CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 091135Orig1s000

Name: Dextromethorphan Polistirex Extended-Release Oral Suspension (OTC)

Sponsor: Tris Pharma, Inc.

Approval Date: May 25, 2012

Indication: For temporary relief of cough due to minor throat and bronchial irritation as may occur with the common cold or with inhaled irritants.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 091135Orig1s000

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 091135Orig1s000

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 091135

Tris Pharma, Inc.
Attention: W. Scott Groner
Director, Regulatory Affairs
2033 Route 130
Monmouth Junction, NJ 08852

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated January 9, 2009, 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 Dextromethorphan Hydrobromide, 30 mg/5 mL) (OTC).

Reference is made to the tentative approval letter issued by this office on April 20, 2011, and to your amendments dated August 3, August 11, and November 11, 2011.

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 Division of Bioequivalence has determined your Dextromethorphan Polistirex Extended-release Oral Suspension, (equivalent to Dextromethorphan Hydrobromide, 30 mg/5 mL), to be bioequivalent to the reference listed drug product (RLD) Delsym Extended-release Cough Suppressant, 30 mg/5 mL, of Reckitt Benckiser. As noted in our communication dated July 28, 2011, your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

The RLD upon which you have based your ANDA, Delsym Cough Suppressant of Reckitt Benckiser, is subject to a period of patent protection. As noted in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations

(the “Orange Book”), U.S. Patent No. 5,980,882 (the '882 patent), is scheduled to expire on April 16, 2017.

Your ANDA contains a paragraph IV certification under section 505(j)(2)(A)(vii)(IV) of the Act stating that the ‘882 patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Dextromethorphan Polistirex Extended-release Oral Suspension, 30 mg/5 mL, under this ANDA. You have notified the agency that Tris Pharma, Inc. (Tris) complied with the requirements of section 505(j)(2)(B) of the Act, and that litigation was initiated against Tris for infringement of the '882 patent within the statutory 45-day period in the United States District Court for the District of New Jersey [Reckitt Benckiser Inc. and UCB Manufacturing, Inc. v. Tris Pharma, Inc., Civil Action No. 09-cv-03125]. Although this litigation remains ongoing, the 30-month period identified in section 505(j)(5)(B)(iii) of the Act, during which time FDA was precluded from approving your ANDA, expired In addition, you have informed the agency that on December 21, 2011, the United States District Court granted Tris Pharma’s motion for summary judgment.

With respect to 180-day generic drug exclusivity, we note that Tris was the first ANDA applicant to submit a substantially complete ANDA with a paragraph IV certification to the '882 patent. Therefore, with this approval, Tris is eligible for 180-days of generic drug exclusivity for Dextromethorphan Polistirex Extended-release Oral Suspension, 30 mg/5 mL. This exclusivity, which is provided for under section 505(j)(5)(B)(iv) of the Act, will begin to run from the date of the commercial marketing identified in section 505(j)(5)(B)(iv). Please submit correspondence to this ANDA informing the agency of the date the exclusivity begins to run.

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

Postmarketing 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.

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/U_CM072392.pdf. The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

{See appended electronic signature page}

Keith Webber, Ph.D.
Deputy Director
Office of Pharmaceutical Science
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/

ROBERT L WEST

05/25/2012

Deputy Director, Office of Generic Drugs
for Keith Webber, Ph.D.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 091135Orig1s000

TENTATIVE APPROVAL LETTER

Food and Drug Administration
Rockville, MD 20857

ANDA 091135

Tris Pharma, Inc.
Attention: W. Scott Groner
Director, Regulatory Affairs and Compliance
2033 Route 130
Monmouth Junction, NJ 08852

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated January 9, 2009, 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 Dextromethorphan Hydrobromide, 30 mg/5 mL) (OTC).

Reference is also made to your amendments dated August 14, September 25, October 9, and October 29, 2009; August 26, October 1, October 13, November 18, and December 16, 2010; and January 27, March 4, March 29, and April 14, 2011.

We have completed the review of this ANDA, and based upon the information you have presented to date we have concluded that the drug is safe and effective for use as recommended in the submitted labeling. However, we are unable to grant final approval to your ANDA at this time because of the patent issue noted below. Therefore, the ANDA is **tentatively approved**. This determination is based upon information available to the agency at this time (i.e., information in your ANDA and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product). This determination is subject to change on the basis of new information that may come to our attention. This letter does not address issues related to the 180-day exclusivity provisions under section 505(j)(5)(B)(iv) of the Act.

The reference listed drug (RLD) upon which you have based your ANDA, Delsym Cough Suppressant, 30 mg/5 mL, of Reckitt Benckiser, is subject to a period of patent protection. As noted in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"), U.S. Patent No. 5,980,882 (the '882 patent), is scheduled to expire on April 16, 2017.

Your ANDA contains a paragraph IV certification under section 505(j)(2)(A)(vii)(IV) of the Act stating that the '882 patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Dextromethorphan Polistirex Extended-release Oral Suspension, 30 mg/5 mL, under this ANDA. You notified the agency that Tris Pharma, Inc. (Tris) complied with the requirements of section 505(j)(2)(B) of the Act, and that litigation for infringement of the '882 patent was brought against Tris within the statutory 45-day period in the United States District Court for the District of New Jersey [Reckitt Benckiser Inc. and UCB Manufacturing, Inc. v. Tris Pharma, Inc., Civil Action No. 09-cv-03125].

Therefore, final approval cannot be granted until:

1. a. the expiration of the 30-month period provided for in section 505(j)(5)(B)(iii),

   b. the date the court decides[1] that the '882 patent is invalid or not infringed (see sections 505(j)(5)(B)(iii)(I), (II), and (III) of the Act), or

   c. the '882 patent has expired, and

2. The agency is assured there is no new information that would affect whether final approval should be granted.

Please note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the Act.

[1] This decision may be either a decision of the district court or the court of appeals, whichever court is the first to decide that the patent is invalid or not infringed.

To reactivate your ANDA prior to final approval, please submit a "MINOR AMENDMENT – FINAL APPROVAL REQUESTED" 90 days prior to the date you believe that your ANDA will be eligible for final approval. This amendment should provide the legal/regulatory basis for your request for final approval and should include a copy of a court decision, or a settlement or licensing agreement, as appropriate. It should also identify changes, if any, in the conditions under which the ANDA was tentatively approved, i.e., updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. This amendment should be submitted even if none of these changes were made, and it should be designated clearly in your cover letter as a MINOR AMENDMENT – FINAL APPROVAL REQUESTED.

In addition to the amendment requested above, the agency may request at any time prior to the date of final approval that you submit an additional amendment containing the requested information. Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your ANDA, or may result in a delay in the issuance of the final approval letter.

Any significant changes in the conditions outlined in this ANDA as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (cGMPs) are subject to agency review before final approval of the application will be made. Such changes should be categorized as representing either "major" or "minor" changes, and they will be reviewed according to OGD policy in effect at the time of receipt. The submission of multiple amendments prior to final approval may also result in a delay in the issuance of the final approval letter.

This drug product may not be marketed without final agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under section 301 of the Act. Also, until the agency issues the final approval letter, this drug product will not be deemed to be approved for marketing under section 505 of the Act, and will not be listed in the "Orange Book."

For further information on the status of this application, or prior to submitting additional amendments, please contact Sarah Nguyen, Project Manager, at (240) 276-8467.

Sincerely yours,

{See appended electronic signature page}

Keith Webber, Ph.D.
Deputy Director
Office of Pharmaceutical Science
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/

ROBERT L WEST

04/20/2011

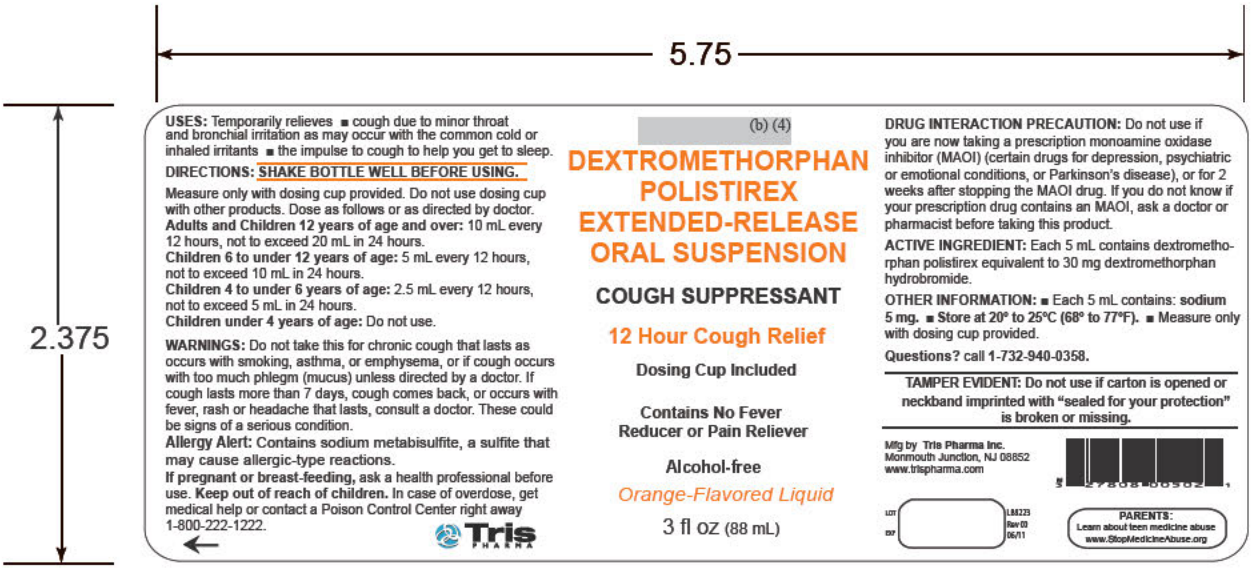
Deputy Director, Office of Generic Drugs
for Keith Webber, Ph.D.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 091135Orig1s000

LABELING



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 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 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.
Allergy Alert: Contains sodium metabisulfite, a sulfite that may cause allergic-type reactions.
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 1-800-222-1222.

Tris PHARMA

(b) (4)

DEXTROMETHORPHAN POLISTIREX EXTENDED-RELEASE ORAL SUSPENSION

COUGH SUPPRESSANT

12 Hour Cough Relief

Dosing Cup Included

Contains No Fever Reducer or Pain Reliever

Alcohol-free

Orange-Flavored Liquid

3 fl OZ (88 mL)

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 5 mg.** ■ **Store at 20° to 25°C (68° to 77°F).** ■ Measure only with dosing cup provided.

Questions? call **1-732-940-0358.**

TAMPER EVIDENT: Do not use if carton is opened or neckband imprinted with "sealed for your protection" is broken or missing.

Mfg by Tris Pharma Inc.
Monmouth Junction, NJ 08852
www.trispharma.com

LOT
EXP

LM223
Rev 03
06/11

PARENTS:
Learn about teen medicine abuse
www.StopMedicineAbuse.org

12 Hour Cough Relief

DEXTROMETHORPHAN
POLISTIREX
EXTENDED-RELEASE
ORAL SUSPENSION

TAMPER EVIDENT:
Do not use if carton is opened or neckband imprinted with "sealed for your protection" 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.
Allergy Alert: Contains sodium metabisulfite, a sulfite that may cause allergic-type reactions.

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
- side effects occur. You may report side effects to FDA at 1-800-FDA-1088.
- 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 1-800-222-1222.

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 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 5 mg**
■ store at 20° to 25°C (68° to 77°F) ■ dosing cup provided

Inactive ingredients D&C Red #30, D&C Yellow #10, flavor, glycerin, high fructose corn syrup, methylparaben, polysorbate 80,

(b) (4)

Tris PHARMA

DEXTROMETHORPHAN
POLISTIREX
EXTENDED-RELEASE
ORAL SUSPENSION

COUGH
SUPPRESSANT

12
HOUR
Cough Relief

DOSING CUP INCLUDED

Alcohol-free

**Contains
No Fever Reducer
or Pain Reliever**

PARENTS:
Learn about teen medicine abuse
www.StopMedicineAbuse.org

(b) (4)

Tris PHARMA

DEXTROMETHORPHAN
POLISTIREX
EXTENDED-RELEASE
ORAL SUSPENSION

COUGH
SUPPRESSANT

12
HOUR
Cough Relief

DOSAGE CUP INCLUDED

*Orange-Flavored Liquid
for Children and Adults*

Contains sodium metabisulfite, a sulfite that may cause allergic-type reactions

Alcohol-free

3 fl oz (88 mL)

3 27808 00502 1

LOT

EXP

Drug Facts (continued)

polyvinyl acetate, povidone, propylparaben, purified water, sodium metabisul ite, sodium polystyrene sulfonate, sucrose, tartaric acid, tragacanth gum, triacetin, xanthan gum

Questions? call 1-732-940-0358
You may also report side effects to this phone number.

COUGH
SUPPRESSANT

12
HOUR
Cough Relief

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

Orange-Flavored Liquid

Manufactured by:
Tris Pharma, Inc.
Monmouth Junction, NJ 08852
www.trispharma.com

LB8224 11/11 Rev 00

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 091135Orig1s000

LABELING REVIEWS

APPROVAL SUMMARY
*****This Approval Summary supersedes Approval Summary dated August 22, 2011)**
LABELING REVIEW #6
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 091135

Date of Submission: November 11, 2011

Applicant's Name: Tris Pharma, Inc.

Established Name: Dextromethorphan Polistirex Extended-release Oral Suspension (Equivalent to 30 mg Dextromethorphan Hydrobromide per 5 mL)

Propriety Name: None

BASIS OF APPROVAL:
APPROVAL SUMMARY

CONTAINER LABEL:
Satisfactory in FPL, April 14, 2011

CARTON LABEL:
Satisfactory in FPL, November 11, 2011

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Delsym® (Dextromethorphan Polistirex Extended-release Oral Suspension, 30 mg per 5 mL)
NDA Number: 018658
NDA Drug Name: Delsym® (Dextromethorphan Polistirex Extended-release Oral Suspension, Equivalent to 30 mg Dextromethorphan Hydrobromide per 5 mL)
NDA Firm: Reckitt Benckiser Inc.
Date of Approval of NDA Insert and supplement #: 018658/S-029, approved May 16, 2011
Has this been verified by the MIS system for the NDA? Yes – see note in FTR below
Was this approval based upon an OGD labeling guidance? No
Other Comments:

FOR THE RECORD:

1. **Model Labeling**:

   Review is based on the labeling of Reckitt Benckiser Inc.'s Delsym®", NDA 018658/S-029, approved May 16, 2011.

2. **Patents and Exclusivities (P&E):**

   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	Firm Filed
N018658	001	5980882	Apr 16, 2017		Y			IV

There are no unexpired exclusivities for this drug product.

3. Inactive Ingredients :

The listing of inactive ingredients are: D&C Red #30, D&C Yellow #10, flavor, glycerin, high fructose corn syrup, methylparaben, polysorbate 80, polyvinyl acetate, povidone, propylparaben, purified water, sodium metabisulfite, sodium polystyrene sufonate, sucrose, tartaric acid, tragacanth gum, triacetin, and xanthan gum.

**Firm was requested to include a warning statement for sodium metabisulfite on the carton and container.

4. Manufacturing Facility (3.2.P.3.1):

3.2.P.3.1 Manufacturer

This module contains information regarding the drug product manufacturer for Dextromethorphan Polistirex Extended Release Oral Suspension, including manufacturer address, responsibility, registration number, and cGMP statement.

1. Manufacturer Address:

Tris Pharma, Inc.
2033 Route 130
Monmouth Junction, NJ 08852
Contact: W. Scott Groner
Phone: 732-940-0358

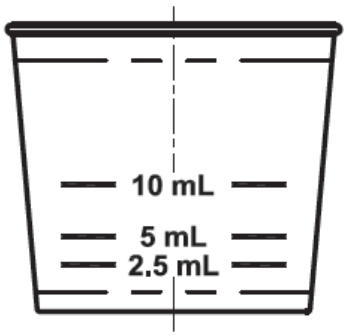
5. Product Description:
RLD (Delsym®)

Available in 3 fl oz and 5 fl oz grape and orange flavors for both pediatric and adult graphics.

Reference ID: 3046429

ANDA - Tris Pharma, Inc. is available in 3 fl oz orange flavor. Please note that there was an oversight in the former labeling review (b) (4).

Firm (b) (4) retained "mL" on the measuring cup:



In addition, firm revised the carton labeling to exclude the following statement: (b) (4). This statement was included in the carton labeling by mistake.

6. **USP**:

This drug product is not subject to a USP monograph.

7. **Container Closure System: (Chemistry Review#1)**

(b) (4)

[redacted]

8. **Storage Condition/Dispensing:**

NDA: Store at 20-25°C (68-77°F)

ANDA: Store at 20-25°C (68-77°F)

9. **SPL**:

Firm did not submit SPL; however firm may submit SPL post approval.

Date of Review:	November 17, 2011	Date of Submission: November 11, 2011
Primary Reviewer:	Jeanne Skanchy	
Team Leader:	John Grace	

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

/s/

JEANNE SKANCHY
11/18/2011

JOHN F GRACE
11/18/2011

APPROVAL SUMMARY
FULL APPROVAL
LABELING REVIEW #6
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 091135 (OTC)

Date of Submission: August 11, 2011

Applicant's Name: Tris Pharma, Inc.

Established Name: Dextromethorphan Polistirex Extended-release Oral Suspension (Equivalent to 30 mg Dextromethorphan Hydrobromide per 5 mL)

Propriety Name: None

BASIS OF APPROVAL:
APPROVAL SUMMARY

CONTAINER LABEL:
Satisfactory in FPL, August 11, 2011

CARTON LABEL:
Satisfactory in FPL, August 11, 2011

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Delsym® (Dextromethorphan Polistirex Extended-release Oral Suspension, 30 mg per 5 mL)
NDA Number: 018658
NDA Drug Name: Delsym® (Dextromethorphan Polistirex Extended-release Oral Suspension, Equivalent to 30 mg Dextromethorphan Hydrobromide per 5 mL)
NDA Firm: Reckitt Benckiser Inc.
Date of Approval of NDA Insert and supplement #: 018658/S-029 (approved May 16, 2011)
Has this been verified by the MIS system for the NDA? Yes – see note in FTR below
Was this approval based upon an OGD labeling guidance? No
Other Comments:

**Please note that NDA 018658/S-028, approved November 10, 2010, was a manufacturing supplement approved for alternate oval-shaped immediate containers for the 3 and 5 fluid ounce packaging sizes.

FOR THE RECORD:

1. **Model Labeling**:

   Review is based on the labeling of Reckitt Benckiser Inc.'s Delsym®", NDA 018658/S-029, approved May 16, 2011.

2. Patents and Exclusivities (P&E):

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	Firm Filed
N018658	001	5980882	Apr 16, 2017		Y			IV

There are no unexpired exclusivities for this drug product.

Firm certified a PIV to patent '882 and was sued within 45 days.

3. Inactive Ingredients :

The listing of inactive ingredients are: D&C Red #30, D&C Yellow #10, flavor, glycerin, high fructose corn syrup, methylparaben, polysorbate 80, polyvinyl acetate, povidone, propylparaben, purified water, sodium metabisulfite, sodium polystyrene sulfonate, sucrose, tartaric acid, tragacanth gum, triacetin, and xanthan gum.

4. Manufacturing Facility (3.2.P.3.1):

3.2.P.3.1 Manufacturer

This module contains information regarding the drug product manufacturer for Dextromethorphan Polistirex Extended Release Oral Suspension, including manufacturer address, responsibility, registration number, and cGMP statement.

1. Manufacturer Address:

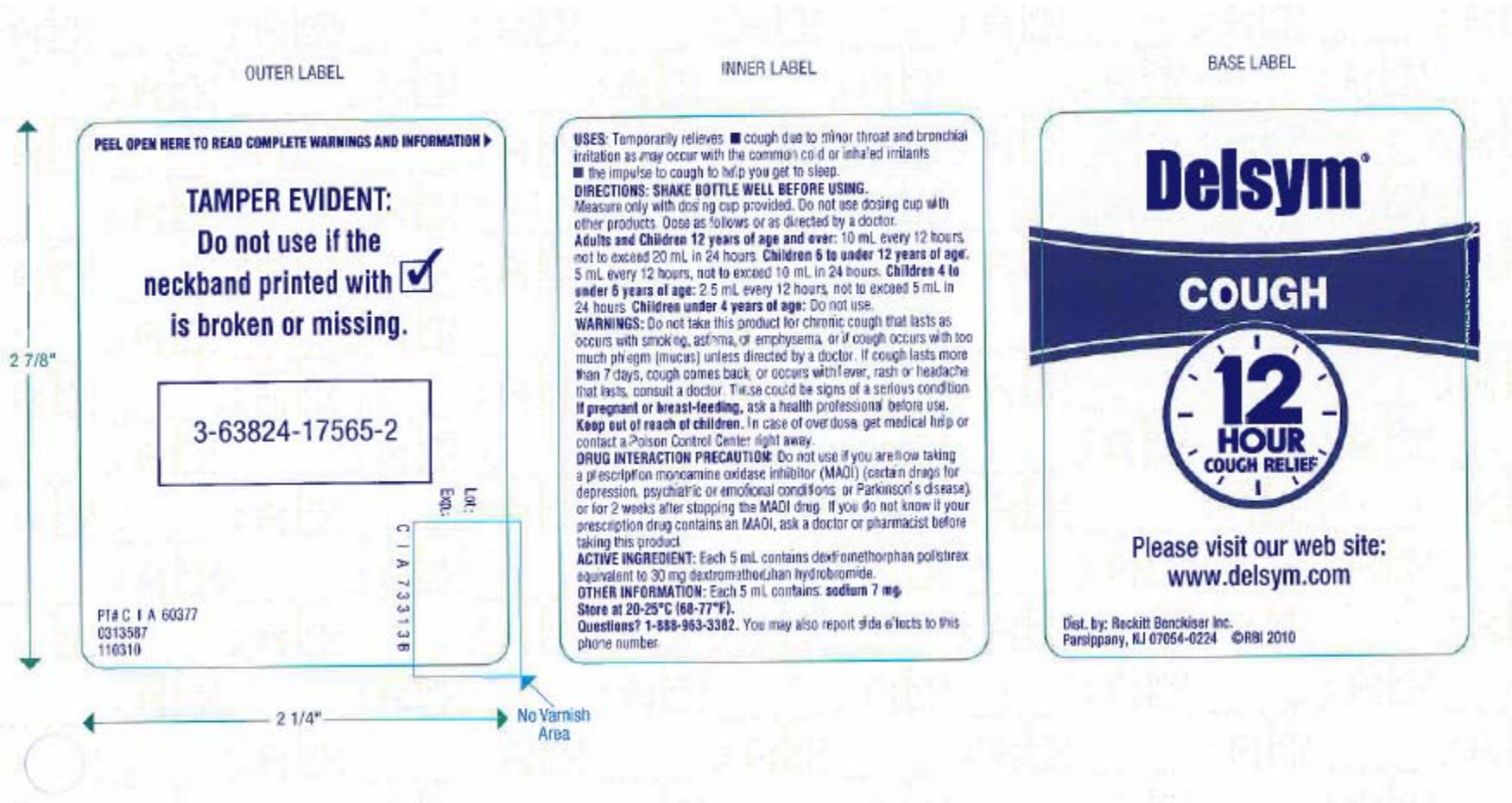
Tris Pharma, Inc.
2033 Route 130
Monmouth Junction, NJ 08852
Contact: W. Scott Groner
Phone: 732-940-0358

5. Product Description:
RLD (Delsym®)

Available in 3 fl oz and 5 fl oz grape and orange flavors for both pediatric and adult graphics.

