formulation, ii) manufacturing process, iii) in-process controls, iv) specifications, v) site, vi) equipment, etc.

(2) Please inform the Division of Chemistry (DC), Office of Generic Drugs, of the manufacturing of the new batch of the test product, and submit to the Division of Chemistry the complete Chemistry Manufacturing and Controls (CMC) data and documentation of the new test lot for evaluation by the DC.

(3) Please submit to the DBI the Certificates of Analysis (COA) for the new test lot and the unexpired reference lot used in the additional request dissolution testing. Please clearly indicate the dissolution testing date.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

DALE P CONNER
09/24/2012

BIOEQUIVALENCE AMENDMENT

ANDA 203133

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Pl.
Rockville, MD 20855-2810

APPLICANT: Amneal Pharmaceuticals

TEL: 631-952-0214 Ext. 331

ATTN: Pavan Kumar

FAX: 631-299-3995

FROM: Teresa Ramson

FDA CONTACT PHONE: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on July 7, 2011, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Dextromethorphan Polistirex Extended-Release Suspension, 30 mg/5 mL.

Reference is also made to your amendment submitted on June 14, 2012.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached ____ page(s). This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review.** Your cover letter should clearly indicate:

Bioequivalence Response to Information Request

If applicable, please clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this **communication with your response.**
Please submit a copy of your amendment in an archival (blue) jacket and unless submitted electronically through the gateway, a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents is:*

Office of Generic Drugs
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855-2810

ANDAs will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

Please submit your response in electronic format. This will improve document availability to review staff.

BIOEQUIVALENCE DEFICIENCIES

ANDA:	203133
APPLICANT:	Amneal Pharmaceuticals
DRUG PRODUCT:	Dextromethorphan Polistirex Extended-Release Suspension, 30 mg/5 mL

The Division of Bioequivalence (DB) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence (BE) studies will be conducted later. The following deficiency has been identified:

Your proposal to change the FDA-recommended specifications for your test product, Dextromethorphan Polistirex Extended-Release Suspension, 30 mg/5 mL, is not acceptable based on unacceptable supportive data. The DB does not agree with your statement that [redacted] (b) (4) The DB observed that the results showed the opposite direction of change. By comparing the dissolution results of the biostudy test lot # BB-ST-10012B (manufactured in December 2010), provided in the original submission, with the dissolution results of the same lot at 17 months old, the data indicated that the dissolution mean value decreased from 92% to 86% at the 6-hour time point.

The dissolution specifications are generally established based on the dissolution data on **12 units** of the fresh biostudy test lot (not stored lot) that has been shown bioequivalent in bioequivalence studies. Therefore, the dissolution testing data on the stored lots, as submitted by you in the current amendment, are not acceptable for supporting your proposed change in specifications. The dissolution data for batch # BB-ST-10012B manufactured in December 2010, and for the Process Engineering (PE) Batch # BB-PE-10-012 manufactured in November 2010 were obtained when they were at least 17 and 18 month old, respectively.

You may submit additional dissolution data of at least three ***fresh*** production lots to support your proposed revision of the dissolution specifications.
Alternatively, please acknowledge your acceptance of the following FDA-recommended dissolution method and specifications:

Dissolution Medium:	500 mL of 0.1N HCl at 37°C ± 0.5°C for 1 hour followed with addition of 400 mL of phosphate buffer (final pH 6.8) containing 0.25 M Sodium chloride after 1hr sampling.
USP Apparatus:	II (Paddle)
RPM:	50
Temperature:	37°C± 0.5°C
Specifications	Acid Stage: 1 hr (b) (4) Buffer Stage: 30 min: (b) (4) 60 min: (b) (4) 360 min (6 hrs) NLT (b) (4)

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

DALE P CONNER
07/24/2012

BIOEQUIVALENCE AMENDMENT

ANDA 203133

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Pl.
Rockville, MD 20855-2810

APPLICANT: Amneal Pharmaceuticals

TEL: 631-952-0214 Ext. 331

ATTN: Pavan Kumar

FAX: 631-299-3995

FROM: Teresa Ramson

FDA CONTACT PHONE: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on July 7, 2011, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Dextromethorphan Polistirex Extended-Release Suspension, 30 mg/5 mL.

Reference is also made to your amendment submitted on April 24, 2012.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached ____ page(s). This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review.** Your cover letter should clearly indicate:

Bioequivalence Response to Information Request

If applicable, please clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this **communication with your response.**
Please submit a copy of your amendment in an archival (blue) jacket and unless submitted electronically through the gateway, a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents is:*

Office of Generic Drugs
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855-2810

ANDAs will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

Please submit your response in electronic format. This will improve document availability to review staff.

ANDA:	203133
APPLICANT:	Amneal Pharmaceuticals
DRUG PRODUCT:	Dextromethorphan Polistirex Extended-Release Suspension, 30 mg/5 mL

The Division of Bioequivalence I (DBI) has completed its review of the dissolution portion of the submission acknowledged on the cover sheet. The review of the bioequivalence studies will be conducted later. The following deficiency has been identified:

Your dissolution testing is acceptable. Based on the submitted dissolution data, the DBI recommends the dissolution method and specifications below. Please acknowledge the following FDA-recommended dissolution method and specifications.

Dissolution Medium:	500 mL of 0.1N HCl at 37°C ± 0.5°C for 1 hour followed with addition of 400 mL of phosphate buffer (final pH 6.8) containing 0.25 M Sodium chloride after 1hr sampling.
USP Apparatus:	II (Paddle)
RPM:	50
Temperature:	37°C± 0.5°C
Specifications	Acid Stage: 1 hr (b) (4) Buffer Stage: 30 min: (b) (4) 60 min: (b) (4) 360 min (6 hrs) NLT (b) (4)

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

DALE P CONNER
05/15/2012

BIOEQUIVALENCE AMENDMENT

ANDA 203133

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Pl.
Rockville, MD 20855-2810

APPLICANT: Amneal Pharmaceuticals

TEL: 631-952-0214 Ext. 207

ATTN: Arlin Frias

FAX: 631-299-3995

FROM: Teresa Ramson

FDA CONTACT PHONE: (240) 276-8782

Dear Sir or Madam:

This facsimile is in reference to the bioequivalence data submitted on July 7, 2011, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Dextromethorphan Polistirex Extended-Release Suspension, 30 mg/5 mL.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached ____ page(s). This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review.** Your cover letter should clearly indicate:

Bioequivalence Response to Information Request

If applicable, please clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this **communication with your response.**
Please submit a copy of your amendment in an archival (blue) jacket and unless submitted electronically through the gateway, a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents is:*

Office of Generic Drugs
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855-2810

ANDAs will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

Please submit your response in electronic format. This will improve document availability to review staff.