Reference ID: 3004178


2 7/8"
2 1/4"
Delsym
Dextromethorphan Polistirex
Extended-Release Suspension (Cough Suppressant)
COUGH
12 HOUR COUGH RELIEF
Orange
Flavored Liquid
Alcohol-free
Contains No Fever Reducer or Pain Reliever
FRONT LABEL



Reference ID: 3004178

Graphic leading to next panel

Headings: 5.75 pt. Helvetica Bold Condensed

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:
Exp:

C I A 7 3 1 3 8

PT# C I A 60377
0313587
110310

2 7/8"

2 1/4"

No Varnish Area

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.

Body text: 5.75 pt. Helvetica Condensed with 6.35 pt. leading

BASE LABEL

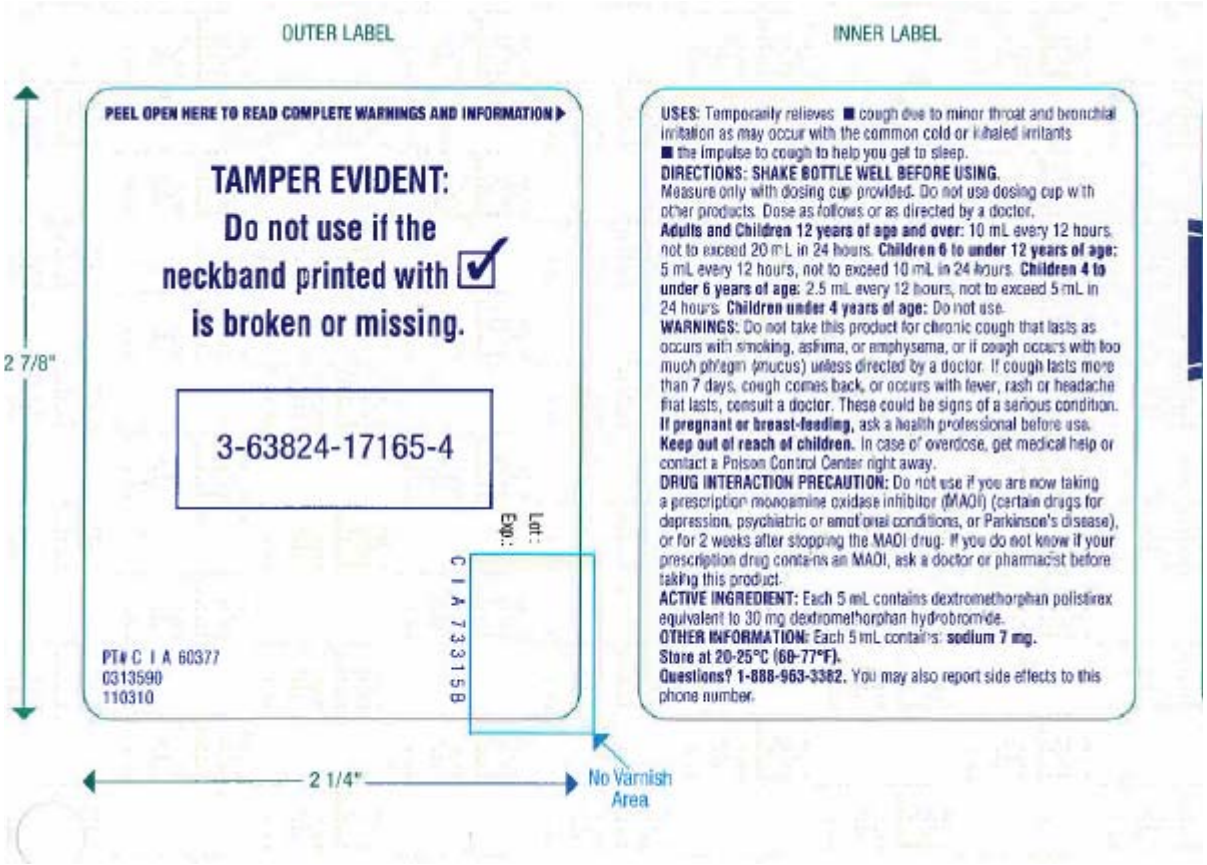
Delsym®

COUGH

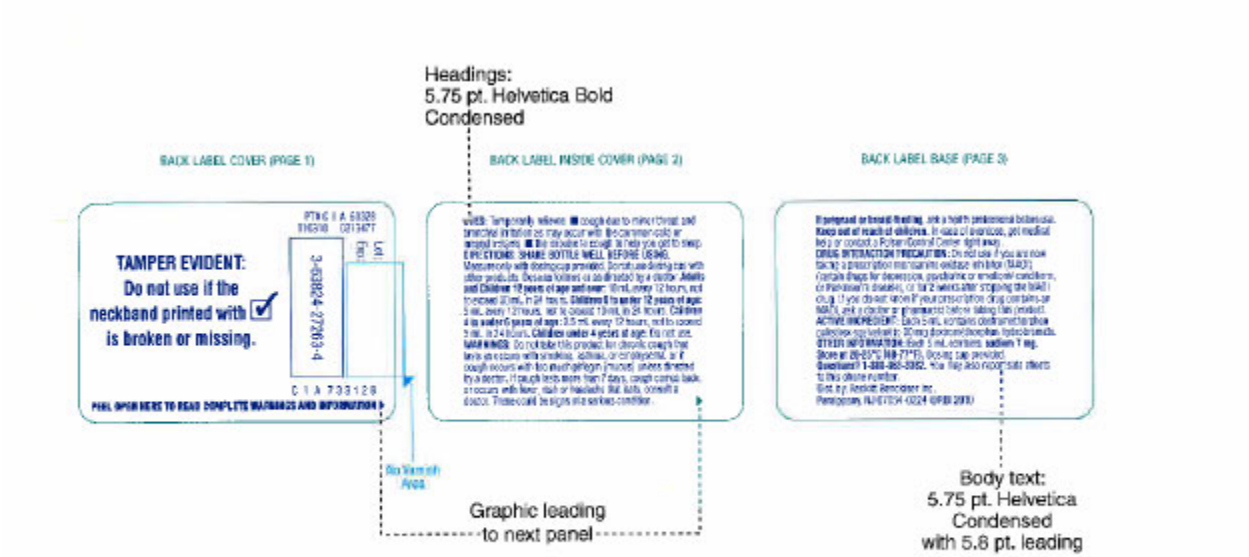
12 HOUR COUGH RELIEF

Please visit our web site:
www.delsym.com

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



Reference ID: 3004178


Headings:
5.75 pt. Helvetica Bold
Condensed
BACK LABEL COVER (PAGE 1)
BACK LABEL INSIDE COVER (PAGE 2)
BACK LABEL BASE (PAGE 3)
TAMPER EVIDENT:
Do not use if the neckband printed with ☑ is broken or missing.
Graphic leading
to next panel
Body text:
5.75 pt. Helvetica
Condensed
with 5.8 pt. leading


Delsym
COUGH
12 HR
grape
FRONT LABEL
2 1/4"
1 5/8"

Reference ID: 3004178

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IMMEDIATELY FOLLOWING THIS PAGE

(b) (4)

6. **USP**:

This drug product is not subject to a USP monograph. However, there is a USP monograph titled Dextromethorphan Hydrobromide Oral Solution.

7. Container Closure System: (Chemistry Review#1)

(b) (4)

8. Storage Condition/Dispensing:

NDA: Store at 20-25°C (68-77°F)

ANDA: Store at 20-25°C (68-77°F)

9. SPL:

DEXTROMETHORPHAN POLISTIREX
dextromethorphan polistirex suspension, extended release

Product Information			
Product Type	HUMAN OTC DRUG	Item Code (Source)	NDC: (b) (4)
Route of Administration	ORAL	DEA Schedule	

Active Ingredient/Active Moiety		
Ingredient Name	Basis of Strength	Strength
DEXTROMETHORPHAN HYDROBROMIDE (DEXTROMETHORPHAN)	DEXTROMETHORPHAN HYDROBROMIDE	30 mg in 5 mL

Inactive Ingredients	
Ingredient Name	Strength
SODIUM POLYSTYRENE SULFONATE	
POVIDONE	
(b) (4)	
TRIACETIN	
(b) (4)	
TARTARIC ACID	
SODIUM METABISULFITE	
HIGH FRUCTOSE CORN SYRUP	
SUCROSE	
GLYCERIN	
METHYLPARABEN	
PROPYLPARABEN	
(b) (4)	
XANTHAN GUM	
POLYSORBATE 80	
D&C RED NO. 30	
D&C YELLOW NO. 10	

Product Characteristics			
Color	ORANGE	Score	
Shape		Size	

Flavor	ORANGE	Imprint Code	
Contains			

Packaging

#	Item Code	Package Description	Multilevel Packaging
1	NDC: (b) (4)	88 mL in 1 BOTTLE, PLASTIC	None

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA091135	(b) (4)	

Labeler - Tris Pharma Inc (947472119)

Registrant - Tris Pharma Inc (947472119)

Establishment

Name	Address	ID/FEI	Operations
Tris Pharma Inc		947472119	MANUFACTURE

Establishment

Name	Address	ID/FEI	Operations
(b) (4)			

Revised: 12/2011 Tris Pharma Inc

SPL Data elements are consistent with the labeling submitted and with the application.

Date of Review:	August 18, 2011	Date of Submission: August 11, 2011	
Primary Reviewer:	Jeanne Skanchy		
Team Leader:	John Grace		

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/s/

JEANNE SKANCHY
08/22/2011

JOHN F GRACE
08/22/2011

APPROVAL SUMMARY
*****This Labeling Approval Summary supersedes Labeling Approval Summary dated April 5, 2011)**
LABELING REVIEW #5
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 091135

Date of Submission: April 14, 2011

Applicant's Name: Tris Pharma, Inc.

Established Name: Dextromethorphan Polistirex Extended-release Oral Suspension (Equivalent to 30 mg Dextromethorphan Hydrobromide per 5 mL)

Propriety Name: None

BASIS OF APPROVAL:
APPROVAL SUMMARY

CONTAINER LABEL:
Satisfactory in FPL, April 14, 2011

CARTON LABEL:
Satisfactory in FPL, April 14, 2011

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Delsym® (Dextromethorphan Polistirex Extended-release Oral Suspension, 30 mg per 5 mL)
NDA Number: 018658
NDA Drug Name: Delsym® (Dextromethorphan Polistirex Extended-release Oral Suspension, Equivalent to 30 mg Dextromethorphan Hydrobromide per 5 mL)
NDA Firm: Reckitt Benckiser Inc.
Date of Approval of NDA Insert and supplement #: 018658/S-027 (approved April 8, 2010)
Has this been verified by the MIS system for the NDA? Yes – see note in FTR below
Was this approval based upon an OGD labeling guidance? No
Other Comments:

**Please note that NDA 018658/S-028, approved November 10, 2010, was a manufacturing supplement approved for alternate oval-shaped immediate containers for the 3 and 5 fluid ounce packaging sizes.

FOR THE RECORD:

1. **Model Labeling**:

   Review is based on the labeling of Reckitt Benckiser Inc.'s Delsym®", NDA 018658/S-027, approved April 8, 2010.

2. **Patents and Exclusivities (P&E):**

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	Firm Filed
N018658	001	5980882	Apr 16, 2017		Y			IV

There are no unexpired exclusivities for this drug product.

Firm certified a PIV to patent '882 and was sued within 45 days.

3. **Inactive Ingredients :**

The listing of inactive ingredients are: D&C Red #30, D&C Yellow #10, flavor, glycerin, high fructose corn syrup, methylparaben, polysorbate 80, polyvinyl acetate, povidone, propylparaben, purified water, sodium metabisulfite, sodium polystyrene sufonate, sucrose, tartaric acid, tragacanth gum, triacetin, and xanthan gum.

4. **Manufacturing Facility (3.2.P.3.1):**

3.2.P.3.1 Manufacturer

This module contains information regarding the drug product manufacturer for Dextromethorphan Polistirex Extended Release Oral Suspension, including manufacturer address, responsibility, registration number, and cGMP statement.

1. Manufacturer Address:

Tris Pharma, Inc.
2033 Route 130
Monmouth Junction, NJ 08852
Contact: W. Scott Groner
Phone: 732-940-0358

5. **Product Description:**
RLD (Delsym®)

Available in 3 fl oz and 5 fl oz grape and orange flavors for both pediatric and adult graphics.

US Pat. 5,980,882 0245657 062109 Lot:

3-63824-17165-4 Exp.:

PT# C I A 70222A C I A 71974B

NDC 63824-171-65

Delsym

dextromethorphan polistirex extended-release suspension

COUGH SUPPRESSANT

12 Hour Cough Relief

Contains No Fever Reducer or Pain Reliever

SEE NEW DOSING DIRECTIONS

Alcohol-free

Grape-Flavored Liquid

148 mL (5 fl oz)

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).
Dosing cup provided.
Questions? 1-888-963-3382

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

Distributed by: Reckitt Benckiser Inc. Parsippany, NJ 07054-0224 ©RBI 2009

2 3/32" 2 15/16" 7 7/16"

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

71975B

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

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, methylparaben, polyethylene glycol 3350, polysorbate 80, propylene glycol, propylparaben, purified water, sucrose, trapicanth, vegetable oil, xanthan gum

Questions? 1-888-963-3382

US Pat. 5,980,882 C I A 71975B
PT# C I A 60133
082409 0245643

Reckitt Benckiser

Distributed by: Reckitt Benckiser Inc., Parsippany, NJ 07054-0224 ©RBI 2009

12 Hour Cough Relief

Delsym

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

NDC 63824-171-65

12 Hour Cough Relief

Delsym

dextromethorphan polistirex extended-release suspension

COUGH SUPPRESSANT

SEE NEW DOSING DIRECTIONS

12 HOUR Cough Relief

Grape-Flavored Liquid

Alcohol-free

148 mL (5 fl oz)

3-63824-17165-4

Lot No.:

Exp. Date:

12 Hour Cough Relief

Delsym

dextromethorphan polistirex extended-release suspension

COUGH SUPPRESSANT

DELSYM® DOSING
SHAKE WELL BEFORE USE.
Measure only with dosing cup provided.
Do not use dosing cup with other products.

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

Reference ID: 2934849

Cover

PHYSICIAN SAMPLE – NOT TO BE SOLD

Delsym®

dextromethorphan polistirex
extended-release suspension

COUGH SUPPRESSANT

15 mL (1/2 fl oz)

DOSING CUP INCLUDED

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

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 ▶**

Lift Here

Back of Cover

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.

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. ▶

Base

C I A 702800

Lot :

Exp.:

PHYSICIAN SAMPLE – NOT TO BE SOLD

Delsym®

dextromethorphan polistirex
extended-release suspension

COUGH SUPPRESSANT

15 ml (1/2 fl oz)

Other information: Each 5 mL contains: sodium 7 mg. Store at 20°-25°C (68°-77°F). Dosing cup provided.

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

Questions? 1-888-863-3382

US Pat. 5,980,882

Distributed by:
Reckitt Benckiser Inc.
Parsippany, NJ 07054-0224

0245849

090909 PT# C I A 60057

(b) (4)

6. **USP**:

   This drug product is not subject to a USP monograph.

7. Container Closure System: (Chemistry Review#1)

(b) (4)

8. Storage Condition/Dispensing:

NDA: Store at 20-25°C (68-77°F)

ANDA: Store at 20-25°C (68-77°F)

9. Firm complied with OGD's request to include a sulfite statement in the labeling to alert or inform consumers that sodium metabisulfite is included in the formulation of this drug product. Please see emails from OGD and DNRD.

From: Chang, Nancy
Sent: Wednesday, April 13, 2011 7:50 AM
To: Skanchy, Jeanne; Sayeed, Vilayat A
Cc: Catterson, Debra M; Grace, John F; Hixon, Dena R
Subject: RE: Sulfites Warning PR (1985) and FR (1986)

That sounds reasonable to me.
Thanks,
Nancy

From: Skanchy, Jeanne
Sent: Wednesday, April 13, 2011 7:21 AM
To: Sayeed, Vilayat A; Chang, Nancy
Cc: Catterson, Debra M; Grace, John F; Hixon, Dena R
Subject: RE: Sulfites Warning PR (1985) and FR (1986)

Per 21 CFR 201.22 (b) states: (b) The labeling required by Sec. Sec. 201.57 and 201.100(d) for prescription drugs for human use containing a sulfite, except epinephrine for injection when intended for use in allergic or other emergency situations, shall bear the warning statement ``Contains (insert the name of the sulfite, e.g., sodium metabisulfite), a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.'' This statement shall appear in the ``Warnings'' section of the labeling.

As you can see that the sulfite warning statement is long and the statement is to be included in the Warning section of the insert. Should firm include in their labeling (container and carton) that this product contains sulfites in the principal display panel and/or warning section? Will this suffice?

From: Sayeed, Vilayat A
Sent: Tuesday, April 12, 2011 5:46 PM
To: Chang, Nancy; Skanchy, Jeanne; Grace, John F; Hixon, Dena R
Cc: Catterson, Debra M
Subject: RE: Sulfites Warning PR (1985) and FR (1986)

Agree

Vilayat A. Sayeed, Ph.D.
Director, Division of Chemistry III
FDA/CDER/OPS/OGD
7500 Standish Place
MPN II Rockville, MD 20855
Office (240) 276-8486, fax (240) 276-8474
Vilayat.Sayeed@FDA.HHS.GOV

From: Chang, Nancy
Sent: Tuesday, April 12, 2011 5:43 PM
To: Chang, Nancy; Sayeed, Vilayat A; Skanchy, Jeanne; Grace, John F; Hixon, Dena R
Cc: Catterson, Debra M
Subject: RE: Sulfites Warning PR (1985) and FR (1986)

I can't help but adding too that the apparent discrepancy in labeling requirements for OTC vs Rx doesn't make any sense --- why on earth should there be more of a buyer beware approach for OTC's? OTC's are supposed to be safer and more idiot-proof because of the lack of a learned intermediary. All the more reason to ask for the warning labeling.

From: Chang, Nancy
Sent: Tuesday, April 12, 2011 5:34 PM
To: Sayeed, Vilayat A; Skanchy, Jeanne; Grace, John F; Hixon, Dena R
Cc: Catterson, Debra M
Subject: RE: Sulfites Warning PR (1985) and FR (1986)

Given that the agency has gone so far as to identify a safety concern with this ingredient in at least some individuals, my own opinion is actually that we shouldn't be approving generics with such ingredients; however, since that doesn't seem to be the way the wind is blowing, I do agree that at least having some prominent labeling is appropriate. It is one thing to say that individuals with known sulfite sensitivities should know to look, but there is also a population out there who don't know, and a prominent sulfite warning might help them to identify and recognize a sulfite sensitivity.

From: Sayeed, Vilayat A
Sent: Tuesday, April 12, 2011 4:21 PM
To: Skanchy, Jeanne; Grace, John F; Chang, Nancy; Hixon, Dena R
Cc: Catterson, Debra M
Subject: RE: Sulfites Warning PR (1985) and FR (1986)

Jeanne

The conditions of approval of an application OTC are not the same as monograph OTC. The FR notice provides an option for including a warning, so please go ahead and request the applicant to include a warning in the label to address the added risk in the ANDA formulation that is not present in the NDA. Adding a warning to the applications OTC generics will make us consistent in how we are handling the risk in the Rx generic product line.

Nancy/Dean

Please let me know if you concur with this call

Thanks

Vilayat

Vilayat A. Sayeed, Ph.D.
Director, Division of Chemistry III
FDA/CDER/OPS/OGD
7500 Standish Place
MPN II Rockville, MD 20855
Office (240) 276-8486, fax (240) 276-8474
Vilayat.Sayeed@FDA.HHS.GOV

From: Skanchy, Jeanne
Sent: Tuesday, April 12, 2011 1:37 PM
To: Grace, John F; Sayeed, Vilayat A
Subject: FW: Sulfites Warning PR (1985) and FR (1986)

Hi John and Vilayat,

I have received information from DNRD. Please see attachment and email.

Thank you,

Jeanne

From: Rowley, Ayana
Sent: Tuesday, April 12, 2011 10:56 AM
To: Skanchy, Jeanne
Subject: FW: Sulfites Warning PR (1985) and FR (1986)

Hi Jeanne,

Attached are the PR and FR for the Sulitfite Warning. Apparently, the agency decided that the warning was not needed on OTC drug products because the FDA felt that consumers with this allergy would know to read the ingredient list. In reviewing the rules, it seems that there was (or is) a "voluntary" option for the manufacture to place the warning on the label. I would presume that leaves the door open to perhaps ask the manufacture to place it on the label.

Please let me know if you have any additional questions.