ANDA:	203133
APPLICANT:	Amneal Pharmaceuticals
DRUG PRODUCT:	Dextromethorphan Polistirex Extended-Release Suspension, 30 mg/5 mL

The Division of Bioequivalence has completed its review of the dissolution portion of the submission acknowledged on the cover sheet. The review of the bioequivalence studies will be conducted later. The following deficiency has been identified:

You have conducted dissolution testing using the dissolution method recommended in the FDA dissolution method website, as well as your proposed dissolution method. The dissolution was shown to be incomplete at the last sampling time point of 3 hours, based on the FDA-recommended method (with a mean of 36% and 30% for the test and reference product, respectively). On the other hand, the dissolution relatively quickly reached a mean of (b) (4) for the test product at 4 hours, based on your proposed method which uses (b) (4) (b) (4). In order to fully and properly evaluate all available methods, and determine the most appropriate method and specifications for your test product, we recommend that you conduct additional dissolution testing using the following method which uses no surfactant: The testing should be done in 500 mL of 0.1N HCl at 37°C ± 0.5°C for 1 hour, followed with addition of 400 mL of phosphate buffer (final pH 6.8), at 37°C ± 0.5°C, after 1 hr sampling, using USP apparatus II (Paddle) at 50 rpm. The recommended sampling times are 30, 60, 90, and 180 minutes and until at least 80% of the labeled amount of the drug is dissolved.

Comparative dissolution profiles of all additional dissolution testing should include individual dosage unit data as well as the mean, range, and relative standard error (%RSD) at each time point for twelve dosage units of each lot tested. Please also provide summary tables for the dissolution testing data in eCTD table format.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

DALE P CONNER
03/06/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION Consult No: 2011-0554	
TO *(Division/Office)* DNCE - HFD-560 Thru: Melissa Furness, ONP HFD-560			FROM: Shannon Hill	
DATE: 9/8/2011	IND NO.	~TYPE~ NO. 203133	TYPE OF DOCUMENT ~TYPE_OF_DOCUMENT~	DATE OF DOCUMENT 7/8/2011
NAME OF DRUG Dextromethorphan Polistirex Extended-release Suspension		PRIORITY CONSIDERATION 60 days	CLASSIFICATION OF DRUG Antitussive	DESIRED COMPLETION DATE 11/6/2011
NAME OF FIRM Amneal Pharmaceuticals				

REASON FOR REQUEST

I. GENERAL

Γ NEW PROTOCOL	Γ PRE NDA MEETING	Γ RESPONSE TO DEFICIENCY LETTER
Γ PROGRESS REPORT	Γ END OF PHASE II MEETING	Γ FINAL PRINTED LABELING
Γ NEW CORRESPONDENCE	Γ RESUBMISSION	Γ LABELING REVISION
Γ DRUG ADVERTISING	Γ SAFETY/EFFICACY	Γ ORIGINAL NEW CORRESPONDENCE
Γ ADVERSE REACTION REPORT	Γ PAPER NDA	Γ FORMULATIVE REVIEW
Γ MANUFACTURING CHANGE/ADDITION	Γ CONTROL SUPPLEMENT	X *OTHER ('specify below)*
Γ MEETING PLANNED BY _____		

II.BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
Γ TYPE A OR B NDA REVIEW Γ END QF PHASE II MEETING Γ CONTROLLED STUDI ES Γ PROTOCOL REVIEW Γ OTHER	Γ CHEMISTRY Γ PHARMACOLOGY Γ BIOPHARMACEUTICS Γ OTHER

III.BIOPHARMACEUTICS

DISSOLUTION	DEFICIENCY LETTER RESPONSE
PROTOCOL-- BIOPHARMACEUTICS	BIOAVAILABILITY STUDIES
IN--VIVO WAIVER REQUEST	PHASE IV STUDIES

IV.DRUG EXPERIENCE

PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL	REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES	_SUMMARY OF ADVERSE EXPERIENCE
CASE REPORTS OF SPECIFIC *REACTIONS(List below)*	POISON RISK ANALYSIS
COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP	

V. SCIENTIFIC INVESTIGATIONS

CLINICAL	PRECLINICAL

COMMENTS
OGD is requesting a Pharm/Tox review for Sodium Polystyrene Sulfonate USP (b) (4)
(b) (4)

SIGNATURE OF REQUESTER	METHOD OF DE LIVERY *(Check one)* MAIL HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

FORM FDA 3291 (7/83)

cc: ANDA
Drug File Folder

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

/s/

SHANNON L HILL
09/08/2011

TRANG Q TRAN
09/12/2011

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 203133

Amneal Pharmaceuticals
Attention: Alpesh Patel
131 Chambers Brook Road
Branchburg, NJ 08876

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to the telephone conversation(s) dated August 17, 2011 and August 25, 2011 and your correspondence dated August 25, 2011 and September 2, 2011.

NAME OF DRUG: Dextromethorphan Polistirex Extended-release Suspension, 30 mg/5 mL

DATE OF APPLICATION: July 7, 2011

DATE (RECEIVED) ACCEPTABLE FOR FILING: July 8, 2011

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

  1) Each owner of the patent or the representative designated by the owner to receive the notice;

2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet “PATENT AMENDMENT” with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

- You must submit a copy of a copy of a court order or

judgment or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Martin Shimer, Chief, Regulatory Support Branch, at (240) 276-8675.

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Sarah Nguyen
Project Manager
240-276-8467

Sincerely yours,

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

MARTIN H Shimer
09/09/2011
Signing for Wm Peter Rickman

ANDA FILING CHECKLIST

(CTD or eCTD FORMAT)

FOR COMPLETENESS AND ACCEPTABILITY of an APPLICATION

ANDA: 203133
APPLICANT: AMNEAL PHARMACEUTICALS
RELATED APPLICATION(S): NA

DRUG NAME: DEXTROMETHORPHAN POLISTREX
DOSAGE FORM: EXTENDED-RELEASE SUSPENSION, EQ. 30 MG/5 ML

LETTER DATE: **JULY 7, 2011**
RECEIVED DATE: JULY 8, 2011

☒ P-IV
☐ FIRST GENERIC
☐ EXPEDITED REVIEW REQUEST (Approved/Denied)
☐ PEPFAR

Electronic or Paper Submission: Gateway Type II DMF# (b) (4)

BASIS OF SUBMISSION:
NDA/ANDA: 18-658
FIRM: RECKITT BENCKISER
RLD: DELSYM

****Document Room Note: for New Strength amendments and supplements, if specific reviewer(s) have already been assigned for the original, please assign to those reviewer(s) instead of the default random team(s).**

Review Team:

CHEM Team: **DC3 TM 31** ☒ **Activity**	Bio Team: **DBE 1 TM8: Shriniwas Nerurkar** ☒ **Activity**
CHEM Team Leader: Guoping Sun ☒ **No Assignment Needed in DARRTS**	Bio PM: Teresa Ramson ☐ **FYI**
CHEM RPM: **Sarah Nguyen** ☒ **FYI**	Clinical Endpoint Team: **(No)** ☐ **Activity**
DMF Review Team Leader: **Aloka Srinivasan** ☒ **FYI**	
Labeling Reviewer: **Nour, Burhan** ☒ **Activity**	Micro Review: **(No)** ☐ **Activity**