Ayana K. Rowley, Pharm.D.
Interdisciplinary Scientist (IDS)
Division of Nonprescription Regulation Development
Office of Drug Evaluation IV (ODE IV)
Phone: 301-796-4005

From: ROWLEYA [mailto:Ayana.Rowley@fda.hhs.gov]
Sent: Tuesday, April 12, 2011 10:49 AM
To: Rowley, Ayana
Subject: Sulfites Warning PR (1985) and FR (1986)

Date of Review:	April 18, 2011	Date of Submission: April 14, 2011
Primary Reviewer:	Jeanne Skanchy	
Team Leader:	John Grace	

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2 PAGES WERE WITHHELD IN FULL AS B4 (DRAFT LABELING) IMMEDIATELY FOLLOWING THIS PAGE

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

/s/

JEANNE SKANCHY
04/18/2011

JOHN F GRACE
04/18/2011

APPROVAL SUMMARY
***This Labeling Approval Summary supersedes Labeling Approval Summary dated October 19, 2010)
LABELING REVIEW #4
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 091135

Date of Submission: March 29, 2011

Applicant's Name: Tris Pharma, Inc.

Established Name: Dextromethorphan Polistirex Extended-release Oral Suspension (Equivalent to 30 mg Dextromethorphan Hydrobromide per 5 mL)

Propriety Name: None

BASIS OF APPROVAL:
APPROVAL SUMMARY

CONTAINER LABEL:
Satisfactory in FPL, October 1, 2010.

CARTON LABEL:
Satisfactory in FPL. March 29, 2011

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Delsym® (Dextromethorphan Polistirex Extended-release Oral Suspension, 30 mg per 5 mL)
NDA Number: 018658
NDA Drug Name: Delsym® (Dextromethorphan Polistirex Extended-release Oral Suspension, Equivalent to 30 mg Dextromethorphan Hydrobromide per 5 mL)
NDA Firm: Reckitt Benckiser Inc.
Date of Approval of NDA Insert and supplement #: 018658/S-027 (approved April 8, 2010)
Has this been verified by the MIS system for the NDA? Yes – see note in FTR below
Was this approval based upon an OGD labeling guidance? No
Other Comments:

FOR THE RECORD:

1. **Model Labeling**:

   Review is based on the labeling of Reckitt Benckiser Inc.'s Delsym®", NDA 018658/S-027, approved April 8, 2010.

2. **Patents and Exclusivities (P&E):**

   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	Firm Filed
N018658	001	5980882	Apr 16, 2017		Y			IV

There are no unexpired exclusivities for this drug product.

Firm certified a PIV to patent '882 and was sued within 45 days.

3. Inactive Ingredients :

The listing of inactive ingredients are: D&C Red #30, D&C Yellow #10, flavor, glycerin, high fructose corn syrup, methylparaben, polysorbate 80, polyvinyl acetate, povidone, propylparaben, purified water, sodium metabisulfite, sodium polystyrene sufonate, sucrose, tartaric acid, tragacanth gum, triacetin, and xanthan gum.

4. Manufacturing Facility (3.2.P.3.1):

3.2.P.3.1 Manufacturer

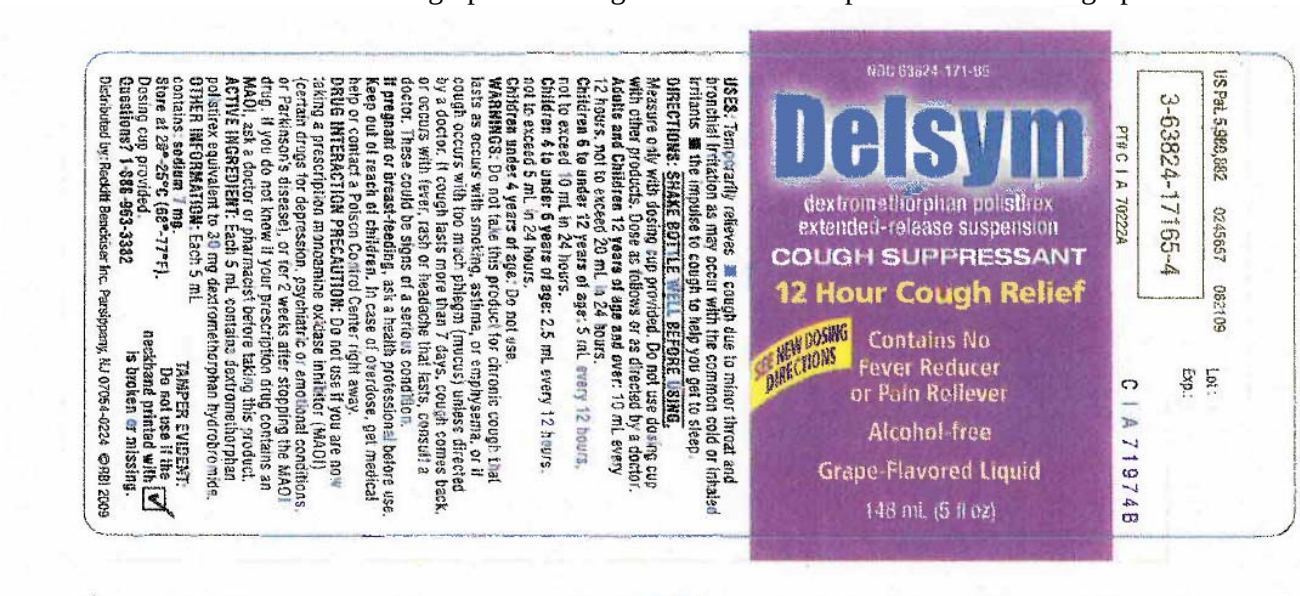
This module contains information regarding the drug product manufacturer for Dextromethorphan Polistirex Extended Release Oral Suspension, including manufacturer address, responsibility, registration number, and cGMP statement.

1. Manufacturer Address:

Tris Pharma, Inc.
2033 Route 130
Monmouth Junction, NJ 08852
Contact: W. Scott Groner
Phone: 732-940-0358

5. Product Description:
RLD (Delsym®)

Available in 3 fl oz and 5 fl oz grape and orange flavors for both pediatric and adult graphics.



Reference ID: 2926990

Back of Cover

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.

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. ➤

C I A 702800

Lot:

Exp.:

PHYSICIAN SAMPLE – NOT TO BE SOLD

Delsym®

dextromethorphan polistirex extended-release oral suspension

COUGH SUPPRESSANT

15 ml (1/2 fl oz)

Other information: Each 5 mL contains: sodium 7 mg. Store at 20°-25°C (68°-77°F). Dosing cup provided.

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

Questions? 1-888-963-3382

US Pat. 5,980,882

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Parsippany, NJ 07054-0224

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090909 PT# C I A 60057

Base

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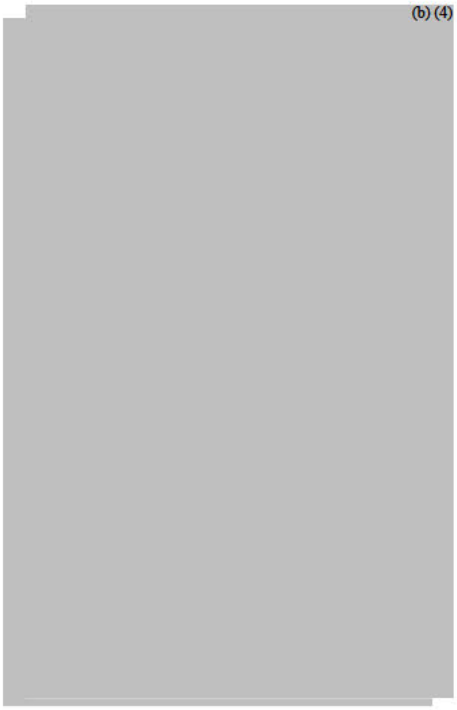
(b) (4)

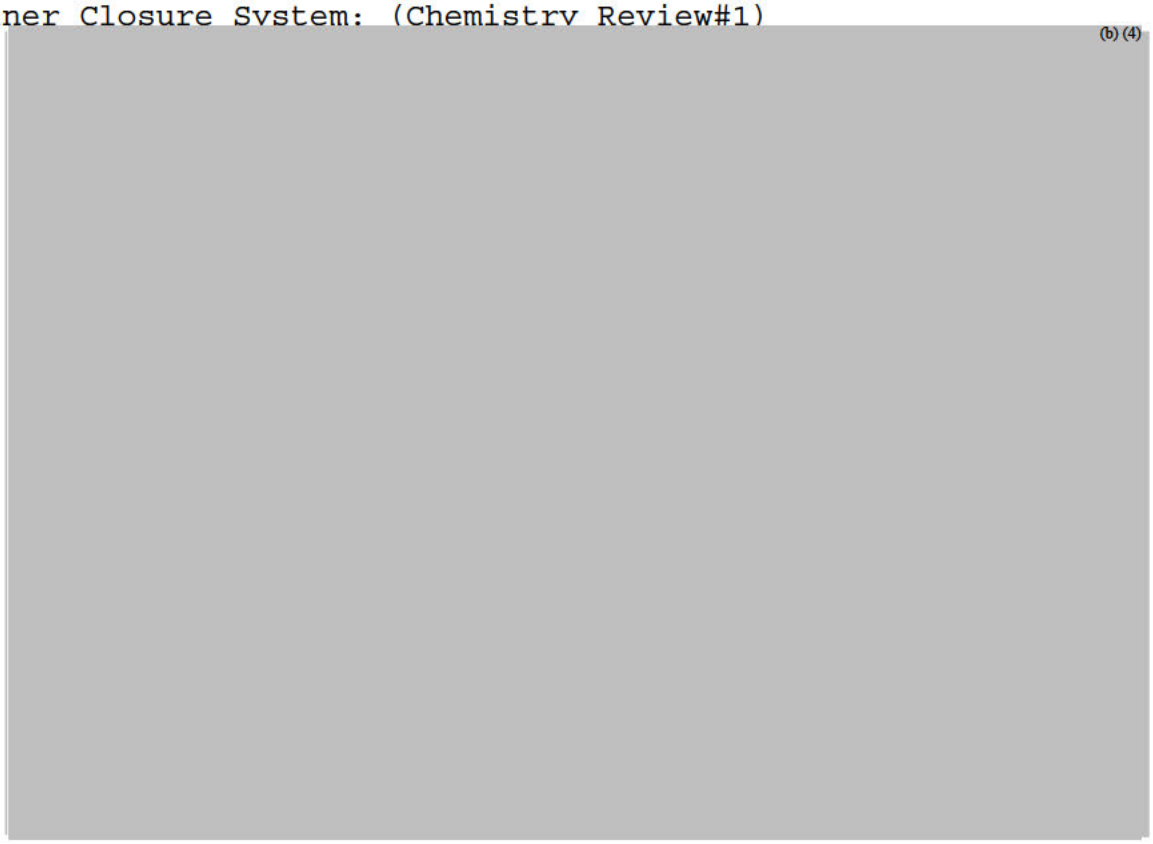


6. **USP**:

This drug product is not subject to a USP monograph.

7. Container Closure System: (Chemistry Review#1)

(b) (4)



8. **Storage Condition/Dispensing:**

NDA: Store at 20-25°C (68-77°F)

ANDA: Store at 20-25°C (68-77°F)

Date of Review: March 31, 2011 Date of Submission: March 29, 2011

Primary Reviewer: Jeanne Skanchy

Team Leader: John Grace

2 PAGES WERE WITHHELD IN FULL AS B4 (CCI/TS) IMMEDIATELY FOLLOWING THIS PAGE

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

/s/

JEANNE SKANCHY
04/01/2011

JOHN F GRACE
04/05/2011

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING #3
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 091135

Date of Submission: October 1, 2010

Applicant's Name: Tris Pharma, Inc.

Established Name: Dextromethorphan Polistirex Extended-release Oral Suspension, 30 mg per 5 mL

Propriety Name: None

REMS required?
☐ Yes ☒ No

REMS acceptable?
☐ Yes ☐ No ☒ n/a

BASIS OF APPROVAL:
APPROVAL SUMMARY

CONTAINER LABELS:
Satisfactory in PDF, October 1, 2010.

CARTON LABELS:
Satisfactory in PDF, October 1, 2010.

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Delsym® (Dextromethorphan Polistirex Extended-release Oral Suspension, 30 mg per 5 mL)
NDA Number: 018658
NDA Drug Name: Delsym® (Dextromethorphan Polistirex Extended-release Oral Suspension, 30 mg per 5 mL)
NDA Firm: Reckitt Benckiser Inc.
Date of Approval of NDA Insert and supplement #: 018658/S-027 (approved April 8, 2010)
Has this been verified by the MIS system for the NDA? Yes – see note in FTR below
Was this approval based upon an OGD labeling guidance? No
Other Comments:

FOR THE RECORD:

1. **Model Labeling**:

   Review is based on the labeling of Reckitt Benckiser Inc.'s Delsym®", NDA 018658/S-027, approved 4/8/2010.

2. Patents and Exclusivities (P&E):

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.

Firm filed PIV and was sued.

3. **Inactive Ingredients :**

The listing of inactive ingredients are: D&C Red #30, D&C Yellow #10, flavor, glycerin, high fructose corn syrup, methylparaben, polysorbate 80, polyvinyl acetate, povidone, propylparaben, purified water, sodium metabisulfite, sodium polystyrene sufonate, sucrose, tartaric acid, tragacanth gum, triacetin, and xanthan gum.

4. **Manufacturing Facility (3.2.P.3.1):**

3.2.P.3.1 Manufacturer

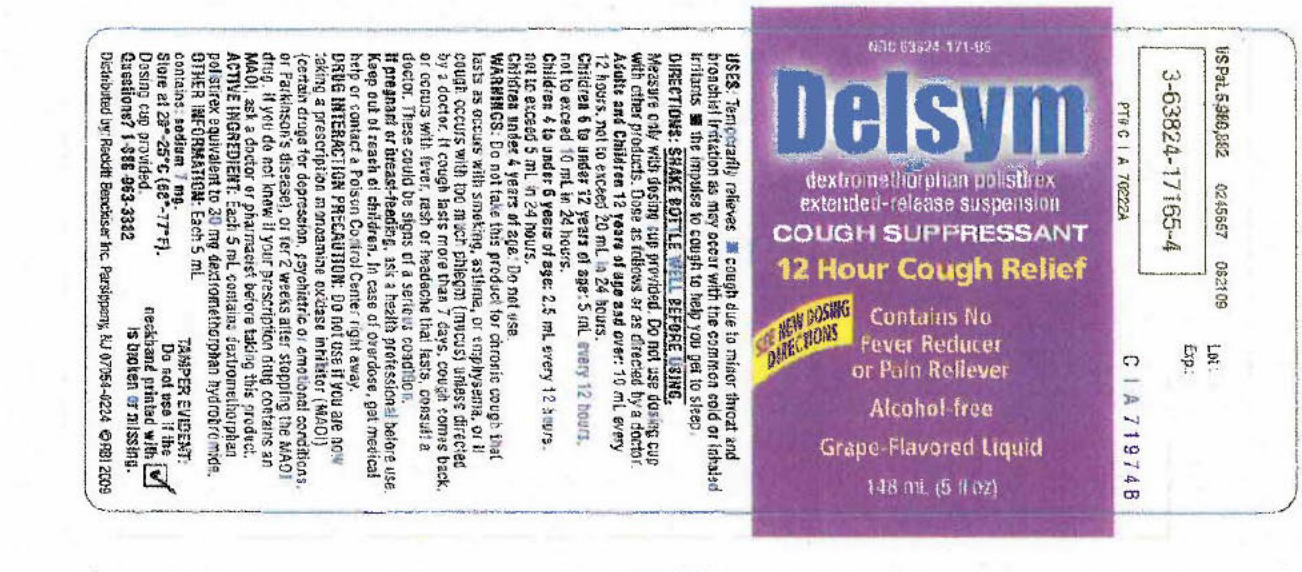
This module contains information regarding the drug product manufacturer for Dextromethorphan Polistirex Extended Release Oral Suspension, including manufacturer address, responsibility, registration number, and cGMP statement.

1. Manufacturer Address:

Tris Pharma, Inc.
2033 Route 130
Monmouth Junction, NJ 08852
Contact: W. Scott Groner
Phone: 732-940-0358

5. **Product Description:**
RLD (Delsym®)

Available in 3 fl oz and 5 fl oz grape and orange flavors for both pediatric and adult graphics.




2 3/32"
2 15/16"
7 1/16"
TAMPER EVIDENT
Do not use if the neckband printed with ✓ is broken or missing.
Delsym
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
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, methylparaben, polyethylene glycol 3350, polysorbate 80, propylene glycol, propylparaben, purified water, sucrose, tragacanth, vegetable oil, xanthan gum
Questions? 1-888-963-3382
US Pat. 5,980,882
C I A 71975B
PTY C I A 60133
Reckitt Benckiser
082409 0245643
Distributed by: Reckitt Benckiser Inc., Parsippany, NJ 07054-0224 ©RBI 2009
71975B
12 Hour Cough Relief
Delsym
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
12 Hour Cough Relief
Delsym
NDC 63824-171-65
dextromethorphan polistirex extended-release suspension
COUGH SUPPRESSANT
SEE NEW DOSING DIRECTIONS
12 HOUR Cough Relief
Grape-Flavored Liquid
Alcohol-free
148 mL (5 fl oz)
3-63824-17165-4
Lot No.:
Exp. Date:
12 Hour Cough Relief
Delsym
dextromethorphan polistirex extended-release suspension
COUGH SUPPRESSANT
DELSYM® DOSING
SHAKE WELL BEFORE USE.
Measure only with dosing cup provided.
Do not use dosing cup with other products.
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


PHYSICIAN SAMPLE – NOT TO BE SOLD
Delsym
dextromethorphan polistirex extended-release suspension
COUGH SUPPRESSANT
15 mL (1/2 fl oz)


DOSING CUP INCLUDED
TAMPER EVIDENT: Do not use if the neckband printed with ☑ is broken or missing.
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
Lift Here

Cover

Back of Cover

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.

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. ➤

C I A 702800

Lot:

Exp.:

PHYSICIAN SAMPLE – NOT TO BE SOLD

Delsym®

dextromethorphan polistirex extended-release suspension

COUGH SUPPRESSANT

15 ml (1/2 fl oz)

Other information: Each 5 mL contains: **sodium** 7 mg. Store at 20°-25°C (68°-77°F). Dosing cup provided.

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

Questions? **1-888-963-3382**

US Pat. 5,968,862

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Parsippany, NJ 07054-0224

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090909 PT# C I A 60057

Base

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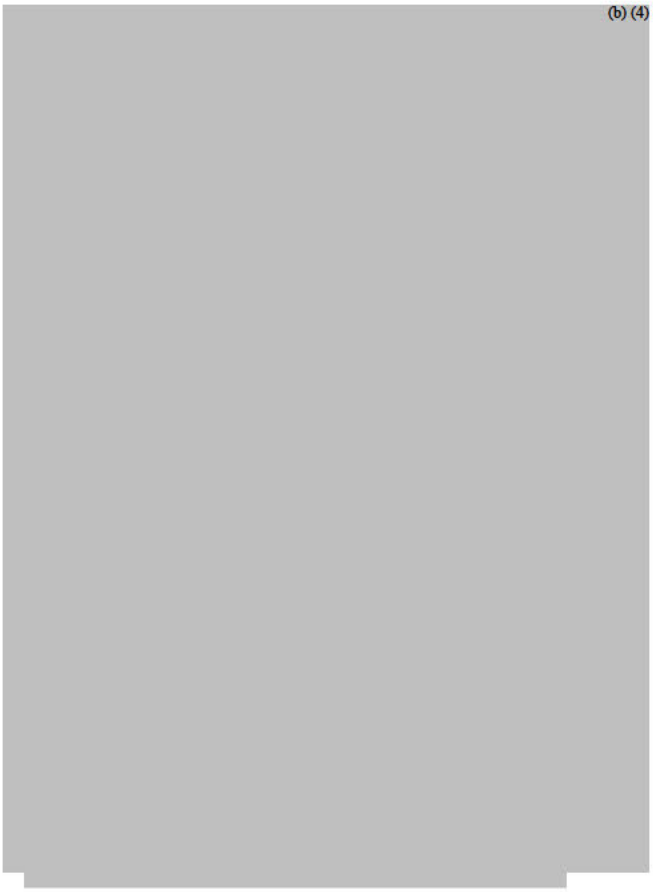
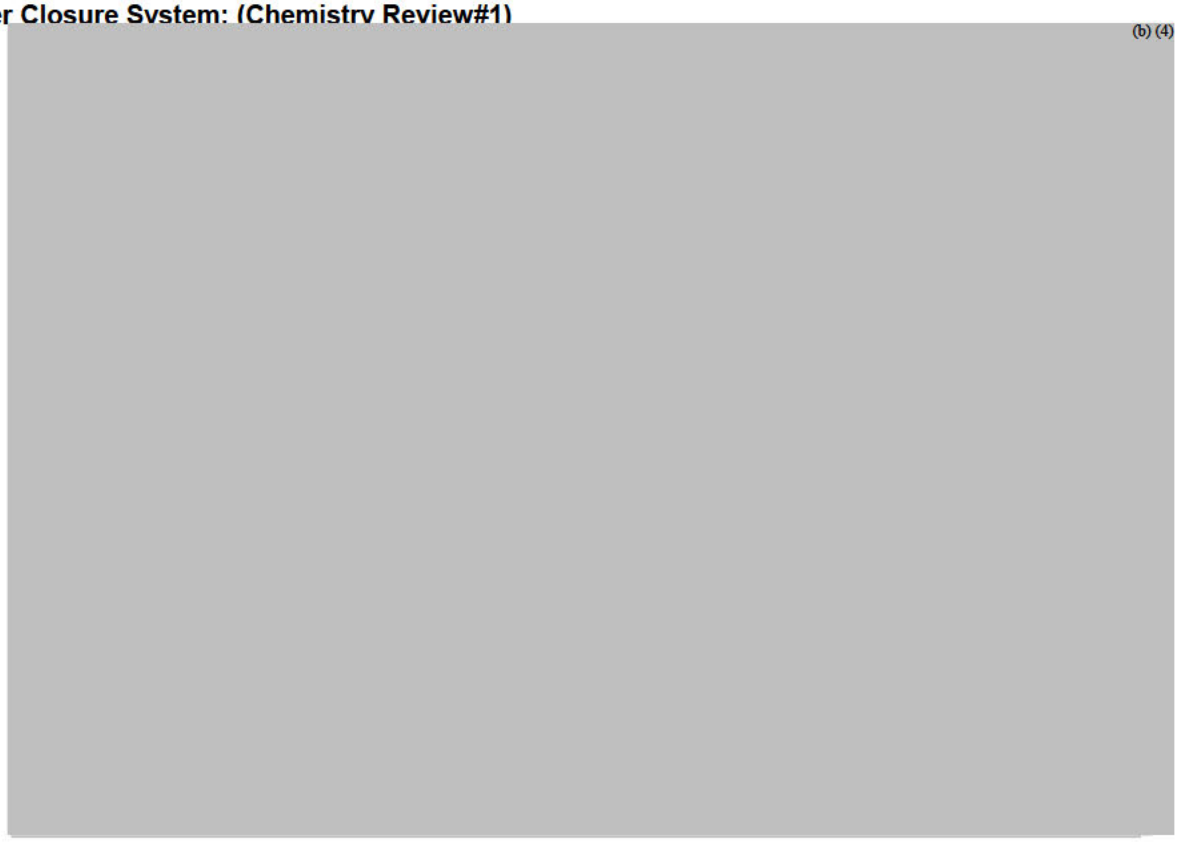


6. **USP**:

   This product is not subject to a USP monograph.

7. **Container Closure System: (Chemistry Review#1)**



8. Storage Condition/Dispensing:

NDA: Store at 20-25°C (68-77°F)

ANDA: Store at 20-25°C (68-77°F)

Date of Review:	October 12, 2010	Date of Submission: October 1, 2010
Primary Reviewer:	Jeanne Skanchy	
Team Leader:	John Grace	

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

/s/

JEANNE SKANCHY
10/14/2010

JOHN F GRACE
10/19/2010

REVIEW OF PROFESSIONAL LABELING #2
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 091135

Date of Submission: August 26, 2010

Applicant's Name: Tris Pharma, Inc.

Established Name: Dextromethorphan Polistirex Extended-release Oral Suspension, 30 mg per 5 mL

Propriety Name: None

Labeling Deficiencies:

A. CONTAINER & CARTON LABELS:

Please revise established name to read, "DEXTROMETHORPHAN POLISTIREX EXTENDED-RELEASE ORAL SUSPENSION".

B. DOSAGE CUP:

Please provide the final printed labeling (FPL) for the dosage cup.

Please submit labels and labeling in electronic format.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. 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.

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with the last approved labeling of the Reference Listed Drug with all differences annotated and explained.

BASIS OF APPROVAL:
APPROVAL SUMMARY

CONTAINER LABELS:
Please see comment above.

CARTON LABELS:
Please see comment above.

DOSAGE CUP:
Please see comment above.

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Delsym® (Dextromethorphan Polistirex Extended-release Oral Suspension, 30 mg per 5 mL)
NDA Number: 018658
NDA Drug Name: Delsym® (Dextromethorphan Polistirex Extended-release Oral Suspension, 30 mg per 5 mL)
NDA Firm: Reckitt Benckiser Inc.
Date of Approval of NDA Insert and supplement #: 018658/S-027 (approved April 8, 2010)

Has this been verified by the MIS system for the NDA? Yes – see note in FTR below
Was this approval based upon an OGD labeling guidance? No
Other Comments:

FOR THE RECORD:

1. **Model Labeling**:

   Review is based on the labeling of Reckitt Benckiser Inc.'s Delsym®", NDA 018658/S-027, approved 4/8/2010.

2. **Patents and Exclusivities (P&E):**

   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.

   Firm filed PIV and was sued.

3. **Inactive Ingredients :**

   The listing of inactive ingredients are: D&C Red #30, D&C Yellow #10, flavor, glycerin, high fructose corn syrup, methylparaben, polysorbate 80, polyvinyl acetate, povidone, propylparaben, purified water, sodium metabisulfite, sodium polystyrene sufonate, sucrose, tartaric acid, tragacanth gum, triacetin, and xanthan gum.

4. **Manufacturing Facility (3.2.P.3.1):**

3.2.P.3.1 Manufacturer

This module contains information regarding the drug product manufacturer for Dextromethorphan Polistirex Extended Release Oral Suspension, including manufacturer address, responsibility, registration number, and cGMP statement.

1. Manufacturer Address:

   Tris Pharma, Inc.
   2033 Route 130
   Monmouth Junction, NJ 08852
   Contact: W. Scott Groner
   Phone: 732-940-0358

5. **Product Description:**
   RLD (Delsym®)

   Available in 3 fl oz and 5 fl oz grape and orange flavors for both pediatric and adult graphics.

US Pat. 5,980,882 0245657 062109 Lot:
Exp.:

3-63824-17165-4

PT# C I A 70222A C I A 71974B

NDC 63824-171-65

Delsym

dextromethorphan polistirex extended-release suspension

COUGH SUPPRESSANT

12 Hour Cough Relief

Contains No Fever Reducer or Pain Reliever

SEE NEW DOSING DIRECTIONS

Alcohol-free

Grape-Flavored Liquid

148 mL (5 fl oz)

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).
Dosing cup provided.
Questions? 1-888-963-3382

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

Distributed by: Reckitt Benckiser Inc. Parsippany, NJ 07054-0224 ©RBI 2009

2 3/32" 2 15/16" 7 7/16"

TAMPER EVIDENT
Do not use if the neckband printed with ▲ is broken or missing

Delsym

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

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, methylparaben, polyethylene glycol 3350, polysorbate 80, propylene glycol, propylparaben, purified water, sucrose, trehalose, vegetable oil, xanthan gum

Questions? 1-888-963-3382

US Pat. 5,980,882 C I A 71975B
PT# C I A 60133
082409 0245643

Reckitt Benckiser

Distributed by: Reckitt Benckiser Inc., Parsippany, NJ 07054-0224 ©RBI 2009

71975B

12 Hour Cough Relief

Delsym

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

12 Hour Cough Relief

Delsym

NDC 63824-171-65

dextromethorphan polistirex extended-release suspension

COUGH SUPPRESSANT

SEE NEW DOSING DIRECTIONS

12 HOUR Cough Relief

Grape-Flavored Liquid

Alcohol-free

148 mL (5 fl oz)

3-63824-17165-4

Lot No.:

Exp. Date:

12 Hour Cough Relief

Delsym

dextromethorphan polistirex extended-release suspension

COUGH SUPPRESSANT

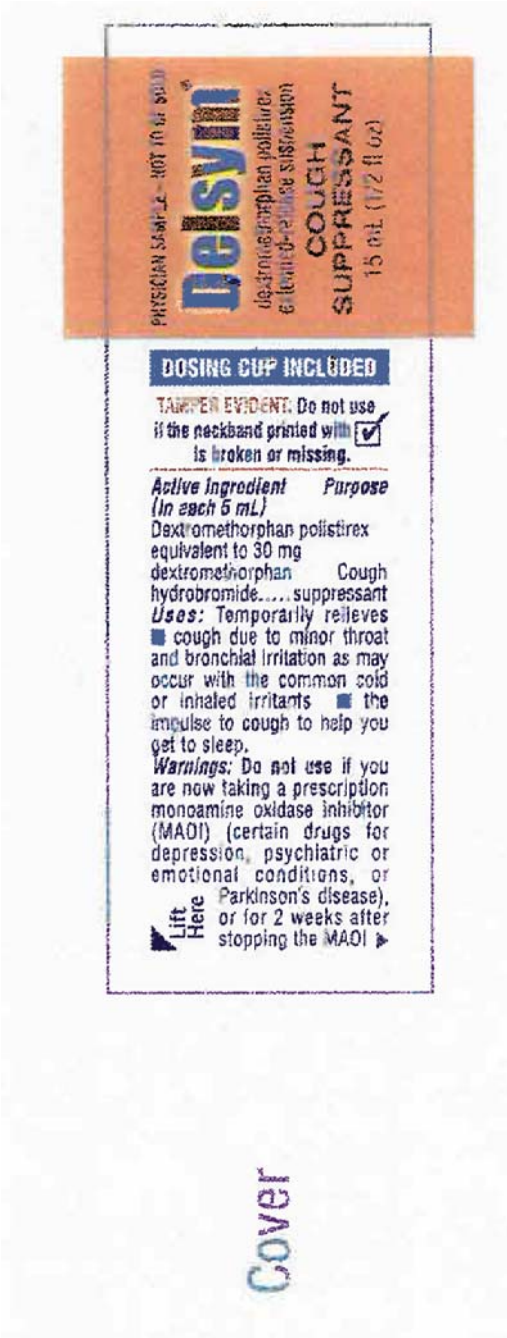
DELSYM® DOSING
SHAKE WELL BEFORE USE.
Measure only with dosing cup provided.
Do not use dosing cup with other products.

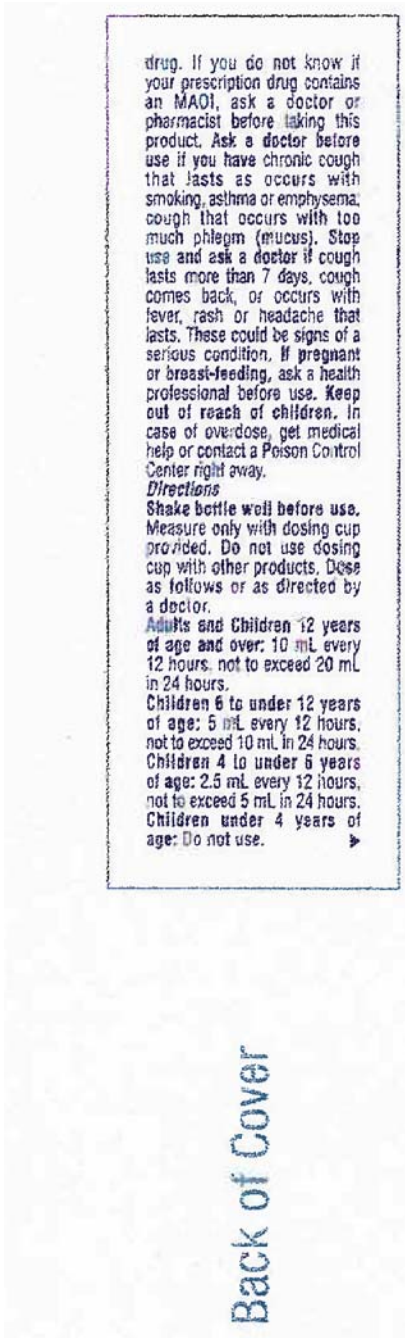
Age (yr)	Dose
12 years to adult	10 mL EVERY 12 HOURS
6 to under 12	5 mL EVERY 12 HOURS
4 to under 6	2.5 mL EVERY 12 HOURS
Under 4	Do not use

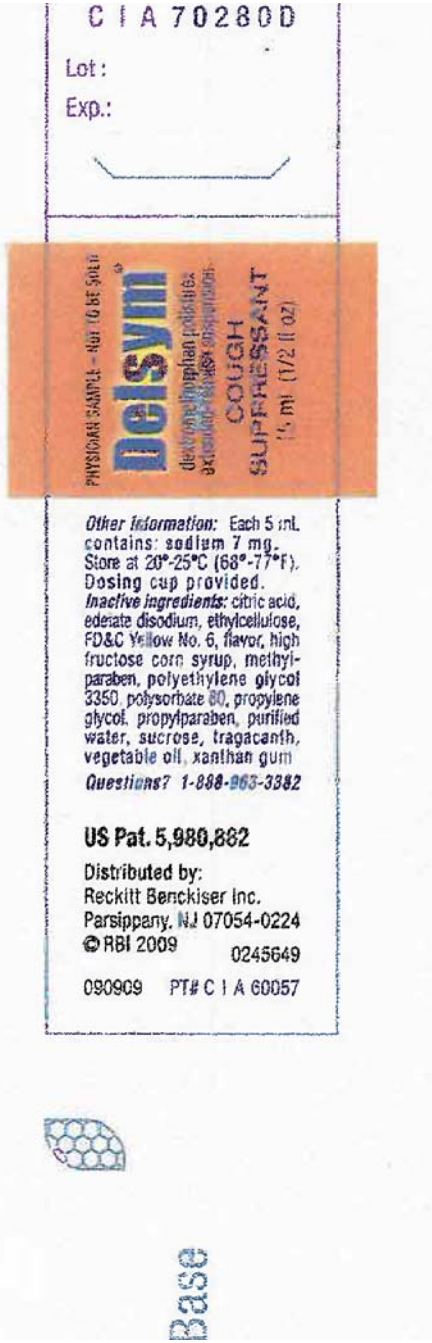
See back panel for full dosing directions

Dosing Cup Included

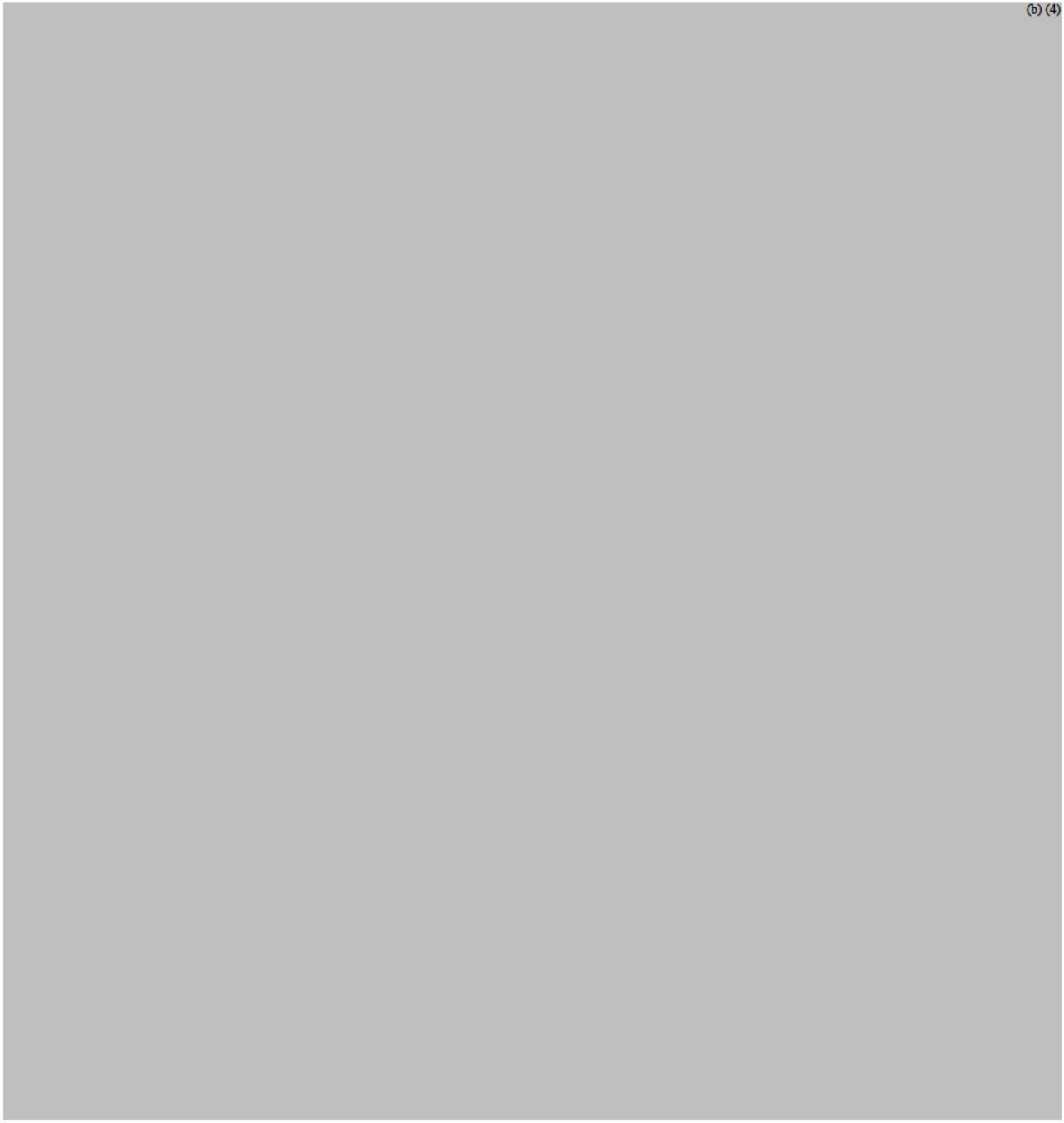
Contains No Fever Reducer or Pain Reliever


PHYSICIAN SAMPLE – NOT TO BE SOLD
Delsym
dextromethorphan polistirex
extended-release suspension
COUGH SUPPRESSANT
15 mL (1/2 fl oz)
DOSING CUP INCLUDED
TAMPER EVIDENT. Do not use if the neckband printed with is broken or missing.
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
Lift Here
Cover


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.
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.
Back of Cover


C I A 70280D
Lot :
Exp.:
PHYSICIAN SAMPLE – NOT TO BE SOLD
Delsym
COUGH SUPPRESSANT
15 ml (1/2 fl oz)
Other Information: Each 5 mL contains: sodium 7 mg.
Store at 20°-25°C (68°-77°F).
Dosing cup provided.
Inactive ingredients: citric acid, edetate disodium, ethylcellulose, FD&C Yellow No. 6, flavor, high fructose corn syrup, methylparaben, polyethylene glycol 3350, polysorbate 80, propylene glycol, propylparaben, purified water, sucrose, tragacanth, vegetable oil, xanthan gum
Questions? 1-888-963-3382
US Pat. 5,980,882
Distributed by:
Reckitt Benckiser Inc.
Parsippany, NJ 07054-0224
© RBI 2009
0245649
090909 PT# C I A 60057
Base

1 PAGE WAS WITHHELD IN FULL AS B4 (DRAFT LABELING) IMMEDIATELY FOLLOWING THIS PAGE

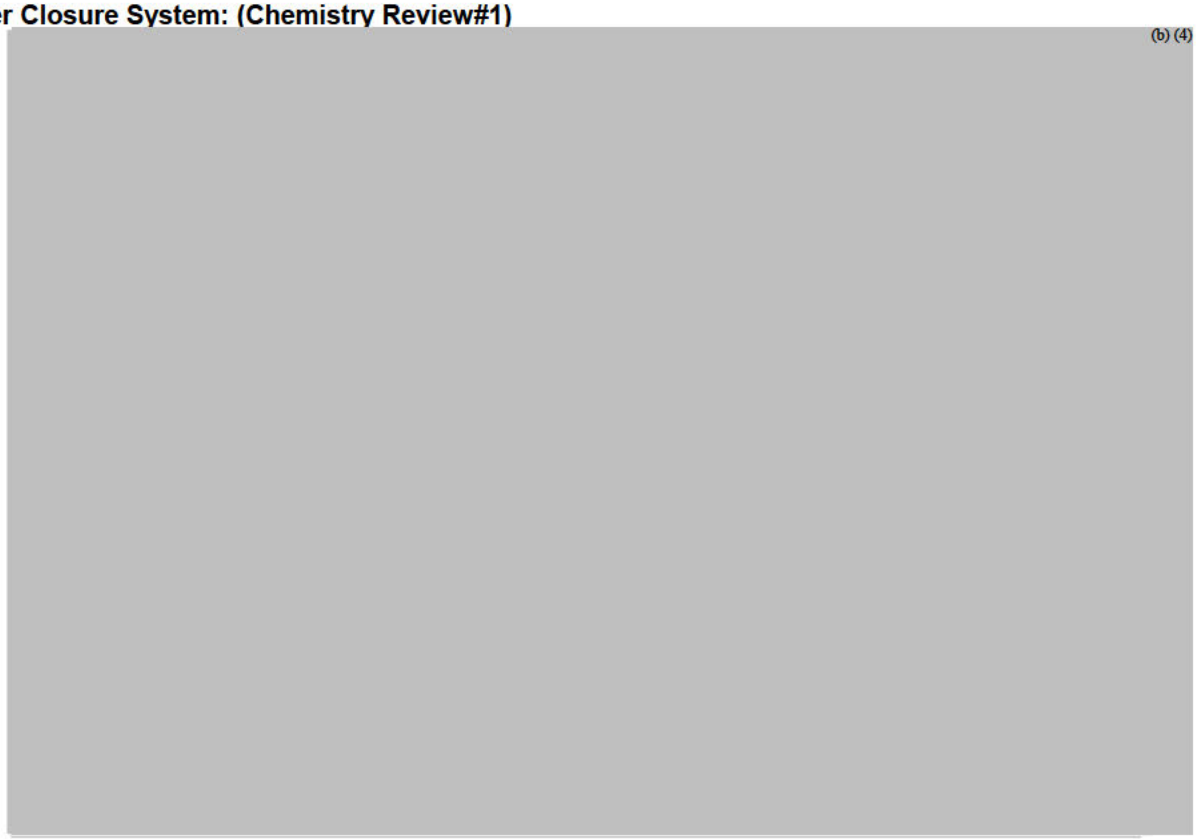


6. **USP**:

This product is not subject to a USP monograph.

7. Container Closure System: (Chemistry Review#1)

(b) (4)



8. Storage Condition/Dispensing:

NDA: Store at 20-25°C (68-77°F)

ANDA: Store at 20-25°C (68-77°F)

Date of Review:	September 13, 2010	Date of Submission: August 26, 2010
Primary Reviewer:	Jeanne Skanchy	
Team Leader:	John Grace	

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

/s/

JEANNE SKANCHY
09/14/2010

JOHN F GRACE
09/20/2010

REVIEW OF PROFESSIONAL LABELING #1
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number:	091135
Date of Submissions:	January 9, 2009 and October 29, 2009
Applicant's Name:	Tris Pharma, Inc.
Established Name:	Dextromethorphan Polistirex Extended-release Oral Suspension, 30 mg per 5 mL
Propriety Name:	None

Labeling Deficiencies:

A. CARTON LABELS:

1. We note that the [redacted] (b) (4) . Please revise so that the strength and the established name are prominent in the principal display panel.

2. In the "*Directions*" section, please add "Do not use dosing cup with other products."

3. In the "*DOSING*" section, please add "Measure only with dosing cup provided. Do not use dosing cup with other products." after "SHAKE WELL BEFORE USE."

B. CONTAINER LABELS:

In the "WARNINGS" section, please revise to read "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."

Please submit labels and labeling in electronic format.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. 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.

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with the last approved labeling of the Reference Listed Drug with all differences annotated and explained.

BASIS OF APPROVAL:
APPROVAL SUMMARY

CONTAINER LABELS:
Please see comments above.

CARTON LABELS:
Please see comments above.