Regulatory Reviewer: **Shannon Hill** Date: **September 7, 2011**	Recommendation: ☒ **FILE** ☐ **REFUSE to RECEIVE**

Comments: EC - 1 YES
Therapeutic Code: 6010400 ANTITUSSIVE
On Cards: YES
Archival copy: **ELECTRONIC (GATEWAY)**
Sections: I

- **For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to: http://www.fda.gov/cder/regulatory/ersr/ectd.htm**
- **For a Comprehensive Table of Contents Headings and Hierarchy please go to: http://www.fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf**
- **For more CTD and eCTD informational links see the final page of the ANDA Checklist**
- **A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage http://www.fda.gov/cder/ogd/**

1. Edit Application Property Type in DARRTS where applicable for

a. First Generic Received
☐ Yes ☒ No
b. Market Availability
☐ Rx ☒ OTC
c. Pepfar
☐ Yes ☒ No
d. Product Type
☐ Small Molecule Drug
e. USP Drug Product (at time of filing review)
☐ Yes ☒ No

2. Edit Submission Patent Records
☐ Yes
3. Edit Contacts Database with Bioequivalence Recordation where applicable
☒ Yes
4. EER (in Draft)
☒ Yes

ADDITIONAL COMMENTS REGARDING THE ANDA:

1. Ask firm to confirm Conditions of Use section 1.12.12; indicates Rx, however proposed labeling, NDA label & indicate OTC; received 8/25/2011
2. Ask firm to submit Analytical Procedures and Validation of Analytical Procedures for Orange flavor [redacted] (b) (4)
3. Ask firm to submit the quantitative composition of Orange flavor [redacted] (b) (4) from supplier (do not have access to DMF's); ≤ 0.1% used therefore no justification required
4. Ask firm to submit Pharm/Tox Information for the inactive ingredient, Sodium Polystyrene Sulfonate; [redacted] (b) (4); only a portion of the pharmtox report was submitted on 8/25/2011
5. Spoke with Meghana Patel for Alpesh Patel on 8/17/2011 @ 1:40 pm.
6. Emailed Alpesh Patel on 8/25/2011 to request the full pharm/tox report for the inactive, Sodium Polystyrene Sulfonate; the firm submitted a portion of the report and a reference to the DMF; received 9/2/2011
7. Consult Request completed 9/7/2011 (copy attached)

MODULE 1: ADMINISTRATIVE

		COMMENT (S)
1.1	**Signed and Completed Application Form (356h)** (Rx/OTC Status) Yes (original signature)	
1.1.2	**Establishment Information:** Yes 1. Drug Substance Manufacturer 2. Drug Product Manufacturer 3. Outside Testing Facility(ies)	
1.2	**Cover Letter** Yes	
1.2.1	**Form FDA 3674** (PDF) B	
*	**Table of Contents** (paper submission only) N/A	
1.3.2	**Field Copy Certification** (N/A for E-Submissions) N/A (original signature)	
1.3.3	**Debarment Certification-GDEA** (Generic Drug Enforcement Act)/Other: (no qualifying statement) 1. Debarment Certification (original signature) Yes 2. List of Convictions statement (original signature) Yes	
1.3.4	**Financial Certifications** Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) Yes Disclosure Statement (Form FDA 3455) N/A	
1.3.5	**Patent Information** Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations **Patent Certification** 1. Patent number(s) 5980882 2. Paragraph: (Check all certifications that apply) MOU ☐ PI ☐ PII ☐ PIII ☐ PIV ☒ (Statement of Notification) ☒ 3. Expiration of Patent(s): 4/16/2017 a. Pediatric exclusivity submitted? N/A b. Expiration of Pediatric Exclusivity? N/A 4. Exclusivity Statement: YES State marketing intentions? No unexpired exclusivity **Patent and Exclusivity Search Results from query on Appl No 018658 Product 001 in the OB_OTC list.** **Appl No** | **Prod No** | **Patent No** | **Patent Expiration** | **Drug Substance Claim** | **Drug Product Claim** | **Patent Use Code** | **Delist Requested** N018658 | 001 | 5980882 | Apr 16, 2017 | | **Y** | | **There is no unexpired exclusivity for this product.**	
1.4.1	**References** Letters of Authorization 1. DMF letters of authorization a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient Yes b. Type II DMF# DEXTROMETHORPHAN POLISTREX - (b) (4) c. Type III DMF authorization letter(s) for container closure Yes; (b) (4) 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) N/A	

	(b) (4)	
1.12.4	**Request for Comments and Advice** - Proprietary name requested No If Yes, did the firm provide the request as a separate electronic amendment labeled "Proprietary Name Request" at initial time of filing 1. Yes N/A 2. No - contact the firm to submit the request as a separate electronic amendment.	
1.12.11	**Basis for Submission** NDA#: 18-658 Ref Listed Drug: DELSYM Firm: RECKITT BENCKISER **ANDA suitability petition required?** N/A If Yes, provide petition number and copy of approved petition **ANDA Citizen's Petition Required?** N/A If Yes, provide petition number and copy of petition	

MODULE 1: ADMINISTRATIVE (Continued)

		COMMENT (S)
1.12.12	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use Same 2. Active ingredients Same 3. Inactive ingredients Justified 4. Route of administration Same 5. Dosage Form Same 6. Strength Same	
1.12.14	**Environmental Impact Analysis Statement** **(**cite 21CFR 25.31, if applicable) Yes	
1.12.15	**Request for Waiver** Request for Waiver of In-Vivo BA/BE Study(ies) N/A	
1.14.1	**Draft Labeling** (Multi Copies N/A for E-Submissions) **1.14.1.1** 4 copies of draft for paper submission only (each strength and container) Yes **1.14.1.2** 1 side by side labeling comparison of containers and carton with all differences visually highlighted and annotated Yes **1.14.1.3** 1 package insert (content of labeling) and SPL submitted electronically Yes	
1.14.3	**Listed Drug Labeling** **1.14.3.1** 1 side by side labeling (package and patient insert) comparison with	Package insert not

	all differences visually highlighted and annotated Yes **1.14.3.3** RLD package insert, 1 RLD label and 1 RLD container label Yes	included/OTC

MODULE 2: SUMMARIES

		COMMENT (S)
2.3	**Quality Overall Summary (QOS)** **E-Submission: PDF** Yes **Word Processed e.g., MS Word** Yes A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage http://www fda.gov/cder/ogd/ **Question based Review (QbR)** Yes **2.3.S Drug Substance (Active Pharmaceutical Ingredient)** Yes 2.3.S.1 General Information 2.3.S.2 Manufacture 2.3.S.3 Characterization 2.3.S.4 Control of Drug Substance 2.3.S.5 Reference Standards or Materials 2.3.S.6 Container Closure System 2.3.S.7 Stability **2.3.P Drug Product** Yes 2.3.P.1 Description and Composition of the Drug Product 2.3.P.2 Pharmaceutical Development 2.3.P.2.1 Components of the Drug Product 2.3.P.2.1.1 Drug Substance 2.3.P.2.1.2 Excipients 2.3.P.2.2 Drug Product 2.3.P.2.3 Manufacturing Process Development 2.3.P.2.4 Container Closure System 2.3.P.3 Manufacture 2.3.P.4 Control of Excipients 2.3.P.5 Control of Drug Product 2.3.P.6 Reference Standards or Materials 2.3.P.7 Container Closure System 2.3.P.8 Stability	
2.7	**Clinical Summary (Bioequivalence)**Model BE Data Summary Tables **E-Submission: PDF** Yes **Word Processed: e.g., MS Word** Yes **2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods** **2.7.1.1 Background and Overview** Table 1. Submission Summary Yes Table 4. Bioanalytical Method Validation Yes Table 6. Formulation Data Yes **2.7.1.2 Summary of Results of Individual Studies** Table 5. Summary of In Vitro Dissolution Yes **2.7.1.3 Comparison and Analyses of Results Across Studies** Table 2. Summary of Bioavailability (BA) Studies Yes Table 3. Statistical Summary of the Comparative BA Data Yes **2.7.1.4 Appendix** Yes **2.7.4.1.3 Demographic and Other Characteristics of Study Population** Table 7. Demographic Profile of Subjects Completing the Bioequivalence Study Yes **2.7.4.2.1.1 Common Adverse Events** Table 8. Incidence of Adverse Events in Individual Studies Yes	

MODULE 3: 3.2.S DRUG SUBSTANCE

<table>
<tr><th></th><th></th><th>COMMENT (S)</th></tr>
<tr><td>3.2.S.1</td><td>General Information (Do not refer to DMF) Yes
3.2.S.1.1 Nomenclature
3.2.S.1.2 Structure
3.2.S.1.3 General Properties</td><td></td></tr>
<tr><td>3.2.S.2</td><td>Manufacturer
Drug Substance (Active Pharmaceutical Ingredient)
1. Name and Full Address(es)of the Facility(ies) Yes
2. Contact name, phone and fax numbers, email address Yes
3. Specify Function or Responsibility Yes
4. Type II DMF number for API Yes; (b) (4)
5. CFN or FEI numbers Yes
Table 1. Drug Substance Establishment Information
<table>
<tr><th colspan="2">API MANUFACTURER & LOCATION OF FACILITY:</th></tr>
<tr><td>Manufacturing & Testing site</td><td rowspan="3">(b) (4)</td></tr>
<tr><td>Contact Person
(address for communication):</td></tr>
<tr><td>US Agent (Contact Address):</td></tr>
</table></td><td></td></tr>
<tr><td>3.2.S.3</td><td>Characterization Yes
Provide the following in tabular format:
1. Name of Impurity(ies)
2. Structure of Impurity(ies)
3. Origin of Impurity(ies)</td><td></td></tr>
</table>

3.2.S.4 Control of Drug Substance (Active Pharmaceutical Ingredient)

3.2.S.4.1 Specification Yes

Testing specifications and data from drug substance manufacturer(s)

3.2.S.4.2 Analytical Procedures Yes

3.2.S.4.3 Validation of Analytical Procedures

(API that is USP or reference made to DMF, must provide verification of USP or DMF procedures) N/A

1. Spectra and chromatograms for reference standards and test samples Yes
2. Samples-Statement of Availability and Identification of:
   a. Drug Substance Yes
   b. API lot number(s)

1.4 Sample Statement of API

Upon request by the FDA, samples of the drug substance, Dextromethorphan Hydrobromide (API) as per the **following lot numbers and receiving numbers**; utilized in the manufacture of the **ANDA/Bio Submission Batch # BB-ST-10012; Dextromethorphan Polistirex Extended Release Suspension equivalent to 30 mg /5 mL of Dextromethorphan Hydrobromide** shall be made available. In addition, any applicable reference standards, with appropriate identification shall be made available. Amneal Pharmaceuticals maintains a sample-retention program, for any material utilized in the manufacture of a test batch or production batch.

Manufacturer Lot # (b) (4)	Dextromethorphan Hydrobromide, USP API		Dextromethorphan Polistirex ER Suspension eq. to 30 mg/5 mL of Dextromethorphan Hydrobromide
	Amneal RM Code	Amneal Branchburg Receiving #	
S-3140910	01-1080	103098	ANDA/Bio Submission Batch # BB-ST-10012

3.2.S.4.4 Batch Analysis

1. COA(s) specifications and test results from drug substance mfgr(s) Yes
2. Applicant certificate of analysis Yes

3.2.S.4.5 Justification of Specification Yes

3.2.S.5 Reference Standards or Materials (Do not refer to DMF) Yes

3.2.S.6 Container Closure Systems Yes

3.2.S.7 Stability

1. Retest date or expiration date of API Yes

The stability conclusion, packaging & storage and proposed retest date are included as Appendix 2. Based on the stability result, the **re-test period for the product is proposed for** (b) (4)

MODULE 3: 3.2.P DRUG PRODUCT

		COMMENT (S)
3.2.P.1	**Description and Composition of the Drug Product** 1. Unit composition with indication of the function of the inactive ingredient(s) Yes 2. Inactive ingredients and amounts are appropriate per IIG (per/dose justification) Yes pharmtox data received for sodium polystyrene sulfonate, USP (b) (4) on 9/2/2011 3. Conversion from % to mg/dose values for inactive ingredients (if applicable) Yes 4. Elemental iron: provide daily elemental iron calculation or statement of adherence to 21CFR73.1200 (calculation of elemental iron intake based on **maximum daily dose (MDD)** of the drug product is preferred if this section is applicable) N/A 5. Injections: If the reference listed drug is packaged with a drug specific diluent then the diluent must be Q1/Q2 and must be provided in the package configuration N/A	
3.2.P.2	**Pharmaceutical Development** Pharmaceutical Development Report Yes	
3.2.P.3	**Manufacture** **3.2.P.3.1 Drug Product** (Finished Dosage Manufacturer and Outside Contract Testing Laboratories) 1. Name and Full Address(es)of the Facility(ies) Yes 2. Contact name, phone and fax numbers, email address Yes 3. Specify Function or Responsibility Yes 4. CGMP Certification (from both applicant and drug product manufacturer if different entities) Yes 5. CFN or FEI numbers Yes	

1 Page(s) has been Withheld in Full as b4 (CCI/TS) following this page

(b) (4)

[redacted]

3.2.P.3.2 Batch Formula Yes

3.2.P.3.3 Description of Manufacturing Process and Process Controls

1. Description of the Manufacturing Process Yes
2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified Yes
3. Master packaging records for intended marketing container(s) Yes
4. If sterile product N/A
5. Reprocessing Statement (cite 21CFR 211.115, submitted by the drug product manufacturer and the applicant, if different entities) Yes