BASIS OF APPROVAL:

Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Delsym® (Dextromethorphan Polistirex Extended-release Oral Suspension, 30 mg per 5 mL)
NDA Number: 018658
NDA Drug Name: Delsym® (Dextromethorphan Polistirex Extended-release Oral Suspension, 30 mg per 5 mL)
NDA Firm: Reckitt Benckiser Inc.
Date of Approval of NDA Insert and supplement #: 018658/S-027 (approved April 8, 2010)
Has this been verified by the MIS system for the NDA? Yes – see note in FTR below
Was this approval based upon an OGD labeling guidance? No
Other Comments:

FOR THE RECORD:

1. **Model Labeling**:

Review is based on the labeling of Reckitt Benckiser Inc.'s Delsym®", NDA 018658/S-027, approved 4/8/2010.

2. **Patents and Exclusivities (P&E):**

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.

Firm filed PIV and was sued.

3. **Inactive Ingredients :**

The listing of inactive ingredients are: D&C Red #30, D&C Yellow #10, flavor, glycerin, high fructose corn syrup, methylparaben, polysorbate 80, polyvinyl acetate, povidone, propylparaben, purified water, sodium metabisulfite, sodium polystyrene sufonate, sucrose, tartaric acid, tragacanth gum, triacetin, and xanthan gum.

4. **Manufacturing Facility (3.2.P.3.1):**

3.2.P.3.1 Manufacturer

This module contains information regarding the drug product manufacturer for Dextromethorphan Polistirex Extended Release Oral Suspension, including manufacturer address, responsibility, registration number, and cGMP statement.

1. Manufacturer Address:

Tris Pharma, Inc.
2033 Route 130
Monmouth Junction, NJ 08852
Contact: W. Scott Groner
Phone: 732-940-0358

5. **Product Description:**

RLD (Delsym®)

Available in 3 fl oz and 5 fl oz grape and orange flavors for both pediatric and adult graphics.

US Pat. 5,980,882 0245657 062109 Lot:

3-63824-17165-4 Exp.:

PT# C I A 70222A C I A 71974B

NDC 63824-171-65

Delsym

dextromethorphan polistirex extended-release suspension

COUGH SUPPRESSANT

12 Hour Cough Relief

Contains No Fever Reducer or Pain Reliever

SEE NEW DOSING DIRECTIONS

Alcohol-free

Grape-Flavored Liquid

148 mL (5 fl oz)

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).
Dosing cup provided.
Questions? 1-888-963-3382

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

Distributed by: Reckitt Benckiser Inc. Parsippany, NJ 07054-0224 ©RBI 2009

2 3/32" 2 15/16"

7 7/16"

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

Delsym

71975B

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

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, methylparaben, polyethylene glycol 3350, polysorbate 80, propylene glycol, propylparaben, purified water, sucrose, tragacanth, vegetable oil, xanthan gum

Questions? 1-888-963-3382

US Pat. 5,980,882 C I A 71975B
PTY C I A 60133
082409 0245643

Reckitt Benckiser

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12 Hour Cough Relief

Delsym

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

12 Hour Cough Relief

NDC 63824-171-65

Delsym

dextromethorphan polistirex extended-release suspension

COUGH SUPPRESSANT

SEE NEW DOSING DIRECTIONS

12 HOUR Cough Relief

Grape-Flavored Liquid

Alcohol-free

148 mL (5 fl oz)

3-63824-17165-4

Lot No.:

Exp. Date:

12 Hour Cough Relief

Delsym

dextromethorphan polistirex extended-release suspension

COUGH SUPPRESSANT

DELSYM® DOSING
SHAKE WELL BEFORE USE.
Measure only with dosing cup provided.
Do not use dosing cup with other products.

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

PHYSICIAN SAMPLE – NOT TO BE SOLD

Delsym®

dextromethorphan polistirex extended-release suspension

COUGH SUPPRESSANT

15 mL (1/2 fl oz)

DOSING CUP INCLUDED

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

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 ▶

Lift Here

Cover

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.

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. ▶

Back of Cover

C I A 70280D

Lot :

Exp.:

PHYSICIAN SAMPLE – NOT TO BE SOLD

Delsym®

dextromethorphan polistirex extended-release suspension

COUGH SUPPRESSANT

15 mL (1/2 fl oz)

Other Information: Each 5 mL contains: **sodium 7 mg.** Store at 20°-25°C (68°-77°F). **Dosing cup provided.**

Inactive Ingredients: citric acid, edetate disodium, ethylcellulose, FD&C Yellow No. 6, flavor, high fructose corn syrup, methylparaben, polyethylene glycol 3350, polysorbate 80, propylene glycol, propylparaben, purified water, sucrose, tragacanth, vegetable oil, xanthan gum

Questions? 1-888-963-3382

US Pat. 5,980,882

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090909 PT# C I A 60057

Base

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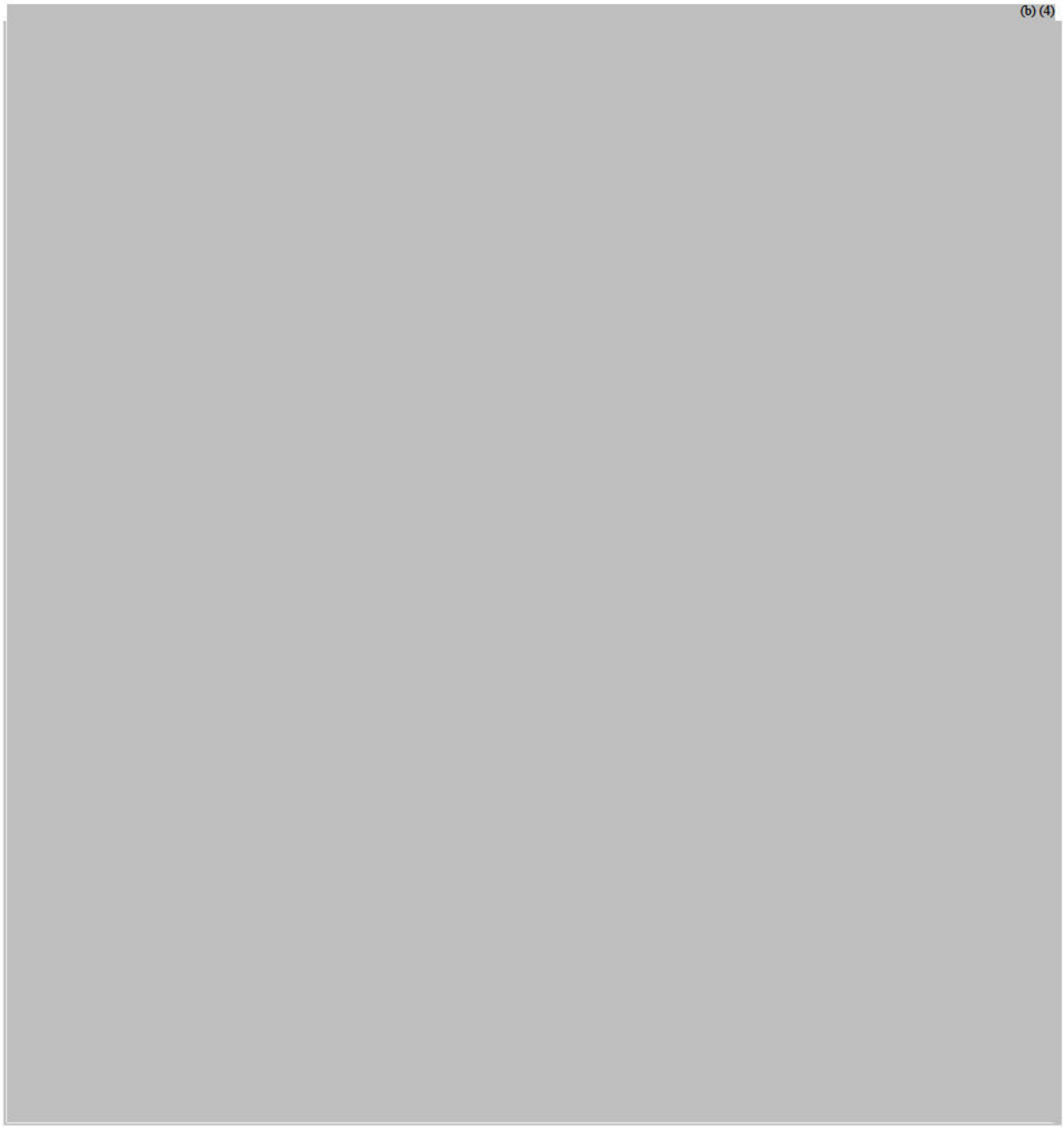
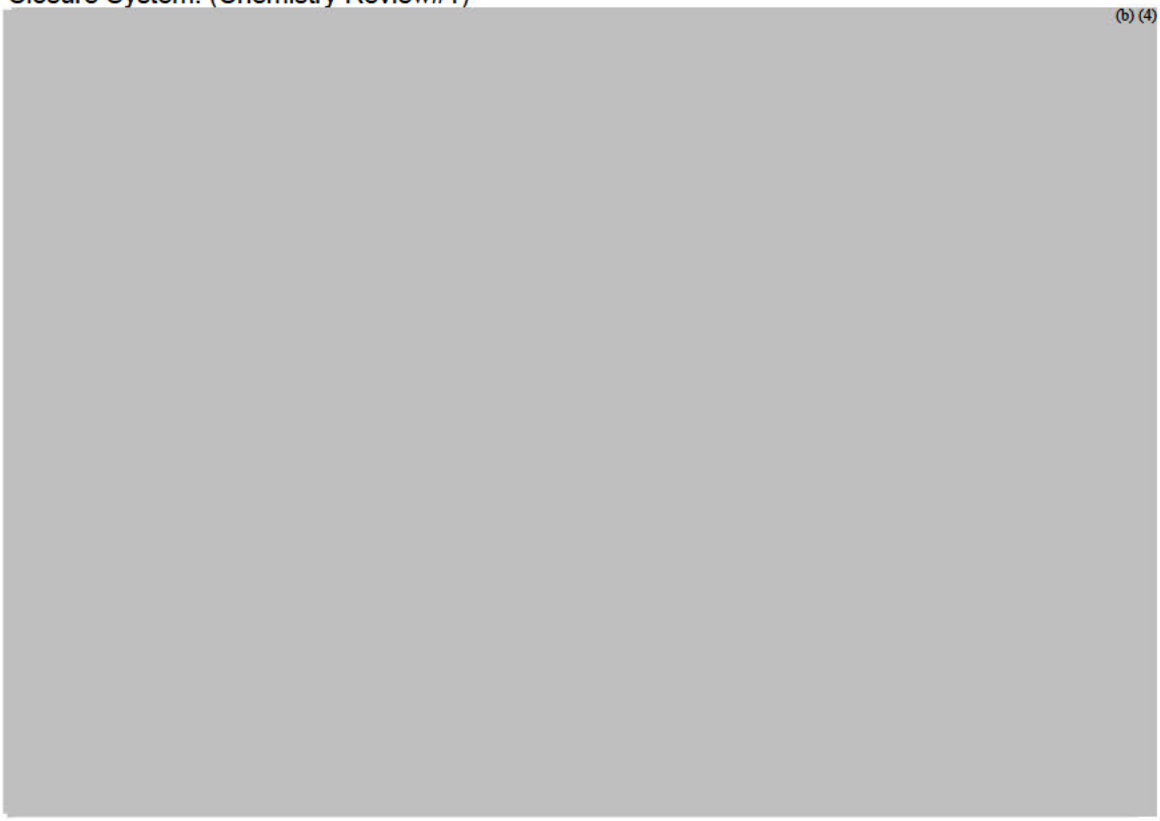


6. **USP**:

This product is not subject to a USP monograph.

7 . Container Closure System: (Chemistry Review#1)

(b) (4)



8. Storage Condition/Dispensing:

NDA: Store at 20-25°C (68-77°F)

ANDA: Store at 20-25°C (68-77°F)

Date of Review:	August 10, 2010	Date of Submissions: January 9, 2009 and October 29, 2009
Primary Reviewer:	Jeanne Skanchy	
Team Leader:	John Grace	

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91135	ORIG-1	TRIS PHARMA INC	DEXTROMETHORPHAN POLISTIREX

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

/s/

JEANNE SKANCHY
08/11/2010

JOHN F GRACE
08/17/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 091135Orig1s000

CHEMISTRY REVIEWS

ANDA 091135

Dextromethorphan Polistirex Extended-release Oral Suspension, 30 mg/5 mL (eq. to Dextromethorphan Hydrobromide 30 mg/5 mL)

Tris Pharma, Inc.

Ping Jin, Ph.D.

Office of Generic Drugs
Division of Chemistry III
Team 31

Table of Contents

Chemistry Review Data Sheet

1. **ANDA #:** 91-135

2. **REVIEW #:** 4

3. **REVIEW DATE:** 6-Dec-2011

4. **REVIEWER:** Ping Jin, Ph.D.

5. **PREVIOUS DOCUMENTS:**

Previous Documents	Document Date
Original Submission (*Including information on USP<467> compliance*)	01-09-2009
Date Acceptance for Filing	01-12-2009
Amendment *(Sq. 01. Response to regulatory support comments)*	05-06-2009
Amendment *(Sq. 02. Patent amendment)*	05-18-2009
Amendment *(Sq. 03.* (b) (4)	06-12-2009
Amendment *(Sq. 04. Patent amendment)*	07-23-2009
Amendment *(Sq. 07. Revision of drug product specification)*	10-09-2009
Amendment *(response to deficiency letter)*	02-18-2010
Minor Amendment *(response to deficiency letter)*	10-13-2010
Minor Amendment	11-18-2010
Telephone Amendment	12-16-2010
Telephone Amendment	01-27-2011

6. **SUBMISSION(S) BEING REVIEWED:**

Submission(s) Reviewed	Document Date
Amendment	3-Aug-2011
Amendment	11-Aug-2011
Amendment	11-Nov-2011

7. **NAME & ADDRESS OF APPLICANT:**

Name and Address of Applicant:

Name: **Tris Pharma, Inc.**

Address: 2033 Route 130
Monmouth Junction, NJ 08852

Representative: **W. Scott Groner**

Telephone: 732-940-0358

Fax: 732-940-0374

Drug Product Manufacturing Facility

Tris Pharma, Inc.

(*the same address of the applicant*)

US Agent:

(N/A)

8. DRUG PRODUCT NAME:

a) Proprietary Name: None

b) Non-Proprietary Name (USAN): Dextromethorphan Polistirex Extended Release Oral Suspension

9. LEGAL BASIS FOR SUBMISSION:

Innovator Product: Delsym® (Dextromethorphan Polistirex) Extended-release Oral Solution (Approval date: Oct. 8, 1982)

Innovator Company: Reckitt Benckiser (NDA # 18-658)

Patent Data: **Paragraph IV Patent Certification Regarding U.S. Patent No.** 5980882 which will expire on April 16, 2017:

U.S. Patent No. 5,980,882, listed as expiring on April 16, 2017 is invalid, unenforceable, and/or will not be infringed by the manufacture, use, or sale of Tris' Dextromethorphan Polistirex Extended Release Suspension, eq. to 30 mg dextromethorphan hydrobromide per 5 mL, for which this abbreviated new drug application ("ANDA") is submitted.

Exclusivity Data: There is no unexpired exclusivity for this product

10. PHARMACOL. CATEGORY: Antitussive

11. DOSAGE FORM: Oral Solution

12. STRENGTH/POTENCY: 30 mg/5 mL (eq. to 30 mg Dextromethorphan HBr/5 mL)

Maximum Daily Dosage: **120 mg** (20 mL DP)

13. ROUTE OF ADMINISTRATION: Oral

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

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____ SPOTS product – Form Completed

__X__ Not a SPOTS product

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

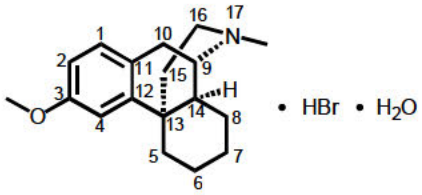
Chemical Name: Dextromethorphan Hydrobromide Monohydrate

3-Methoxy-17-methyl-9α, 13α, 14α-morphinan Hydrobromide Monohydrate

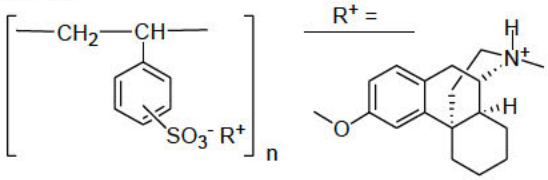
Or: 3-Methoxy-17-methyl-9*S*, 13*S*, 14*S*-morphinan Hydrobromide Monohydrate

Chemistry Review Data Sheet

Molecular Formula: $C_{18}H_{25}NO \cdot HBr \cdot H_2O$
Molecular Weight: 370.32
CAS Number: 6700-34-1
Structural Formula



Chemical Structure of Polystyrene Sulfonate Polymer Complex with Dextromethorphan Polistirex:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	*Adequate*	11-06-2011	By P. Jin
	IV			3	*Adequate*	04-14-2011	By N. Takiar
	IV			3	*Adequate*	11-19-2009	By A. Mitra
	IV			4	*Adequate*	09-13-1999	By A. Mitra
	IV			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

Chemistry Review Data Sheet

*Pack size of exhibit batch, not proposed for commercial.

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA for Delsym®	18-658	Reference Listed Drug (RLD)

18. STATUS:

CONSULTS/CMC RELATED REVIEWS		RECOMMENDATION	DATE	REVIEWER
Microbiology		N/A		
EES		***Pending***	11/17/2011	
Methods Validation		NA		
Labeling		***Acceptable***	11-18-2011	Jeanne Skanchy
Bioequivalence	*Dissolution Method*	***Acceptable***	07-28-2011	Dehaven, Wayne
	Bioequivalency	***Acceptable***	03-24-2011	Dehaven, Wayne
EA		***Acceptable***	11-12-2009	G.Sun
Radiopharmaceutical		N/A		
Pharm/Tox		N/A		

19. ORDER OF REVIEW:

The application submission(s) covered by this review was taken in the date order of receipt.

Yes __X__ No _____ If no, explain reason(s) below:

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

*The ANDA is **Approvable.***

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

N/A

II. Summary of Chemistry Assessments

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

a. Drug Substance

(i). Description of drug substance

Dextromethorphan Hydrobromide is practically white crystals or crystalline powder, having a faint odor. It is an USP subject. It is sparingly soluble in water; freely soluble in alcohol and in chloroform; insoluble in ether. Its polymorphic form is not reported in literature and not determined either by the applicant.

(ii). Manufacturer of drug substance

Dextromethorphan Hydrobromide drug substance is manufactured by:

(b) (4)

b. Drug Product

(i). Description of drug product

The drug product, Dextromethorphan Polistirex Extended Release Oral Suspension, eq. to 30 mg Dextromethorphan Hydrobromide Per 5 mL is an orange viscous suspension.

(ii). Components of drug product

The drug product contains the following components:

Glycerin USP
Dextromethorphan Hydrobromide USP
High Fructose Corn Syrup
Polysorbate 80 NF
Polyvinyl Acetate (b) (4)
Povidone USP
Methylparaben NF

Propylparaben NF
Sodium Metabisulfite NF
Sodium Polystyrene Sulfonate USP
Sucrose NF
Tartaric Acid NF
Tragacanth Gum NF
Triacetin USP
Xanthan Gum NF
D&C Red No.30 (b) (4)
D&C Yellow No.10 (b) (4)
Flavor (b) (4)
Purified Water USP

No overage appears in drug product. No safety concerns from any excipient.

(iii). Manufacturing process of drug product

The manufacturing process involves the following steps:

(b) (4)

(iv). Test methods for drug product

(b) (4)

Comparison of dissolution method and specifications proposed by the applicant initially and revised specification per FDA recommendation:

Parameter	Proposed by Tris Pharma initially	Revised per FDA Recommendation
Apparatus Speed Medium Volume Temperature	Paddle II 50 rpm 0.1N HCl + 400 mL phosphate buffer after 1 h 500 mL 37 °C	(*The same as proposed by the firm*)
Specification	1 hr: NMT (b) (4) % 3 hr: (b) (4) % 6 hr: (b) (4) % 12 hr: NLT (b) (4) %	1 hr: **NMT** (b) (4) **%** 3 hr: (b) (4) % 6 hr: (b) (4) % 12 hr: NLT (b) (4) %

(b) (4)

(b) (4)

[redacted]

(vii). Storage conditions

Based on the labeling, the storage condition for Tris Pharma's drug product is described as below:

Store at 20°-25°C (68°-77°F)

(viii). Expiration Date

The proposed expiration data for the drug product is ***24 months*** for the proposed marketing container/closure systems.

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

INDICATIONS AND USAGE

Temporarily relieves cough due to minor throat and bronchial irritation as may occur with the common cold or inhaled irritants.

DOSAGE AND ADMINISTRATION

Adults and Children 12 years of age and over:	(b) (4) (10 mL) in 12 h, NMT 20 mL in 24 h
Children 6 to under 12 years of age:	(5 mL) in 12 h, NMT 10 mL in 24 hours
Children 4 to under 6 years of age:	(5 mL) in 12 h, NMT 5 mL in 24 hours

HOW SUPPLIED

Tamper-evident container/closure system with the following statement on bottle label: "TAMPER EVIDENT: Do not use if carton is opened, or if neckband printed "sealed for your protection" is broken or missing".

STORAGE CONDITION:

Store at 20°-25°C (68°-77°F)

C. Basis for Approvability or Not-Approval Recommendation

The CMC section of this ANDA is ***approvable***.

45 PAGES WERE WITHHELD IN FULL AS B4 (CCI/TS) IMMEDIATELY FOLLOWING THIS PAGE

cc: ANDA 91-135
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-630/Ping Jin, Ph.D., Review Chemist/12-6-11

HFD-630/Guoping Sun, Ph.D., Team Leader/12-13-11

HFD-617/Sarah Nguyen, Project Manager/12-14-11

F/T by: SN 12/14/11

V:\Chemistry Division III\Team 31\ANDA REVIEWS\Ping\91135.R04.doc

TYPE OF LETTER: ***APPROVABLE***

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

/s/

PING JIN
12/15/2011

GUOPING SUN
12/16/2011

SARAH K NGUYEN
12/16/2011

ANDA 091135

Dextromethorphan Polistirex Extended-release Oral Suspension, 30 mg/5 mL (eq. to 30 mg Dextromethorphan Hydrobromide Per 5 mL)

Tris Pharma, Inc.