3.2.P.3.4 Controls of Critical Steps and Intermediates Yes

3.2.P.3.5 Process Validation and/or Evaluation

1. Microbiological sterilization validation N/A
2. Filter validation (if aseptic fill) N/A

Demonstration ANDA Batch	Proposed Scale-up
Batch Size: (b) (4)	Batch Size: (b) (4)

3.2.P.4	**Controls of Excipients** (Inactive Ingredients) Source of inactive ingredients identified Yes **3.2.P.4.1 Specifications** 1. Testing specifications (including identification and characterization) Yes 2. Suppliers' COA (specifications and test results) Yes **3.2.P.4.2 Analytical Procedures** Yes; USP **3.2.P.4.3 Validation of Analytical Procedures** Yes **3.2.P.4.4 Justification of Specifications:** 1. Applicant COA Yes	

MODULE 3: 3.2.P DRUG PRODUCT (Continued)

		COMMENT (S)
3.2.P.5	**Controls of Drug Product** **3.2.P.5.1 Specification(s)** Yes **3.2.P.5.2 Analytical Procedures** Yes **3.2.P.5.3 Validation of Analytical Procedures** (if using USP procedure, must provide verification of USP procedure) N/A Samples - Statement of Availability and Identification of: 1. Finished Dosage Form Yes 2. Lot number(s) and strength of Drug Product(s) **1.4 Sample Statement** The samples of **ANDA Submission Batch # BB-ST-10012A** and **BB-ST-10-0012B** of Dextromethorphan Polistirex ER Suspension Equivalent to 30 mg/5 mL of Dextromethorphan HBr is available and will be provided upon agency request. **3.2.P.5.4 Batch Analysis** Certificate of Analysis for Finished Dosage Form Yes **3.2.P.5.5 Characterization of Impurities** Yes **3.2.P.5.6 Justification of Specifications** Yes	
3.2.P.7	**Container Closure System** 1. Summary of Container/Closure System (if new resin, provide data) Yes 2. Components Specification and Test Data Yes 3. Packaging Configuration and Sizes Yes 4. Container/Closure Testing (recommended additional testing for all plastic)Yes a. Solid Orals: water permeation, light transmissionYes b. Liquids: leachables, extractables, light transmissionYes 5. Source of supply and suppliers address Yes	
3.2.P.8	**3.2.P.8.1 Stability (Finished Dosage Form)** 1. Stability Protocol submitted Yes 2. Expiration Dating Period (b) (4) **3.2.P.8.2 Post-approval Stability and Conclusion** Post Approval Stability Protocol and Commitments Yes **3.2.P.8.3 Stability Data** 1. Accelerated stability data a. four (4) time points 0,1,2,3 Yes; upright and sideways **-OR-** b. three (3) time points 0,3,6 (if 3 time points for accelerated stability data are submitted then provide 3 exhibit batches along with 12 months of room temperature stability data –Refer to Guidance for Industry Q1A(R2) Stability Testing of New Drug Substances and Products November 2003, Section B) N/A 2. Batch numbers on stability records the same as the test batch Yes; BB-ST-10012B (3 oz) BB-ST-10012B (5 oz)	

MODULE 3: 3.2.R REGIONAL INFORMATION (Drug Substance)

		COMMENT (S)
3.2.R Drug Substance	**3.2.R.1.S Executed Batch Records for drug substance (if available)** N/A **3.2.R.2.S Comparability Protocols** N/A **3.2.R.3.S Methods Validation Package** Yes Methods Validation Package (3 copies for paper and N/A for E-Submissions) (Required for Non-USP drugs)	

MODULE 3: 3.2.R REGIONAL INFORMATION (Drug Product)

		COMMENT (S)
3.2.R Drug Product	**3.2.R.1.P.1** **Executed Batch Records** Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures) Batch Reconciliation and Label Reconciliation Yes; attached at the end of checklist Bulk Package Reconciliation required if bulk packaging is used to achieve the minimum package requirement. Provide the following information in their respective sections: a. Bulk Package Label (1.14.1) N/A b. Bulk Package Stability (accelerated stability data [0,1,2,3] –**OR**- room temperature [0,3,6]) (3.2.P.8) N/A c. Bulk Package Container and Closure information (3.2.P.7) N/A **3.2.R.1.P.2 Information on Components** Yes **3.2.R.2.P Comparability Protocols** Yes **3.2.R.3.P Methods Validation Package** Yes Methods Validation Package (3 copies for paper and N/A for E-Submissions) (Required for Non-USP drugs)	

MODULE 5: CLINICAL STUDY REPORTS

		COMMENT (S)
5.2	**Tabular Listing of Clinical Studies** Yes	
5.3.1 (complete study data)	**Bioavailability/Bioequivalence** **1. Formulation data same?** a. Comparison of all Strengths (check proportionality of multiple strengths) N/A b. Parenterals, Ophthalmics, Otics and Topicals (21 CFR 314.94 (a)(9)(iii)-(v) N/A **2. Lot Numbers and strength of Products used in BE Study(ies)** ANDA: BB-ST-10012B RLD: 54554 **3. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)	
	5.3.1.2 Comparative BA/BE Study Reports 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) Yes	

Table 3A Summary of Comparative BA Data for Study # ARL/10/408 (Fasting) - Dextromethorphan

Dextromethorphan Polistirex Extended Release Suspension 30mg/5ml Dose (1 X 10 ml) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals (Test A vs Reference B)				
Fasted Bioequivalence Study (Study No. ARL/10/408)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC_{0-t}	25.06	23.31	107.5276	102.5977-112.6943
AUC_{0-inf}	25.51	23.74	107.4409	102.5690-112.5443
C_{max}	1.97	1.77	111.2607	106.5840-116.1426

Study Report Location: fasted-statistical-methods.pdf

Table 3B Summary of Comparative BA Data for Study # ARL/10/409 (Fed) - Dextromethorphan

Dextromethorphan Polistirex Extended Release Suspension 30mg/5ml Dose (1 X 10 ml) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals (Test A vs Reference B)				
Fed Bioequivalence Study (Study No. ARL/10/409)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC_{0-t}	34.92	33.63	103.8389	96.8629-111.3172
AUC_{0-inf}	35.53	34.21	103.8690	96.9404-111.2928
C_{max}	2.38	2.29	104.1626	95.8039-113.2506

Study Report Location: fed-statistical-methods.pdf

2. Summary Bioequivalence tables:
Table 10. Study Information Yes
Table 12. Dropout Information Yes
Table 13. Protocol Deviations Yes

5.3.1.3 In Vitro-In-Vivo Correlation Study Reports

1. Summary Bioequivalence tables Yes
Table 11. Product Information Yes
Table 16. Composition of Meal Used in Fed Bioequivalence Study Yes; Table 26 in ANDA

5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

1. Summary Bioequivalence table:

	Table 9. Reanalysis of Study Samples Yes Table 14. Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses Yes Table 15. SOPs Dealing with Bioanalytical Repeats of Study Samples Yes **Case Report Forms** should be placed under the study to which they pertain, and appropriately tagged. Refer to The eCTD Backbone File Specification for Study Tagging //www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf	
5.4	**Literature References**	
	Possible Study Types:	
Study Type	**IN-VIVO BE STUDY(IES) with PK ENDPOINTS** (i.e., fasting/fed/sprinkle) FASTING AND FED ON 30 MG/5 ML 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) Select 2. EDR Email: Data Files Submitted Select 3. In-Vitro Dissolution Select	
Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** 1. Properly defined BE endpoints (eval. by Clinical Team) Select 2. Summary results meet BE criteria: 90% CI of the proportional difference in success rate between test and reference must be within (-0.20, +0.20) for a binary/dichotomous endpoint. For a continuous endpoint, the test/reference ratio of the mean result must be within (0.80,1.25) Select 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) Select 4. EDR Email: Data Files Submitted Select	
Study Type	**IN-VITRO BE STUDY(IES)** (i.e., in vitro binding assays) Select 1. Study(ies) meets BE criteria (90% CI of 80-125) Select 2. EDR Email: Data Files Submitted Select 3. In-Vitro Dissolution Select	

Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** **1. <u>Solutions</u> (Q1/Q2 sameness)** Select a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming) Select **2. <u>Suspensions</u> (Q1/Q2 sameness):** a. In-Vivo PK Study Select 1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) Select 2. EDR Email: Data Files Submitted Select b. In-Vivo BE Study with Clinical End Points Select 1. Properly defined BE endpoints (eval. by Clinical Team) Select 2. Summary results meet BE criteria (90% CI within +/- 20% of 80-125) Select 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) Select 4. EDR Email: Data Files Submitted Select c. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming) Select	
Study Type	**IN-VIVO BE STUDY(IES) with PD ENDPOINTS** (e.g., topical corticosteroid vasoconstrictor studies) 1. Pilot Study (determination of ED50) Select 2. Pivotal Study (study meets BE criteria 90%CI of 80-125) Select	
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** 1. <u>In-Vivo PK Study</u> Select a. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC) Select b. In-Vitro Dissolution Select c. EDR Email: Data Files Submitted Select 2. <u>Adhesion Study</u> Select 3. <u>Skin Irritation/Sensitization Study</u> Select	

Updated 05/16/2011

Guidance on Dextromethorphan Polistirex

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Dextromethorphan Polistirex

Form/Route: Extended Release Oral Suspension /Oral

Recommended studies: 2 studies

1. Type of study: Fasting
   Design: Single-dose, two-way crossover *in-vivo*
   Strength: 30 mg/5 mL
   Subjects: Normal healthy males and females, general population.
   Additional Comments:

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2. Type of study: Fed
   Design: Single-dose, two-way crossover *in-vivo*
   Strength: 30 mg/5 mL
   Subjects: Normal healthy males and females, general population.
   Additional comments:

Analytes to measure (in appropriate biological fluid): Dextromethorphan and its metabolite Dextrorphan in plasma.

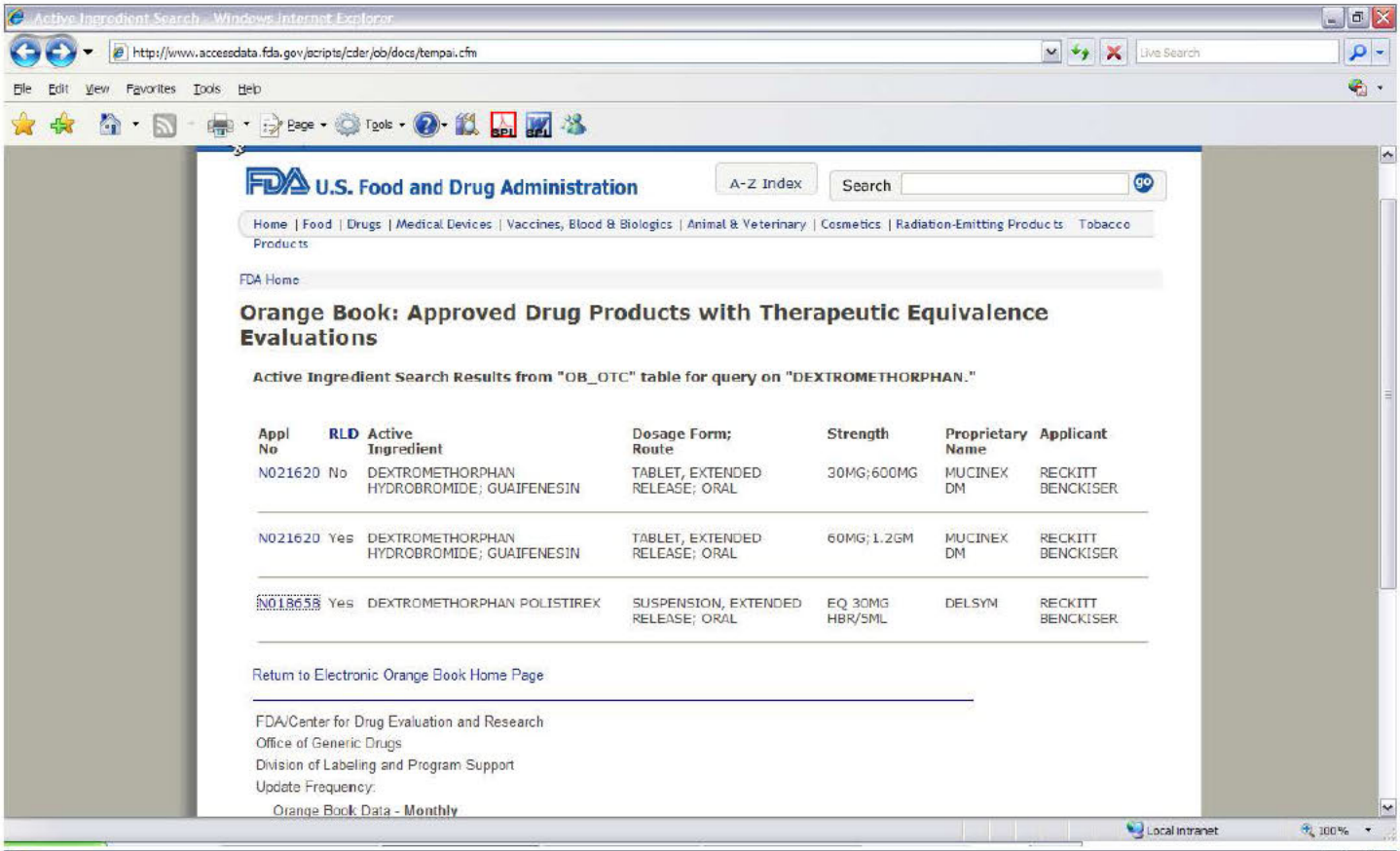
Bioequivalence based on (90% CI): Dextromethorphan
Please submit the metabolite data as supportive evidence of comparable therapeutic outcome. For the metabolite, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and Cmax.