Ping Jin, Ph.D.

Office of Generic Drugs
Division of Chemistry III
Team 31

Table of Contents

Chemistry Review Data Sheet

1. **ANDA #:** 91-135

2. **REVIEW #:** 3

3. **REVIEW DATE:** 02-Nov-2010 / lastly Revised on 31-Jan-2010

4. **REVIEWER:** Ping Jin, Ph.D.

5. **PREVIOUS DOCUMENTS:**

Previous Documents	Document Date
Original Submission (*Including information on USP<467> compliance*)	01-09-2009
Date Acceptance for Filing	01-12-2009
Amendment *(Sq. 01. Response to regulatory support comments)*	05-06-2009
Amendment *(Sq. 02. Patent amendment)*	05-18-2009
Amendment *(Sq. 03.* (b) (4) *)*	06-12-2009 07-23-2009
Amendment *(Sq. 04. Patent amendment)*	10-09-2009
Amendment *(Sq. 07. Revision of drug product specification)*	02-18-2010
Amendment *(response to deficiency letter)*	

6. **SUBMISSION(S) BEING REVIEWED:**

Submission(s) Reviewed	Document Date
Minor Amendment *(response to deficiency letter)*	10-13-2010
Minor Amendment	11-18-2010
Telephone Amendment	12-16-2010
Telephone Amendment	01-27-2011

7. **NAME & ADDRESS OF APPLICANT:**

Name and Address of Applicant:

Name: **Tris Pharma, Inc.**

Address: 2033 Route 130
Monmouth Junction, NJ 08852

Representative: **W. Scott Groner**

Telephone: 732-940-0358

Fax: 732-940-0374

Drug Product Manufacturing Facility

Tris Pharma, Inc.

(*the same address of the applicant*)

US Agent:

(N/A)

8. **DRUG PRODUCT NAME:**

a) Proprietary Name: None

Chemistry Review Data Sheet

b) Non-Proprietary Name (USAN): Dextromethorphan Polistirex Extended Release Oral Suspension

9. LEGAL BASIS FOR SUBMISSION:

Innovator Product: Delsym® (Dextromethorphan Polistirex) Extended-release Oral Solution (Approval date: Oct. 8, 1982)

Innovator Company: Reckitt Benckiser (NDA # 18-658)

Patent Data: **Paragraph IV Patent Certification Regarding U.S. Patent No.** 5980882 which will expire on April 16, 2017:

U.S. Patent No. 5,980,882, listed as expiring on April 16, 2017 is invalid, unenforceable, and/or will not be infringed by the manufacture, use, or sale of Tris' Dextromethorphan Polistirex Extended Release Suspension, eq. to 30 mg dextromethorphan hydrobromide per 5 mL, for which this abbreviated new drug application ("ANDA") is submitted.

Exclusivity Data: There is no unexpired exclusivity for this product

10. PHARMACOL. CATEGORY: Antitussive

11. DOSAGE FORM: Oral Solution

12. STRENGTH/POTENCY: 30 mg/5 mL (eq. to 30 mg Dextromethorphan HBr/5 mL)
Maximum Daily Dosage: **120 mg** (20 mL DP)

13. ROUTE OF ADMINISTRATION: Oral

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

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____ SPOTS product – Form Completed

__X__ Not a SPOTS product

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

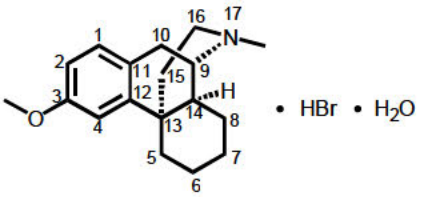
Chemical Name: Dextromethorphan Hydrobromide Monohydrate
3-Methoxy-17-methyl-9α, 13α, 14α-morphinan Hydrobromide Monohydrate
Or: 3-Methoxy-17-methyl-9*S*, 13*S*, 14*S*-morphinan Hydrobromide Monohydrate

Molecular Formula: $C_{18}H_{25}NO \cdot HBr \cdot H_2O$

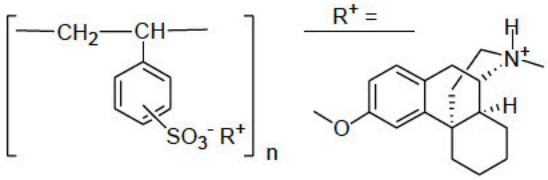
Molecular Weight: 370.32

CAS Number: 6700-34-1

Structural Formula



Chemical Structure of Polystyrene Sulfonate Polymer Complex with Dextromethorphan Polistirex:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	*Adequate*	08-18-2010	By T. Wong
	IV			3	*Adequate*	07/25/2007	By A.YUSUF
	IV			3	*Adequate*	11-19-2009	By A. Mitra
	IV			4	*Adequate*	09-13-1999	By A. Mitra
	IV			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

*Pack size of exhibit batch, not proposed for commercial.

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA for Delsym®	18-658	Reference Listed Drug (RLD)

18. STATUS:

CONSULTS/CMC RELATED REVIEWS		RECOMMENDATION	DATE	REVIEWER
Microbiology		N/A		
EES		***Acceptable***	05-14-2010	A. Inyard
Methods Validation		NA		
Labeling		***Acceptable***	10-19-2010	Jeanne Skanchy
Bioequivalence	*Dissolution Method*	***Deficient****	09-03-2009	Anitha Palamakula
	Bioequivalency	***Deficient***	09-23-2009	Teresa Ramson
EA		***Acceptable***	11-12-2009	G.Sun
Radiopharmaceutical		N/A		
Pharm/Tox		N/A		

* The FDA accepted the applicant's dissolution method but recommended a revision of the dissolution specification on 9-3-09. Tris Pharma accepted the FDA recommended dissolution specification on 10-9-09 and all dissolution data provided up to date met the revised specifications.

19. ORDER OF REVIEW:

The application submission(s) covered by this review was taken in the date order of receipt.

Yes __X__ No _____ If no, explain reason(s) below:

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

*The ANDA is **Approvable.***

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

N/A

II. Summary of Chemistry Assessments

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

a. Drug Substance

(i). Description of drug substance

Dextromethorphan Hydrobromide is practically white crystals or crystalline powder, having a faint odor. It is an USP subject. It is sparingly soluble in water; freely soluble in alcohol and in chloroform; insoluble in ether. Its polymorphic form is not reported in literature and not determined either by the applicant.

(ii). Manufacturer of drug substance

Dextromethorphan Hydrobromide drug substance is manufactured by:

(b) (4)

b. Drug Product

(i). Description of drug product

The drug product, Dextromethorphan Polistirex Extended Release Oral Suspension, eq. to 30 mg Dextromethorphan Hydrobromide Per 5 mL is an orange viscous suspension.

(ii). Components of drug product

The drug product contains the following components:

Glycerin USP
Dextromethorphan Hydrobromide USP
High Fructose Corn Syrup
Polysorbate 80 NF
Polyvinyl Acetate (b) (4)
Povidone USP
Methylparaben NF

Propylparaben NF
Sodium Metabisulfite NF
Sodium Polystyrene Sulfonate USP
Sucrose NF
Tartaric Acid NF
Tragacanth Gum NF
Triacetin USP
Xanthan Gum NF
D&C Red No.30 (b) (4)
D&C Yellow No.10 (b) (4)
Flavor (b) (4)
Purified Water USP

No overage appears in drug product. No safety concerns from any excipient.

(iii). Manufacturing process of drug product

The manufacturing process involves the following steps:

(b) (4)

(iv). Test methods for drug product

(b) (4)

Comparison of dissolution method and specifications proposed by the applicant and recommended by the FDA:

Parameter	Proposed by Tris Pharma initially	Revised per FDA Recommendation
Apparatus	Paddle II	(*The same as proposed by the firm*)
Speed	50 rpm	
Medium	0.1N HCl + 400 mL phosphate buffer after 1 h	
Volume	500 mL	
Temperature	37 °C	
Specification	1 hr: NMT (b) (4) % 3 hr: (b) (4) % 6 hr: (b) (4) % 12 hr: NLT (b) (4) %	1 hr: NMT (b) (4) % 3 hr: (b) (4) % 6 hr: (b) (4) % 12 hr: ***NLT*** (b) (4) *%*

(b) (4)

(b) (4)

[redacted]

(vii). Storage conditions

Based on the labeling, the storage condition for Tris Pharma's drug product is described as below:

Store at 20°-25°C (68°-77°F)

(viii). Expiration Date

The proposed expiration data for the drug product is ***24 months*** for the proposed marketing container/closure systems.

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

INDICATIONS AND USAGE

Temporarily relieves cough due to minor throat and bronchial irritation as may occur with the common cold or inhaled irritants.

DOSAGE AND ADMINISTRATION

Adults and Children 12 years of age and over:	(b) (4) (10 mL) in 12 h, NMT 20 mL in 24 h
Children 6 to under 12 years of age:	(5 mL) in 12 h, NMT 10 mL in 24 hours
Children 4 to under 6 years of age:	(5 mL) in 12 h, NMT 5 mL in 24 hours

HOW SUPPLIED

Tamper-evident container/closure system with the following statement on bottle label: "TAMPER EVIDENT: Do not use if carton is opened, or if neckband printed "sealed for your protection" is broken or missing".

STORAGE CONDITION:

Store at 20°-25°C (68°-77°F)

C. Basis for Approvability or Not-Approval Recommendation

The CMC section of this ANDA is ***approvable***.

44 PAGES WERE WITHHELD IN FULL AS B4 (CCI/TS) IMMEDIATELY FOLLOWING THIS PAGE

cc: ANDA 91-135
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-630/Ping Jin, Ph.D., Review Chemist/12-22-10; 01-31-11

HFD-630/Guoping Sun, Ph.D., Team Leader/01-31-11

HFD-617/Sarah Nguyen, Project Manager/02-02-11

F/T by: 02-02-11

V:\Chemistry Division III\Team 31\ANDA REVIEWS\Ping\91135.R03.doc

TYPE OF LETTER: ***APPROVABLE,*** **Pending Bio**

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

/s/

PING JIN
02/02/2011

GUOPING SUN
02/03/2011

SARAH K NGUYEN
02/04/2011

ANDA 091135

Dextromethorphan Polistirex Extended-release Oral Suspension, 30 mg/5 mL (eq. to 30 mg Dextromethorphan Hydrobromide Per 5 mL)

Tris Pharma, Inc.

Guoping Sun, Ph.D.

Office of Generic Drugs
Division of Chemistry III
Team IV

Table of Contents

Table of Contents

Chemistry Review Data Sheet

1. ANDA #: 91-135

2. REVIEW #: 2

3. REVIEW DATE: 08-31-2010

4. REVIEWER: Guoping Sun, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission (*Including information on USP<467> compliance*)	01-09-2009
Date Acceptance for Filing	01-12-2009
Amendment *(Sq. 01. Response to regulatory support comments)*	05-06-2009
Amendment *(Sq. 02. Patent amendment)*	05-18-2009
Amendment *(Sq. 03.* (b) (4)	06-12-2009
Amendment *(Sq. 04. Patent amendment)*	07-23-2009
Amendment *(Sq. 07. Revision of drug product specification)*	10-09-2009

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment *(response to deficiency letter)*	02-18-2010

7. NAME & ADDRESS OF APPLICANT:

Name and Address of Applicant:

Name: **Tris Pharma, Inc.**

Address: 2033 Route 130
Monmouth Junction, NJ 08852

Representative: **Scott Groner**

Telephone: 732-940-0358

Fax: 732-940-0374

Drug Product Manufacturing Facility

Tris Pharma, Inc.

(*the same address of the applicant*)

US Agent:
(N/A)

8. DRUG PRODUCT NAME:

a) Proprietary Name: None

Chemistry Review Data Sheet

b) Non-Proprietary Name (USAN): Dextromethorphan Polistirex Extended Release Oral Suspension

9. LEGAL BASIS FOR SUBMISSION:

Innovator Product: Delsym® (Dextromethorphan Polistirex) Extended-release Oral Solution (Approval date: Oct. 8, 1982)

Innovator Company: Reckitt Benckiser (NDA # 18-658)

Patent Data: **Paragraph IV Patent Certification Regarding U.S. Patent No.** 5980882 which will expire on April 16, 2017:

U.S. Patent No. 5,980,882, listed as expiring on April 16, 2017 is invalid, unenforceable, and/or will not be infringed by the manufacture, use, or sale of Tris' Dextromethorphan Polistirex Extended Release Suspension, eq. to 30 mg dextromethorphan hydrobromide per 5 mL, for which this abbreviated new drug application ("ANDA") is submitted.

Exclusivity Data: There is no unexpired exclusivity for this product

10. PHARMACOL. CATEGORY: Antitussive

11. DOSAGE FORM: Oral Solution

12. STRENGTH/POTENCY: 30 mg/5 mL (eq. to 30 mg Dextromethorphan HBr/5 mL)

Maximum Daily Dosage: **120 mg** (20 mL DP)

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: ____ Rx __X__ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____ SPOTS product – Form Completed

__X__ Not a SPOTS product

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

Chemical Name: Dextromethorphan Hydrobromide Monohydrate
3-Methoxy-17-methyl-9α, 13α, 14α-morphinan Hydrobromide Monohydrate

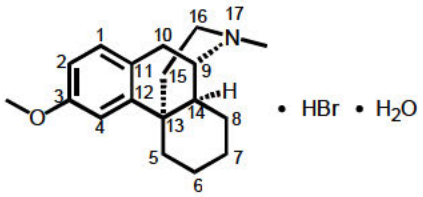
Or: 3-Methoxy-17-methyl-9*S*, 13*S*, 14*S*-morphinan Hydrobromide Monohydrate

Molecular Formula: $C_{18}H_{25}NO \cdot HBr \cdot H_2O$

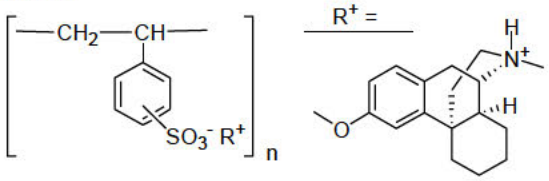
Molecular Weight: 370.32

CAS Number: 6700-34-1

Structural Formula



Chemical Structure of Polystyrene Sulfonate Polymer Complex with Dextromethorphan Polistirex:



17.RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	*Adequate*	08-18-2010	By T. Wong
	IV			3	*Adequate*	07/25/2007	By A.YUSUF
	IV			3	*Adequate*	11-19-2009	By A. Mitra
	IV			4	*Adequate*	09-13-1999	By A. Mitra
	IV			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

*Pack size of exhibit batch, not proposed for commercial.

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA for Delsym®	18-658	Reference Listed Drug (RLD)

18.STATUS:

CONSULTS/CMC RELATED REVIEWS		RECOMMENDATION	DATE	REVIEWER
Microbiology		N/A		
EES		***Acceptable***	05-14-2010	A. Inyard
Methods Validation		NA		
Labeling		***Deficient***	08-17-2010	JEANNE SKANCHY
Bioequivalence	*Dissolution Method*	***Deficient****	09-03-2009	Anitha Palamakula
	Bioequivalency	***Deficient***	09-23-2009	TERESA RAMSON
EA		***Acceptable***	11-12-2009	G.Sun
Radiopharmaceutical		N/A		
Pharm/Tox		N/A		

* The FDA accepted the applicant's dissolution method but recommended a revision of the dissolution specification on 9-3-09. Tris Pharm accepted the FDA recommended dissolution specification on 10-9-09 and all dissolution data provided up to date met the revised specifications.

19.ORDER OF REVIEW:

The application submission(s) covered by this review was taken in the date order of receipt.

Yes __X__ No _____ If no, explain reason(s) below:

The Chemistry Review for ANDA 91-135

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

*The ANDA is **Not Approvable.*** It's recommended a minor not approvable deficiency letter be sent to the sponsor.

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

N/A

II. Summary of Chemistry Assessments

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

a. Drug Substance

(i). *Description of drug substance*

Dextromethorphan Hydrobromide is practically white crystals or crystalline powder, having a faint odor. It is an USP subject. It is sparingly soluble in water; freely soluble in alcohol and in chloroform; insoluble in ether. Its polymorphic form is not reported in literature and not determined either by the applicant.

(ii). *Manufacturer of drug substance*

Dextromethorphan Hydrobromide drug substance is manufactured by:

(b) (4)

b. Drug Product

(i). *Description of drug product*

The drug product, Dextromethorphan Polistirex Extended Release Oral Suspension, eq. to 30 mg Dextromethorphan Hydrobromide Per 5 mL is an orange viscous suspension.

(ii). *Components of drug product*

The drug product contains the following components:

Glycerin USP
Dextromethorphan Hydrobromide USP
High Fructose Corn Syrup
Polysorbate 80 NF
Polyvinyl Acetate (b) (4)
Povidone USP
Methylparaben NF
Propylparaben NF
Sodium Metabisulfite NF
Sodium Polystyrene Sulfonate USP
Sucrose NF
Tartaric Acid NF
Tragacanth Gum NF
Triacetin USP
Xanthan Gum NF
D&C Red No.30 (b) (4)
D&C Yellow No.10 (b) (4)
Flavor (b) (4)
Purified Water USP

No overage appears in drug product. No safety concerns from any excipient.

(iii). Manufacturing process of drug product

The manufacturing process involves the following steps:

- (b) (4)
-
-
-
-

(iv). Test methods for drug product

(b) (4)

Comparison of dissolution method and specifications proposed by the applicant and recommended by the FDA:

Parameter	Proposed by Tris Pharma initially	Revised per FDA Recommendation
Apparatus Speed Medium Volume Temperature	Paddle II 50 rpm 0.1N HCl + 400 mL phosphate buffer after 1 h 500 mL 37 °C	(*The same as proposed by the firm*)
Specification	1 hr: NMT (b) (4) % 3 hr: (b) (4) % 6 hr: (b) (4) % 12 hr: NLT (b) (4) %	1 hr: NMT (b) (4) % 3 hr: (b) (4) % 6 hr: (b) (4) % 12 hr: ***NLT*** (b) (4) %

(b) (4)

[redacted]

(vii). Storage conditions

Based on the labeling, the storage condition for Tris Pharma's drug product is described as below:

Store at 20°-25°C (68°-77°F)

(viii). Expiration Date

The proposed expiration data for the drug product is ***24 months*** for the proposed marketing container/closure systems.

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

INDICATIONS AND USAGE

Temporarily relieves cough due to minor throat and bronchial irritation as may occur with the common cold or inhaled irritants.

DOSAGE AND ADMINISTRATION

Adults and Children 12 years of age and over:	(b) (4) [redacted] (10 mL) in 12 h, NMT 20 mL in 24 h
Children 6 to under 12 years of age:	(5 mL) in 12 h, NMT 10 mL in 24 hours
Children 4 to under 6 years of age:	(5 mL) in 12 h, NMT 5 mL in 24 hours

HOW SUPPLIED

Tamper-evident container/closure system with the following statement on bottle label: "TAMPER EVIDENT: Do not use if carton is opened, or if neckband printed "sealed for your protection" is broken or missing".

STORAGE CONDITION:

Store at 20°-25°C (68°-77°F)

C. Basis for Approvability or Not-Approval Recommendation

CMC of this ANDA is ***not approvable***. Dissolution method is ***acceptable*** but dissolution specification is ***deficient***. Labeling and bioequivalence sections are ***pending*** for review. EES is ***Acceptable***. This ANDA is ***Not Approvable***.

36 PAGES WERE WITHHELD IN FULL AS B4 (CCI/TS) IMMEDIATELY FOLLOWING THIS PAGE

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA#: 091135
APPLICANT: Tris Pharma, Inc.
DRUG PRODUCT: Dextromethorphan Polistirex Extended-release Oral Suspension, 30 mg/5 mL (eq. to 30 mg Dextromethorphan Hydrobromide Per 5 mL)

The deficiencies presented below represent MINOR deficiencies.

1. (b) (4)
2.
3.
4.
5.
6.
7.

8. (b) (4) [redacted]

Sincerely yours,

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 91-135
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-630/Guoping Sun, Ph.D., Review Chemist/08-31-10

HFD-630/Shing Hou Liu, Ph.D., Team Leader/09-08-10

HFD-617/Sarah Nguyen, Project Manager/09-09-10

F/T by: SN 09-09-10

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TYPE OF LETTER: ***NOT APPROVABLE-Minor***

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91135	ORIG-1	TRIS PHARMA INC	DEXTROMETHORPHAN POLISTIREX

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

/s/

GUOPING SUN
09/13/2010
CMC rev. 2, not approvable

SARAH K NGUYEN
09/14/2010

SHING HOU H LIU
09/14/2010

ANDA 091135

Dextromethorphan Polistirex Extended Release Oral Suspension, 30 mg/5 mL (eq. to 30 mg Dextromethorphan Hydrobromide Per 5 mL)

Tris Pharma, Inc.

Guoping Sun, Ph.D.

Office of Generic Drugs
Division of Chemistry III
Team IV

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Chemistry Review Data Sheet

1. ANDA #: 91-135

2. REVIEW #: 1

3. REVIEW DATE: 11-12-2009

4. REVIEWER: Guoping Sun, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NA	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission (*Including information on USP<467> compliance*)	01-09-2009
Date Acceptance for Filling	01-12-2009
Amendment *(Sq. 01. Response to regulatory support comments)*	05-06-2009
Amendment *(Sq. 02. Patent amendment)*	05-18-2009
Amendment *(Sq. 03.* (b) (4)	06-12-2009
Amendment *(Sq. 04. Patent amendment)*	07-23-2009
Amendment *(Patent amendment)*	08-11-2009
Amendment *(Sq. 07. Revision of drug product specification)*	10-09-2009

7. NAME & ADDRESS OF APPLICANT:

Name and Address of Applicant:		***Drug Product Manufacturing Facility***
Name:	**Tris Pharma, Inc.**	**Tris Pharma, Inc.**
Address:	2033 Route 130 Monmouth Junction, NJ 08852	(*the same address of the applicant*)
Representative:	**Scott Groner**	
Telephone:	732-940-0358	
Fax:	732-940-0374	

US Agent:
(N/A)

8. DRUG PRODUCT NAME:

Chemistry Review Data Sheet

a) Proprietary Name: None

b) Non-Proprietary Name (USAN): Dextromethorphan Polistirex Extended Release Oral Suspension

9. LEGAL BASIS FOR SUBMISSION:

Innovator Product: Delsym® (Dextromethorphan Polistirex) Extended-release Oral Solution (Approval date: Oct. 8, 1982)

Innovator Company: Reckitt Benckiser (NDA # 18-658)

Patent Data: **Paragraph IV Patent Certification Regarding U.S. Patent No.** 5980882 which will expire on April 16, 2017:

U.S. Patent No. 5,980,882, listed as expiring on April 16, 2017 is invalid, unenforceable, and/or will not be infringed by the manufacture, use, or sale of Tris' Dextromethorphan Polistirex Extended Release Suspension, eq. to 30 mg dextromethorphan hydrobromide per 5 mL, for which this abbreviated new drug application ("ANDA") is submitted.