Waiver request of in-vivo testing: Not Applicable

Dissolution test method and sampling times:
Please note that a **Dissolution Methods Database** is available to the public at the OGD website at http://www.fda.gov/cder/ogd/index.htm. Please find the dissolution information for this product at this website. A dosage unit for a suspension is the labeled strength (5 ml). A total of 12 units from 12 different bottles should be used.

In addition to the method above, for modified release products, dissolution profiles on 12 dosage units each of test and reference products generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Please include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation. Specifications will be determined upon review of the data submitted in the application.

Finalized May 2008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Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations
Active Ingredient Search Results from "OB_OTC" table for query on "DEXTROMETHORPHAN."
Appl No | RLD | Active Ingredient | Dosage Form; Route | Strength | Proprietary Name | Applicant
N021620 | No | DEXTROMETHORPHAN HYDROBROMIDE; GUAIFENESIN | TABLET, EXTENDED RELEASE; ORAL | 30MG;600MG | MUCINEX DM | RECKITT BENCKISER
N021620 | Yes | DEXTROMETHORPHAN HYDROBROMIDE; GUAIFENESIN | TABLET, EXTENDED RELEASE; ORAL | 60MG;1.2GM | MUCINEX DM | RECKITT BENCKISER
N018658 | Yes | DEXTROMETHORPHAN POLISTIREX | SUSPENSION, EXTENDED RELEASE; ORAL | EQ 30MG HBR/5ML | DELSYM | RECKITT BENCKISER
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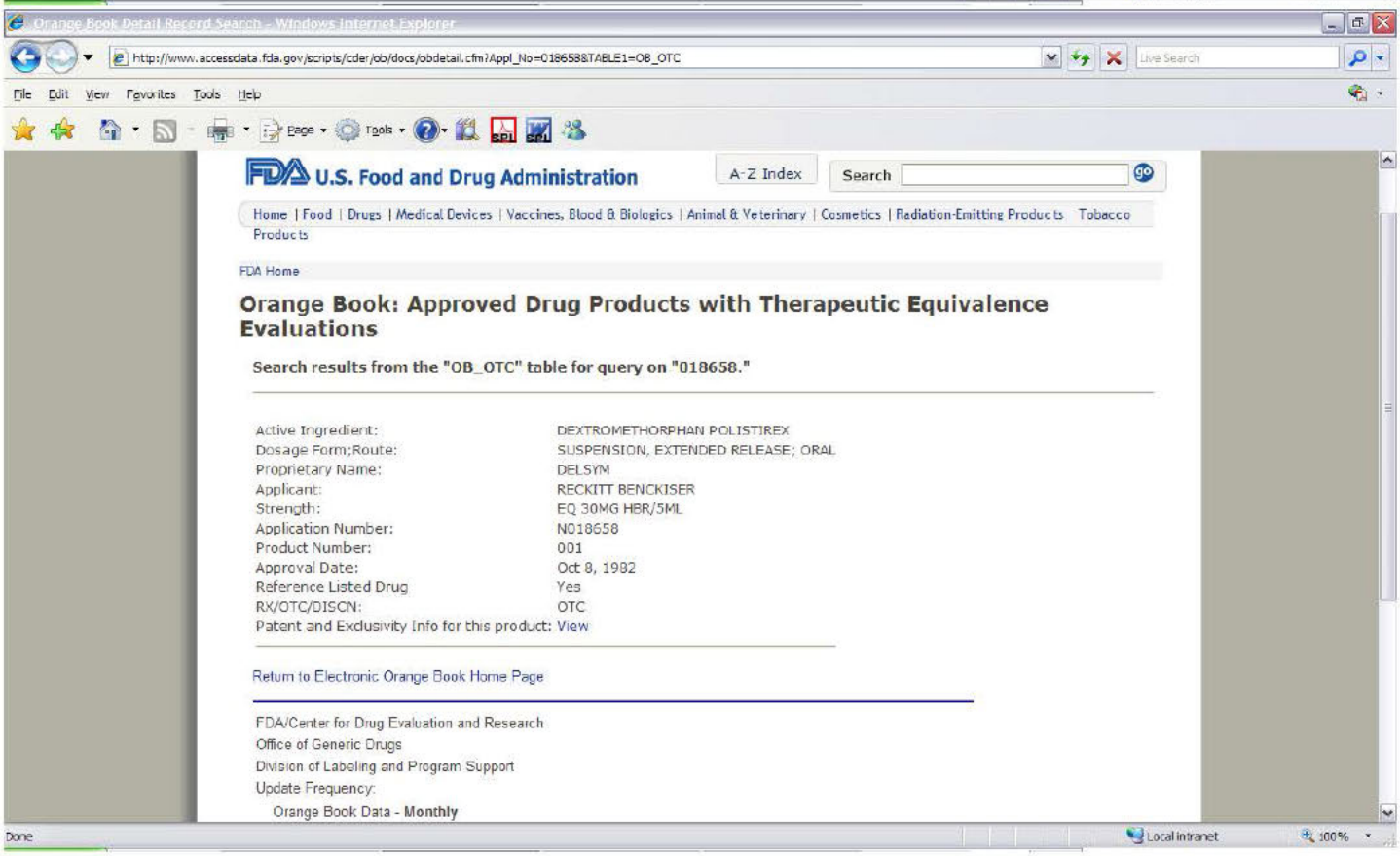
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Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations
Search results from the "OB_OTC" table for query on "018658."
Active Ingredient: DEXTROMETHORPHAN POLISTIREX
Dosage Form;Route: SUSPENSION, EXTENDED RELEASE; ORAL
Proprietary Name: DELSYM
Applicant: RECKITT BENCKISER
Strength: EQ 30MG HBR/5ML
Application Number: N018658
Product Number: 001
Approval Date: Oct 8, 1982
Reference Listed Drug Yes
RX/OTC/DISCN: OTC
Patent and Exclusivity Info for this product: View
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Office of Generic Drugs
Division of Labeling and Program Support
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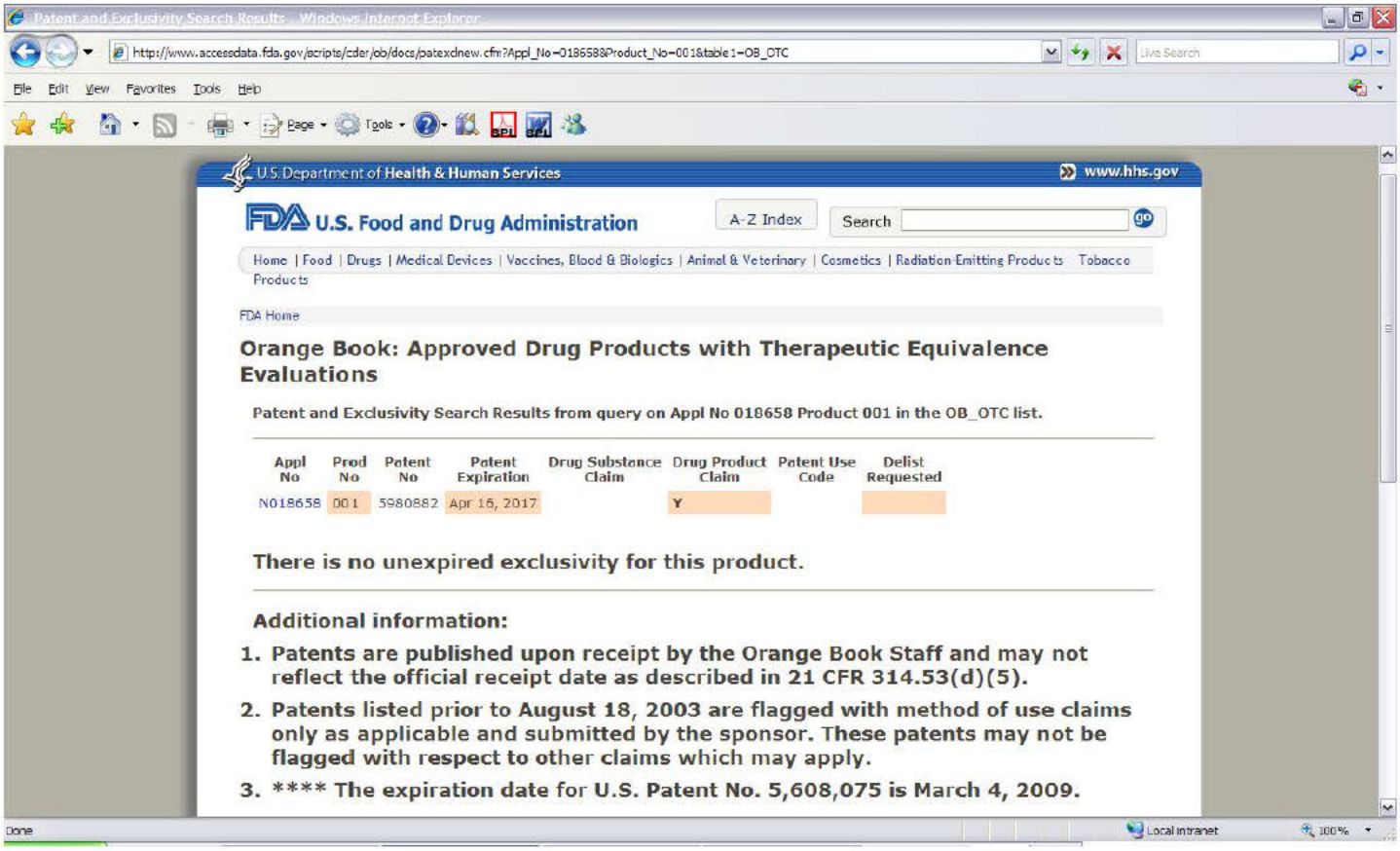

Patent and Exclusivity Search Results - Windows Internet Explorer

http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=018658&Product_No=001&table1=OB_OTC

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Patent and Exclusivity Search Results from query on Appl No 018658 Product 001 in the OB_OTC list.

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N018658	001	5980882	Apr 16, 2017		Y		

There is no unexpired exclusivity for this product.

Additional information:

1. **Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).**
2. **Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.**
3. ****** The expiration date for U.S. Patent No. 5,608,075 is March 4, 2009.**

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Table 5A. Summary of In Vitro Dissolution Study (0.1 N Hydrochloric Acid)

Dissolution Conditions	**Apparatus:**	USP Type II (Paddle)	**Medium:**	0.1 N Hydrochloric Acid
	Speed of Rotation:	50 rpm	**Volume:**	500 mL
	Temperature:	37°C ± 0.5°C	**Tolerance:**	90 minutes: NMT (b) (4) (Q)
Firm's Proposed Specifications	Refer to 3.2.P.5.1 for Finished Product Specification			
Dissolution Testing Site (Name, Address)	Amneal Pharmaceuticals, 131 Chambers Brook Road, Branchburg, NJ 08776			

Analysis Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Active Ingredient Name	No. of Dosage Units	Parameters	Sample Collection Times % Dissolution			
					30 min	60 min	90 min	180 min
05/31/2011	Dextromethorphan Polistirex Extended-Release Suspension 30 mg/5 mL **Batch No.:** BB-ST-10012 **Mfg Date:** 12/01/2010	Dextromethorphan Hydrobromide	12	**Mean**	21	28	32	36
				Min.	(b) (4)			
				Max				
				RSD	9.2	8.4	8.5	6.2
05/31/2011	Delsym® (Dextromethorphan Polistirex Extended-Release Suspension) 30 mg/5 mL **Batch No.:** 54554 **Exp Date:** 03/2013		12	**Mean**	23	25	26	30
				Min.	(b) (4)			
				Max				
				RSD	3.9	3.0	3.4	10.1

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Ingredients	Quantity %w/w	Maximum Potency From FDA's Inactive Ingredient database	Functions
Sodium Polystyrene Sulfonate, USP (b) (4)	(b) (4)		
Polyethylene Glycol 3350 (b) (4) NF			
Ethylcellulose, NF (b) (4)			
Corn Oil, NF			
Tragacanth (b) (4) NF			
Xanthan Gum, NF			
Propylene Glycol, USP			
Methylparaben, NF			
Propylparaben, NF			
Sucrose, NF			
Edetate Disodium, USP			
(b) (4) Citric Acid, USP			
Polysorbate-80 (b) (4)			
FD & C Yellow # 6			
(b) (4) Flavor (b) (4)			

(b) (4)

Table 6 Formulation Data - Dextromethorphan Polistirex ER Suspension, 30 mg/5mL

Ingredients	Quantity in mg/ 5 mL	mg per dose (Dose: 10 mL)	Quantity in %w/v	Quantity in %w/w[1]
Dextromethorphan Hydroboromide	30.00	60.00		(b) (4)
Sodium Polystyrene Sulfonate, USP (b) (4)				(b) (4)
Polyethylene Glycol 3350 (b) (4) NF				
Ethylcellulose, NF (b) (4)				
Corn Oil, NF				
Tragacanth (b) (4) NF				
Xanthan Gum, NF				
Propylene Glycol, USP				
Methylparaben, NF				
Propylparaben, NF				
Sucrose, NF				
Edetate Disodium, USP				
(b) (4) Citric Acid, USP				
Polysorbate-80 (b) (4) NF				
FD & C Yellow # 6				
(b) (4) Flavor (b) (4)				
HCl , NF (b) (4) OR NaOH Pellets, NF				
Purified Water, USP				
				(b) (4)

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