Exclusivity Data: There is no unexpired exclusivity for this product

10. PHARMACOL. CATEGORY: Antitussive

11. DOSAGE FORM: Oral Solution

12. STRENGTH/POTENCY: 30 mg/5 mL (eq. to 30 mg Dextromethorphan HBr/5 mL)

Maximum Daily Dosage: **120 mg** (20 mL DP)

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: ____ Rx __X_ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____ SPOTS product – Form Completed

__X__ Not a SPOTS product

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

Chemical Name: Dextromethorphan Hydrobromide Monohydrate
3-Methoxy-17-methyl-9α, 13α, 14α-morphinan Hydrobromide Monohydrate

Or: 3-Methoxy-17-methyl-9*S*, 13*S*, 14*S*-morphinan Hydrobromide Monohydrate

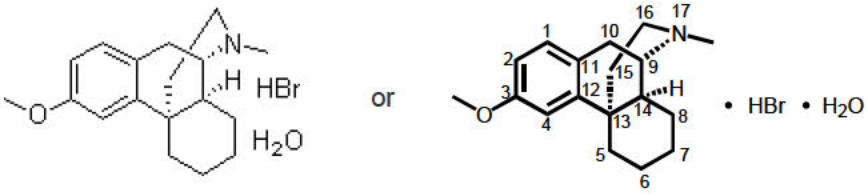
Molecular Formula: $C_{18}H_{25}NO \cdot HBr \cdot H_2O$

Molecular Weight: 370.32

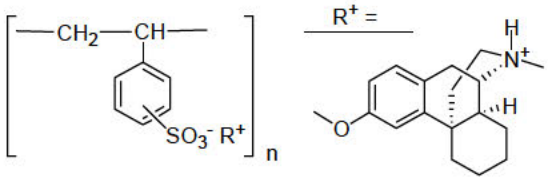
Chemistry Review Data Sheet

CAS Number: 6700-34-1

Structural Formula



Chemical Structure of Polystyrene Sulfonate Polymer Complex with Dextromethorphan Polistirex:



17.RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	*Inadequate*	11-11-09	By G.Sun
	IV			3	Adequate	07/25/2007	By A.YUSUF
	IV			3	*Adequate*	11-19-2009	By A. Mitra
	IV			4	N/A		
	IV			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

*Pack size of exhibit batch, not proposed for commercial.

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available
7 – Other (explain under "Comments")
[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA for Delsym®	18-658	Reference Listed Drug (RLD)

18.STATUS:

CONSULTS/CMC RELATED REVIEWS		RECOMMENDATION	DATE	REVIEWER
Microbiology		N/A		
EES		***Pending***		
Methods Validation		NA		
Labeling		***Pending***		
Bioequivalence	*Dissolution Method*	***Deficient***	09-23-2009	Anitha Palamakula
	Bioequivalency	***Pending***		
EA		***Acceptable***	11-12-2009	G.Sun
Radiopharmaceutical		N/A		
Pharm/Tox		N/A		

19.ORDER OF REVIEW:

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

The Chemistry Review for ANDA 91-135

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The ANDA is ***Not Approvable.*** It's recommended a minor not approvable deficiency letter be sent to the sponsor.

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

N/A

II. Summary of Chemistry Assessments

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

a. Drug Substance

(i). *Description of drug substance*

Dextromethorphan Hydrobromide is practically white crystals or crystalline powder, having a faint odor. It is an USP subject. It is sparingly soluble in water; freely soluble in alcohol and in chloroform; insoluble in ether. Its polymorphic form is not reported in literature and not determined either by the applicant.

(ii). *Manufacturer of drug substance*

Dextromethorphan Hydrobromide drug substance is manufactured by:

(b) (4)

b. Drug Product

(i). *Description of drug product*

The drug product, Dextromethorphan Polistirex Extended Release Oral Suspension, eq. to 30 mg Dextromethorphan Hydrobromide Per 5 mL is an orange viscous suspension.

(ii). *Components of drug product*

The drug product contains the following components:

Glycerin USP

Dextromethorphan Hydrobromide USP
High Fructose Corn Syrup
Polysorbate 80 NF
Polyvinyl Acetate (b) (4)
Povidone USP
Methylparaben NF
Propylparaben NF
Sodium Metabisulfite NF
Sodium Polystyrene Sulfonate USP
Sucrose NF
Tartaric Acid NF
Tragacanth Gum NF
Triacetin USP
Xanthan Gum NF
D&C Red No.30 (b) (4)
D&C Yellow No.10 (b) (4)
Flavor (b) (4)
Purified Water USP

No overage appears in drug product. No safety concerns from any excipient.

(iii). Manufacturing process of drug product

The manufacturing process involves the following steps:

(b) (4)

(iv). Test methods for drug product

(b) (4)

Comparison of dissolution method and specifications proposed by the applicant and recommended by the FDA:

Parameter	Proposed by Tris Pharma initially	Revised per FDA Recommendation
Apparatus	Paddle II	(*The same as proposed by the firm*)
Speed	50 rpm	
Medium	0.1N HCl + 400 mL phosphate buffer after 1 h	
Volume	500 mL	
Temperature	37 °C	
Specification	1 hr: NMT (b) (4) % 3 hr: (b) (4) % 6 hr: (b) (4) % 12 hr: NLT (b) (4) %	1 hr: NMT (b) (4) % 3 hr: (b) (4) % 6 hr: (b) (4) % 12 hr: ***NLT*** (b) (4) *%*

(v). Executed batch and proposed production batches

(b) (4)

[redacted]

(vii). Storage conditions

Based on the labeling, the storage condition for Tris Pharma's drug product is described as below:

Store at 20°-25°C (68°-77°F)

(viii). Expiration Date

The proposed expiration data for the drug product is ***24 months*** for the proposed marketing container/closure systems.

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

INDICATIONS AND USAGE

Temporarily relieves cough due to minor throat and bronchial irritation as may occur with the common cold or inhaled irritants.

DOSAGE AND ADMINISTRATION

Adults and Children 12 years of age and over:	(b) (4) (10 mL) in 12 h, NMT 20 mL in 24 h
Children 6 to under 12 years of age:	(5 mL) in 12 h, NMT 10 mL in 24 hours
Children 4 to under 6 years of age:	(5 mL) in 12 h, NMT 5 mL in 24 hours

HOW SUPPLIED

Tamper-evident container/closure system with the following statement on bottle label: "TAMPER EVIDENT: Do not use if carton is opened, or if neckband printed "sealed for your protection" is broken or missing".

STORAGE CONDITION:

Store at 20°-25°C (68°-77°F)

C. Basis for Approvability or Not-Approval Recommendation

CMC of this ANDA is ***not approvable***. Dissolution method is ***acceptable*** but dissolution specification is ***deficient***. Labeling and bioequivalence sections are ***pending*** for review. EES is ***pending***. This ANDA is ***Not Approvable***.

44 PAGES WERE WITHHELD IN FULL AS B4 (CCI/TS) IMMEDIATELY FOLLOWING THIS PAGE

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA#: 91-135
APPLICANT: Tris Pharma, Inc.
DRUG PRODUCT: Dextromethorphan Polistirex Extended Release Oral Suspension, 30 mg/5 mL (eq. to 30 mg Dextromethorphan Hydrobromide Per 5 mL)

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. (b) (4)

2.

3.

4.

5.

6.

(b) (4)

7. [redacted]

8. [redacted]

9. [redacted]

10. [redacted]

11. [redacted]

12. [redacted]

13. [redacted]

14. [redacted]

15. [redacted]

16. [redacted]

17. [redacted]

18. (b) (4)

19.

20.

21.

22.

23.

24.

25.

26.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please update your room temperature stability data and provide all available data in your next amendment.

2. The review of the labeling and bioequivalence portions of your application are pending. After the reviews are complete, any deficiencies found will be communicated to you under separate covers.

3. The firms referenced in the application relative to the manufacture and testing of the product must be in compliance with cGMPs at the time of approval.

4. Please be advised that the use of in-house or modified compendial analytical methods for testing the drug substance does not relieve you from meeting the compendial standards. In the event of a dispute, the official USP methods will prevail.

Sincerely yours,

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 91-135
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-630/Guoping Sun, Ph.D., Review Chemist/11-12-09

HFD-630/Shing Hou Liu, Ph.D., Team Leader/01-08-10

HFD-617/Sarah Nguyen, Project Manager/01-08-10

F/T by: SN

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TYPE OF LETTER: ***NOT APPROVABLE-Minor***

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91135	ORIG-1	TRIS PHARMA INC	DEXTROMETHORPHAN POLISTIREX

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

/s/

GUOPING SUN
01/12/2010
CMC Rev. #1, NA minor

SARAH K NGUYEN
01/12/2010

SHING HOU H LIU
01/12/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 091135Orig1s000

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW ADDENDUM

ANDA No.	091135		
Drug Product Name	Dextromethorphan Polistirex Extended Release Oral Suspension		
Strength(s)	EQ. 30 mg dextromethorphan hydrobromide per 5 mL		
Applicant Name	Tris Pharma, Inc.		
Address	2033 Route 130 Monmouth Junction, NJ 08852		
Applicant's Point of Contact	W. Scott Groner, Director RA and Compliance		
Contact's Telephone Number	732-940-0358		
Contact's Fax Number	732-940-0374		
Original Submission Date(s)	January 9, 2009 September 25, 2009 (Dissolution Acknowledgement) October 9, 2009 (Stability Amendment)		
Submission Date of Amendment Under Review	March 4, 2011		
Reviewer	Wayne DeHaven, Ph.D.		
Study Number (s)	S08-0445	S08-0446	
Study Type (s)	FASTED	FED	
Strength (s)	60 mg dose (10 mL)	60 mg dose (10 mL)	
Clinical Site	Cetero Research		
Clinical Site Address	400 Fountain Lakes Blvd. St. Charles, MO 63301 (314) 419-6592		
Analytical Site	(b) (4)		
Analytical Site Address			
Overall Review Result	**ADEQUATE**		
DSI Report Result	**ADEQUATE**		

BE Study Tracking/Supporting Document #	**Study/Test Type**	**Strength**	**Review Result**
1	Dissolution	eq. 30 mg / 5 mL	**ADEQUATE**
1	Fasting Study	eq. 30 mg / 5 mL	**ADEQUATE**
1	Fed Study	eq. 30 mg / 5 mL	**ADEQUATE**

ADDENDUM

1 EXECUTIVE SUMMARY

This is an addendum to the previous DBE review which is located in DARRTS [for ANDA #091135 DEHAVEN, WAYNE I 03/24/2011 N/A 03/24/2011 REV-BIOEQ-01(General Review) Original-1 Archive].

In the amendment dated March 4, 2011, Tris Pharma submitted additional information with regard to the dissolution specifications. Specifically, Tris Pharma requested the DBE revisit the 1 hour specification of *NMT* (b)(4)*%*. Tris Pharma is recommending a 1 hour specification of *NMT* (b)(4)*%*. To support their claim, the firm submitted additional stability testing (i.e. dissolution testing results taken every 3 months up to 2 years) on the bio-lot #TB-023A, as well as 0 month testing on a second lot (TB-081A).

These data were overlooked in the previous DBE review mentioned above. This addendum addresses the firms request to change the 1 hour specification from *NMT* (b)(4)*%* to *NMT* (b)(4)*%*.

Because of the firm's request the DBE revisited the 1 hour dissolution specification (NMT (b)(4)%) of the test biolot. As stated on page 17 of the *"Guidance for Industry for Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations"* the dissolution specification is set from the fresh biolot (not on the dissolution of the stored biolot) by adding $\pm$ 10% to the mean % dissolution. Since for the first time point (1 hr) of the test drug product the mean % dissolution of the biolot TB-023A is (b)(4)%, the DBE considers (b)(4)% to (b)(4)% or NMT (b)(4)% as the appropriate specification. Our earlier specification NMT (b)(4)% is overly strict and is not keeping with the guidance. The DBE therefore accepts the firm's request to modify the 1 hour specification of its test product from *NMT* (b)(4)*%* to *NMT* (b)(4)*%* based on the submitted dissolution data from the fresh biolot and based on Guidance for Industry recommendations. However, the firm is informed that the revised specification was not based on stability data submitted in the amendment.

The application is **complete (adequate)**.

2 TABLE OF CONTENTS

3 BACKGROUND

There are four (4) Division of Bioequivalence (DBE) reviews for this application which are located in DARRTS. These reviews are as follows:

1. First Generic Checklist: KITCHENS, KELLY M 04/28/2009 N/A 04/28/2009 FRM-ADMIN-44(DBE Review Request) Original-1 Archive. The submission was found acceptable for filing.

2-3. Two 'dissolution only' reviews: PALAMAKULA, ANITHA 06/25/2009 N/A 06/25/2009 REV-BIOEQ-02(Dissolution Review) Original-1 Archive and PALAMAKULA, ANITHA 09/03/2009 N/A 09/03/2009 REV-BIOEQ-02(Dissolution Review) Original-1 Archive. Per the second 'dissolution only' review, the firm was asked to acknowledge dissolution method and specification.

4. The "full ANDA" review: DEHAVEN, WAYNE I 02/14/2011 N/A 02/14/2011 REV-BIOEQ-01(General Review) Original-1 Archive. The reviewer's calculated confidence intervals (CI) for AUC0-t, AUC∞ and Cmax were within 80.0% - 125.0% for the fasted and fed BE studies. However, the application was considered incomplete (inadequate) due to the following minor deficiencies (summarized):

1. Acknowledge for future submissions that a more appropriate concentration range should be validated to avoid re-assays for above limit of quantitation (ALQ);
2. Clarify the dose used in the fed bioequivalence study; and
3. Submit raw data supporting repeat analysis of samples for high/low internal standard responses.

5. The Amendment review: DEHAVEN, WAYNE I 03/24/2011 N/A 03/24/2011 REV-BIOEQ-01(General Review) Original-1 Archive. The firm responded adequately to the aforementioned deficiencies.

In the amendment dated March 4, 2011, Tris Pharma submitted additional information with regard to the dissolution specifications. Specifically, Tris Pharma requested the DBE revisit the 1 hour specification of *NMT* (b)(4)*%*. Tris Pharma is recommending a 1 hour specification of *NMT* (b)(4)*%*. To support their claim, the firm submitted additional stability testing (i.e. dissolution testing results taken every 3 months up to 2 years) on the bio-lot #TB-023A, as well as 0 month testing on a second lot (TB-081A).

These data were overlooked in the previous DBE review mentioned above (#5). This addendum addresses the firms request to change the 1 hour specification from *NMT* (b)(4)*%* to *NMT* (b)(4)*%*.

4 SUBMISSION SUMMARY

A. Drug Product Information, PK/PD Information, and Relevant DBE History

Please see in DARRTS for ANDA #091135 DEHAVEN, WAYNE I 02/14/2011 N/A 02/14/2011 REV-BIOEQ-01(General Review) Original-1 Archive.

B. Contents of Submission

Study Types	Yes/No?	How many?
Amendment	Yes	1 (March 4, 2011)

C. Review of Submission

Addition Information Submitted by the Firm:

The following specifications were provided by OGD bioequivalence group and Tris accepted in sequence 0006. However, at this time *Tris would like to revisit the 1-hour specification upon review of additional stability data or original test batch and one additional test batch scale.*

Unlike conventional dosage form including extended release solid dosages, liquid sustained release dosage forms are complex in nature. (b) (4) These products involve use of (b) (4)

To support the revised specification request, Tris is providing all current available room temperature stability data reporting *average and range* from the original test batch.

TB-023A (Test Batch) – (b) (4) [Production size batch = (b) (4)]								
Time	**Condition**	**Dissolution (% Release)**						
		1-hr		**3-hr**		**6-hr**		**12-hr**
FDA Interim Specifications		**NMT (b) (4) %**		(b) (4)		(b) (4)		**NLT (b) (4) %**
Initial	Ambient	**30**	(b) (4)	57	(b) (4)	73	(b) (4)	86 (b) (4)
3-mo	25°C/60%RH	**33**	(b) (4)	61	(b) (4)	77	(b) (4)	88 (b) (4)
6-mo	25°C/60%RH	**34**	(b) (4)	66	(b) (4)	81	(b) (4)	91 (b) (4)
9-mo	25°C/60%RH	**33**	(b) (4)	64	(b) (4)	80	(b) (4)	91 (b) (4)
12-mo	25°C/60%RH	**34**	(b) (4)	65	(b) (4)	80	(b) (4)	90 (b) (4)

18-mo	25°C/60%RH	**34**	(b) (4)	65	(b) (4)	81	(b) (4)	90	(b) (4)
24-mo	25°C/60%RH	**35**	(b) (4)	61	(b) (4)	72	(b) (4)	83	(b) (4)

To further support the revised specification request, Tris is providing the initial release data from the additional test batch scale that was recently manufactured prior to full scale batch trials.

TB-081A (Test Batch) – (b) (4) **[Production size batch =** (b) (4) **]**							
Time	**Condition**	**Dissolution (% Release)**					
		1-hr		**3-hr**		**6-hr**	**12-hr**
FDA Interim		**NMT (b) (4) %**		(b) (4) **%**		(b) (4) **%**	**NLT (b) (4) %**
Initial	Ambient	**31**	(b) (4)	56	(b) (4)	72	(b) (4)	85	(b) (4)

Based on data provided and considering the inherent natures of the product, the following revised specifications are proposed:

Time	Current Specification	Proposed New Specification
1-hr	**NMT (b) (4) %**	**NMT (b) (4) %**
3-hr	(b) (4) %	(b) (4) %
6-hr	(b) (4) %	(b) (4) %
12-hr	NLT (b) (4) %	NLT (b) (4) %

Reviewer's comments: Tris Pharma Inc has requested that we change the 1 hour specification from NMT (b) (4) % to NMT (b) (4) % dissolved in 1 hour. In support of this request, Tris Pharma submitted stability testing results from the bio-lot (#TB-023A) as well as an additional lot (#TB-081A) (submitted in the March 4th amendment). The DBE only looks at the initial (ambient) results when setting the specification (i.e. the stability results from 3 months to 24 months are not used). Based on the submitted data, the bio-lot meets the NMT (b) (4) % in 1 hour specification at the L1 level (range = (b) (4)), while the additional lot (#TB-081A) does not meet at the L1 level (range = (b) (4)).

As stated on page 17 of the *"Guidance for Industry for Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations"* the dissolution specification is set from the fresh biolot (not on the dissolution of the stored biolot) by adding ± 10% to the mean % dissolution. Since for the first time point (1 hr) of the test drug product the mean % dissolution of the biolot TB-023A is (b) (4) %, the DBE considers (b) (4) % to (b) (4) % or NMT (b) (4) % as the appropriate specification. Our earlier specification NMT (b) (4) % is overly strict and is not keeping with the guidance. The DBE therefore accepts the firm's request to modify the 1 hour specification of its test product from *NMT (b) (4) %* to *NMT (b) (4) %* based on the submitted dissolution data from the fresh biolot and based on Guidance for Industry recommendations. The firm will be informed that the revised specification was not based on stability data submitted in the amendment.

5 DEFICIENCY COMMENTS

None

6 RECOMMENDATIONS

1. The Division of Bioequivalence (DBE) finds the fasting bioequivalence (BE) study # S08-0445 **complete (adequate)** at this time. Tris Pharma Inc conducted the fasting BE study on its Dextromethorphan Polistirex Extended Release Oral Suspension, EQ. 30 mg dextromethorphan hydrobromide per 5 mL (lot # TB-0023A), comparing it to the corresponding reference product, DELSYM® ER Suspension, EQ 30 mg dextromethorphan hydrobromide per 5 mL (lot # 39469), manufactured by Reckitt Benckiser.

2. The DBE finds the fed BE study # S08-0445 **complete (adequate)** at this time. Tris Pharma Inc conducted the fed BE study on its Dextromethorphan Polistirex Extended Release Oral Suspension, EQ. 30 mg dextromethorphan hydrobromide per 5 mL (lot # TB-0023A), comparing it to the corresponding reference product, DELSYM® ER Suspension, EQ 30 mg dextromethorphan hydrobromide per 5 mL (lot # 39469), manufactured by Reckitt Benckiser.

3. The firm's *in vitro* dissolution testing is **complete (adequate)**. The dissolution testing should be conducted in 500 mL of 0.1 N HCl with addition of 400 mL of Phosphate Buffer after 1 hr sample at 37ºC + 0.5ºC using USP apparatus II (Paddle) at 50 rpm. The test product should meet the following specification(s):

1 hr: NMT (b)(4)%
3 hrs: (b)(4)%
6 hrs: (b)(4)%
12 hrs: NLT (b)(4)%.

The firm should be informed of the above recommendations.

7 COMMENTS FOR OTHER OGD DISCIPLINES

Discipline	Comment
N/A	--

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 091135

APPLICANT: Tris Pharma, Inc.

DRUG PRODUCT: Dextromethorphan Polistirex Extended Release Oral Suspension, EQ. 30 mg Dextromethorphan Hydrobromide per 5 mL

The Division of Bioequivalence (DBE) has completed its review of the "additional information" section from your amendment dated March 4, 2011. In this section, you requested that the Agency change the 1 hour dissolution specification from *NMT* (b)(4)% to *NMT* (b)(4)% dissolved in 1 hour. In support of this request, you submitted stability testing results from the biobatch (#TB-023A) as well as an additional lot (#TB-081A).

Your proposed dissolution specifications based on stability data are not acceptable. Since FDA-recommended dissolution specification is determined based on the data of the freshly manufactured biobatch, which underwent acceptable bioequivalence testing, and not on the aged batches, the rationale used for justifying your proposed dissolution specifications are not acceptable.

However, the DBE has re-evaluated the previously recommended 1 hour specification of *NMT* (b)(4)% and considered it too restrictive with respect to the mean and range of the data at this time point. Therefore, the DBE has revised the recommended specification of *NMT* (b)(4)% to *NMT* (b)(4)% in 1 hour. It is important to emphasize that the revised dissolution specification is based on the original dissolution testing results submitted for the freshly manufactured biobatch, and not on stability data of aged batches.

The DBE acknowledges that you will continue to conduct dissolution testing in 500 mL of 0.1 N HCl at 37°C + 0.5°C, with addition of 400 mL of Phosphate Buffer, at 37°C + 0.5°C, 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:	(b)(4)%
12 hrs:	NLT (b)(4)%

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

8 OUTCOME PAGE

ANDA: 091135

COMPLETED ASSIGNMENT FOR 91135 ID: 14613

Reviewer: DeHaven, Wayne **Date Completed:**

Verifier: **Date Verified:**

Division: Division of Bioequivalence

Description: Dextromethorphan Polistirex Extended Release Oral Suspension; EQ. 30 mg dextromethorphan hydrobromide per 5 mL

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
14613	3/4/2011	Other	Addendum	0	0
				Bean Total:	0

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

/s/

WAYNE I DEHAVEN
07/27/2011

SHRINIWAS G NERURKAR
07/28/2011

HOAINHON N CARAMENICO on behalf of DALE P CONNER
07/28/2011

DIVISION OF BIOEQUIVALENCE AMENDMENT REVIEW

ANDA No.	091135		
Drug Product Name	Dextromethorphan Polistirex Extended Release Oral Suspension		
Strength(s)	EQ. 30 mg dextromethorphan hydrobromide per 5 mL		
Applicant Name	Tris Pharma, Inc.		
Address	2033 Route 130 Monmouth Junction, NJ 08852		
Applicant's Point of Contact	W. Scott Groner, Director RA and Compliance		
Contact's Telephone Number	732-940-0358		
Contact's Fax Number	732-940-0374		
Original Submission Date(s)	January 9, 2009 September 25, 2009 (Dissolution Acknowledgement) October 9, 2009 (Stability Amendment)		
Submission Date of Amendment Under Review	March 4, 2011		
Reviewer	Wayne DeHaven, Ph.D.		
Study Number (s)	S08-0445	S08-0446	
Study Type (s)	FASTED	FED	
Strength (s)	60 mg dose (10 mL)	60 mg dose (10 mL)	
Clinical Site	Cetero Research		
Clinical Site Address	400 Fountain Lakes Blvd. St. Charles, MO 63301 (314) 419-6592		
Analytical Site	(b) (4)		
Analytical Site Address			
Overall Review Result	**ADEQUATE**		
DSI Report Result	**ADEQUATE****		
BE Study Tracking/Supporting Document #	**Study/Test Type**	**Strength**	**Review Result**
1	Dissolution	eq. 30 mg / 5 mL	**ADEQUATE**
1	Fasting Study	eq. 30 mg / 5 mL	**ADEQUATE**
1	Fed Study	eq. 30 mg / 5 mL	**ADEQUATE**

(b) (4)

AMENDMENT REVIEW

1 EXECUTIVE SUMMARY

This is a review of a bioequivalence amendment for ANDA #091135, Dextromethorphan Polistirex Extended Release Oral Suspension, EQ 30 mg dextromethorphan hydrobromide per 5 mL, submitted by Tris Pharma, Inc. This is an over-the-counter (OTC) product. The firm submitted the amendment in response to a three item deficiency letter they received from the DBE on February 16, 2011. In brief, the items were: (1) acknowledge that a more appropriate concentration range should be validated to avoid re-assays for above limit of quantitation (ALQ); (2) clarify the dose used in the fed bioequivalence study; and (3) submit raw data supporting repeat analysis of samples for high/low internal standard responses.

Tris Pharma responded adequately to the aforementioned deficiencies. There are no Division of Scientific Investigations (DSI) inspections which are pending or necessary. The application is now considered **acceptable (adequate)**. The firm should be informed of this recommendation.

2 TABLE OF CONTENTS

3 BACKGROUND

There are four (4) Division of Bioequivalence (DBE) reviews for this application which are located in DARRTS. These reviews are as follows:

1. First Generic Checklist: KITCHENS, KELLY M 04/28/2009 N/A 04/28/2009 FRM-ADMIN-44(DBE Review Request) Original-1 Archive. The submission was found acceptable for filing.

2-3. Two 'dissolution only' reviews: PALAMAKULA, ANITHA 06/25/2009 N/A 06/25/2009 REV-BIOEQ-02(Dissolution Review) Original-1 Archive and PALAMAKULA, ANITHA 09/03/2009 N/A 09/03/2009 REV-BIOEQ-02(Dissolution Review) Original-1 Archive. Per the second 'dissolution only' review, the firm was asked to acknowledge dissolution method and specification.

4. The "full ANDA" review: DEHAVEN, WAYNE I 02/14/2011 N/A 02/14/2011 REV-BIOEQ-01(General Review) Original-1 Archive. The reviewer's calculated confidence intervals (CI) for AUC0-t, AUC∞ and Cmax were within 80.0% - 125.0% for the fasted and fed BE studies. However, the application was considered incomplete (inadequate) due to the following minor deficiencies (summarized):

1. Acknowledge for future submissions that a more appropriate concentration range should be validated to avoid re-assays for above limit of quantitation (ALQ);
2. Clarify the dose used in the fed bioequivalence study; and
3. Submit raw data supporting repeat analysis of samples for high/low internal standard responses.

The current amendment under review is in response to these deficiencies listed above. The DBE review of Tris Pharma's responses to these deficiencies can be found in Section 4C 'Review of Submission' below.

4 SUBMISSION SUMMARY

A. Drug Product Information, PK/PD Information, and Relevant DBE History

Please see in DARRTS for ANDA #091135 DEHAVEN, WAYNE I 02/14/2011 N/A 02/14/2011 REV-BIOEQ-01(General Review) Original-1 Archive.

B. Contents of Submission

Study Types	Yes/No?	How many?
Amendment	Yes	1

C. Review of Submission

Deficiency 1: Please acknowledge for future submissions that a more appropriate standard curve (SC) and quality control (QC) concentration range should be validated, which fully encompasses the expected plasma concentration ranges for all subjects. Specifically, the Agency recommends you avoid situations in which many subject samples have to be re-assayed due to initial measurements determined as being 'above the limit of quantitation (ALOQ)', which was the case for the fasting study #S08-0445.

Response 1: *It is acknowledged that for the fasting study #S08-0445 the initial sample analysis determined that 322 of 2033, 16.3%, subject samples had values above the upper limit of quantitation. For related future studies a more appropriate calibration range with associated quality controls will be validated to better accommodate higher anticipated subject sample concentrations.*

Reviewer's Comments: The firm's response is **adequate**.

Deficiency 2: It was not fully clear whether the fed study #S08-0446 was carried out using a dose of 60 mg (like the fasted study), or a dose of 30 mg as recommended in the draft individual bioequivalence recommendation guidance for the drug product. In the fed study report (page 2 of 547) it lists the dose as 30 mg; however, in the *in vivo* BE summary table, it lists 60 mg as the dose administered. Please clarify which dose was used for the fed bioequivalence (BE) study.

Response 2: *Tris reviewed the fed study report #S08-0446 and would like to clarify that the dose used was 10 mL of the 30mg/5mL strength product, which is equivalent to 60 mg dose, for the fed study.*

Reviewer's Comments: The firm's response is **adequate**.

Deficiency 3: With regard to the repeat analyses, please submit the following additional information:

a. Please submit all appropriate raw data (for fasting and fed BE studies) supporting repeat analysis of samples for high/low internal standard responses (HIS/LIS). These repeats should meet the objective criterion established in the SOP (b) (4), page 8 of 19, which says that results are flagged for repeat when there is a deviation by more than 40% of the mean IS for the entire batch run.

Response 3(a): *Tris has provided in this submission all the appropriate raw data (for fasting and fed BE studies) supporting repeat analysis of the samples for high/low internal standard responses (HIS/LIS). Refer Module 5.3.1.4 for R08-1046 and Module 5.3.1.4 for R09-1047. The following tables lists the samples provided:*

Dextromethorphan #R08-1046			
Subject	**Period**	**Time**	**Reason for Reassay**
2	1	4.5, 10, 36	LIS
2	2	5	LIS
11	1	4	LIS
15	1	4	HIS
20	1	10	LIS
22	2	6.5	LIS
26	1	4.5	LIS
28	1	2	HIS
28	2	2	HIS
32	1	5	LIS
40	2	16	LIS
48	1	16	LIS
48	2	6.5	LIS
57	1	7	LIS
58	2	24	HIS
61	1	16	LIS

Dextrorphan #R08-1046			
Subject	**Period**	**Time**	**Reason for Reassay**
9	1	48, 72	HIS
15	1	16.5, 12	LIS
48	2	6.5	LIS
61	1	8	HIS
61	2	12	HIS
62	1	2	LIS
62	2	4	LIS
63	1	0, 3, 4.5	LIS
63	2	6.5	LIS

Dextromethorphan #R08-1047			
Subject	**Period**	**Time**	**Reason for Reassay**
1	2	12	HIS
11	1	1	HIS
19	1, 2	6	LIS
22	1	0	LIS
22	2	4	HIS
25	2	16	LIS
34	4	4.5	LIS
35	2	0	LIS
37	2	72	HIS

Dextrorphan #R08-1047			
Subject	**Period**	**Time**	**Reason for Reassay**
12	1	16, 24	HIS
13	1	1, 5.5	HIS
13	2	5.5	HIS
34	1	4.5	LIS
35	2	0	LIS
37	2	4	HIS

Reviewer's Comments: The reviewer checked the internal standard (IS) data that was submitted by Tris Pharma in this amendment (Module 5.3.1.4 for R08-1046 and Module 5.3.1.4 for R09-1047). These repeats met the objective criterion established in the SOP (b) (4), page 8 of 19, which says that results are flagged for repeat when there is a deviation by more than 40% of the mean IS for the entire batch run. For instance, the subject #28 2 hour time-points for both period I and II were originally flagged for high internal standard (HIS). The reviewer determined the mean IS for this run as 18908.54. The range (b) (4) is therefore (b) (4) The subject #28 IS values were 28263.1 and 26798.0 for period I and period II, respectively, and clearly greater than 40% larger than the mean IS for this run. Similar results were validated for LIS examples. The firm's response is **adequate**.

b. Please submit the analytical procedure document defining the reason for the "sample processing error" for subject #41, hour 5.5 sample, per SOP (b) (4): Sample Reanalysis and Reporting Criteria.

Response 3(b): *The analytical procedure for Run 08104721 is provided in this submission, which documents the reason for the "sample processing error" for subject 41, hour 5.5. Refer Module 5.3.1.4 page 21 of 24 for the note describing the event.*

Reviewer's Comments: The reviewer checked the analytical procedure document for run 0810472 (page 21). The report indicated that the analyst mistakenly added excess IS to the sample. Therefore, the analyst flagged this sample for repeat. The reviewer finds the firm's response to this deficiency as **acceptable (adequate)**. There are no further questions.

5 DEFICIENCY COMMENTS

None

6 RECOMMENDATIONS

1. The Division of Bioequivalence (DBE) finds the fasting bioequivalence (BE) study # S08-0445 **complete (adequate)** at this time. Tris Pharma Inc conducted the fasting BE study on its Dextromethorphan Polistirex Extended Release Oral Suspension, EQ. 30 mg dextromethorphan hydrobromide per 5 mL (lot # TB-0023A), comparing it to the corresponding reference product, DELSYM® ER Suspension, EQ 30 mg dextromethorphan hydrobromide per 5 mL (lot # 39469), manufactured by Reckitt Benckiser.

2. The DBE finds the fed BE study # S08-0445 **complete (adequate)** at this time. Tris Pharma Inc conducted the fed BE study on its Dextromethorphan Polistirex Extended Release Oral Suspension, EQ. 30 mg dextromethorphan hydrobromide per 5 mL (lot # TB-0023A), comparing it to the corresponding reference product, DELSYM® ER Suspension, EQ 30 mg dextromethorphan hydrobromide per 5 mL (lot # 39469), manufactured by Reckitt Benckiser.

3. The firm's *in vitro* dissolution testing is **acceptable (adequate)**. The dissolution testing should be conducted in 500 mL of 0.1 N HCl with addition of 400 mL of Phosphate Buffer after 1 hr sample at 37ºC + 0.5ºC using USP apparatus II (Paddle) at 50 rpm. The test product should meet the following specification(s):

1 hr: NMT (b)(4)%
3 hrs: (b)(4)%
6 hrs: (b)(4)%
12 hrs: NLT (b)(4)%.

The firm should be informed of the above recommendations.

7 COMMENTS FOR OTHER OGD DISCIPLINES

Discipline	Comment
N/A	--

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 091135

APPLICANT: Tris Pharma, Inc.

DRUG PRODUCT: Dextromethorphan Polistirex Extended Release Oral Suspension, EQ. 30 mg Dextromethorphan Hydrobromide per 5 mL

The Division of Bioequivalence (DBE) has completed its review of your amendment submission dated March 4, 2011, and there are no further questions at this time.

We acknowledge you will conduct dissolution testing for your test product as follows:

The dissolution testing should be conducted in 500 mL of 0.1 N HCl at 37°C + 0.5°C, with addition of 400 mL of Phosphate Buffer, at 37°C + 0.5°C, 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: (b) (4) %
12 hrs: NLT (b) (4) %

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews 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}

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

8 OUTCOME PAGE

ANDA: 091135

Reviewer: DeHaven, Wayne

Date Completed:

Verifier:

Date Verified:

Division: Division of Bioequivalence

Description: Dextromethorphan Polistirex Extended Release Oral Suspension; EQ. 30 mg dextromethorphan hydrobromide per 5 mL

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
13524	3/4/2011	Other	Study Amendment	0	0
				Bean Total:	0

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

/s/

WAYNE I DEHAVEN
03/23/2011

SHRINIWAS G NERURKAR
03/23/2011

HOAINHON N CARAMENICO on behalf of DALE P CONNER
03/24/2011

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	091135	
Drug Product Name	Dextromethorphan Polistirex Extended Release Oral Suspension	
Strength(s)	EQ. 30 mg dextromethorphan hydrobromide per 5 mL	
Applicant Name	Tris Pharma, Inc.	
Address	2033 Route 130 Monmouth Junction, NJ 08852	
Applicant's Point of Contact	W. Scott Groner, Director RA and Compliance	
Contact's Telephone Number	732-940-0358	
Contact's Fax Number	732-940-0374	
Original Submission Date(s)	January 9, 2009	
Submission Dates of Amendments Under Review	September 25, 2009 (Dissolution Acknowledgement) October 9, 2009 (Stability Amendment)	
Reviewer	Wayne DeHaven, Ph.D.	
Study Number (s)	S08-0445	S08-0446
Study Type (s)	FASTED	FED
Strength (s)	60 mg dose (10 mL)	60 mg dose (10 mL)
Clinical Site	Cetero Research	
Clinical Site Address	400 Fountain Lakes Blvd. St. Charles, MO 63301 (314) 419-6592	
Analytical Site	(b) (4)	
Analytical Site Address		

Overall Review Result	**INADEQUATE**		
DSI Report Result	**ADEQUATE****		
BE Study Tracking/Supporting Document #	**Study/Test Type**	**Strength**	**Review Result**
1	Dissolution	eq. 30 mg / 5 mL	**ADEQUATE**
1	Fasting Study	eq. 30 mg / 5 mL	**INADEQUATE**
1	Fed Study	eq. 30 mg / 5 mL	**INADEQUATE**

(b) (4)

1 EXECUTIVE SUMMARY

This application contains the results of fasting and fed bioequivalence (BE) studies comparing a test product, Tris Pharma's Dextromethorphan Polistirex Extended Release (ER) Suspension, EQ. 30 mg dextromethorphan hydrobromide per 5 mL, to the corresponding reference product, DELSYM® ER Suspension, EQ 30 mg dextromethorphan hydrobromide per 5 mL, manufactured by Reckitt Benckiser. 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 subjects. The fasted study was carried out on two groups, while the fed study was conducted on a single group. The TRT*GRP parameter for the fasted study was not significant for AUC0-t, AUC∞ or Cmax, and was therefore dropped from the final analysis. The reviewer's calculated confidence intervals (CI) for AUC_{0-t}, AUC_{∞} and Cmax were within 80.0% - 125.0% for the fasted and fed BE studies. However, the application is **incomplete (inadequate)** at this time due to deficiencies listed in Section 3.10 of this review. The reviewer's calculated results of the BE studies are summarized in the tables below.

FASTED – Dextromethorphan (TRT*GRP dropped):

Dextromethorphan Polistirex 30 mg / 5 mL (2 x 30 mg / 5 mL) Fasted Bioequivalence Study (S08-0445) N=53					
	Least Squares Geometric Mean		Ratio	90% Confidence Intervals	
Parameter	Test	Reference	(T/R)	Lower	Upper
AUC0-t (hr *pg/ml)	47984.97	46415.72	1.03	97.43	109.69
AUC∞ (hr *pg/ml)	33050.42	31466.96	1.05	98.28	112.24
Cmax (pg/ml)	2904.86	2929.23	0.99	93.33	105.38

FED - Dextromethorphan:

Dextromethorphan Polistirex 30 mg / 5 mL (1 x 30 mg / 5 mL) Fed Bioequivalence Study (S08-0446) N=37					
	Least Squares Geometric Mean		Ratio	90% Confidence Intervals	
Parameter	Test	Reference	(T/R)	Lower	Upper
AUC0-t (hr *pg/ml)	33667.37	37341.94	0.90	82.15	98.95
AUC∞ (hr *pg/ml)	32574.28	36001.18	0.90	82.21	99.58
Cmax (pg/ml)	2018.75	2259.84	0.89	81.42	98.01

[1] http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=018658&TABLE1=OB_OTC

In the BE studies, the pharmacokinetic (PK) parameters of the test and reference for the active metabolite, dextrorphan, were comparable. Therefore the metabolite data are supportive.

There are two (2) 'dissolution only' reviews which can be found in DARRTS [please see for ANDA # 091135 PALAMAKULA, ANITHA 06/25/2009 N/A 06/25/2009 REV-BIOEQ-02(Dissolution Review) Original-1 Archive *and* PALAMAKULA, ANITHA 09/03/2009 N/A 09/03/2009 REV-BIOEQ-02(Dissolution Review) Original-1 Archive]. The firm has conducted acceptable comparative dissolution testing using an 'in-house' dissolution method. On September 25, 2009, the firm has acknowledged the following dissolution method and specifications: 500 mL of 0.1 N HCl with addition of 400 mL of Phosphate Buffer after 1 hr at 37°C, using USP Apparatus II (Paddle) at 50 rpm. Specifications = 1 hr: NMT (b) (4)%, 3 hrs: (b) (4)%, 6 hrs: (b) (4)% and 12 hrs: NLT (b) (4)%.

No Division of Scientific Investigations (DSI) inspection is pending or necessary. Clinical site: last routine inspection was completed on 5/5/2010, NAI, base on NDA 022439. Analytical site: last routine inspection completed on (b) (4), based on (b) (4) After reviewing the (b) (4) results of the analytical site inspection for NDA 022503 [see in DARRTS for NDA # 022503 RIVERA-LOPEZ, CAROL M (b) (4) N/A (b) (4) CONSULT REV-DSI-05(Bioequivalence Establishment Inspection Report Review) Original-1 (Type 3- New Dosage Form) Archive], the reviewer concludes that the (b) (4) form 483 deficiencies do not significantly affect these current BE studies under review here.[2]

The application is **incomplete (inadequate)** at this time.

(b) (4)

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Product	Dextromethorphan Polistirex ER Oral Suspension, EQ 30 mg dextromethorphan hydrobromide per 5 mL
Reference Product[3]	DELSYM® ER Suspension, EQ 30 mg dextromethorphan hydrobromide per 5 mL**
RLD Manufacturer	Reckitt Benckiser
NDA No.	018658
RLD Approval Date	October 8, 1982
Indication[2]	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[4,5]

Bioavailability	Dextromethorphan is well absorbed from the gastrointestinal tract.
Food Effect	May be taken with or without food.
Tmax	Approximately 5-6 hours
Metabolism	Dextromethorphan 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, and antitussive activity can last for 5—6 hours.
Drug Specific Issues (if any)	NOTE: On May 20, 2005, the FDA made a public announcement regarding dextromethorphan (DXM) and new trends in the abuse of this drug. The ingestion of pure dextromethorphan in powdered form and in excessive dose can cause death as well as other serious adverse events such as brain damage, seizure, loss of consciousness, and irregular heart beat. Although the reported abuse of dextromethorphan is not new, dextromethorphan is increasingly offered for sale in pure powdered form from questionable sources (e.g., unsanctioned pharmacy websites) and street dealers, and health care professionals should be alert to these new trends. When ingested at recommended dosage levels for intended purposes, dextromethorphan is generally regarded as a safe and effective cough suppressant.

[3] http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=018658&TABLE1=OB_OTC
[4] http://dailymed.nlm.nih.gov/dailymed/search.cfm?startswith=delsym
[5] http://www.clinicalpharmacology-ip.com/Forms/search.aspx?s=delsym

	NOTE: In January 2007, the CDC warned caregivers and healthcare providers of the risk for serious injury or fatal overdose from the administration of cough and cold products to children and infants less than 2 years of age.[33534] This warning followed an investigation of the deaths of three (3) infants less than 6 months of age that were attributed to the inadvertent inappropriate use of these products. The symptoms preceding these deaths have not been clearly defined, and there is a lack of conclusive data describing the exact cause of death. The report estimated that 1519 children less than 2 years of age were treated in emergency departments during 2004—2005 for adverse events related to cough and cold medications. In October 2007, the FDA Nonprescription Drug Advisory Committee and the Pediatric Advisory Committee recommended that nonprescription cough and cold products containing pseudoephedrine, dextromethorphan, chlorpheniramine, diphenhydramine, brompheniramine, phenylephrine, clemastine, or guaifenesin not be used in children less than 6 years of age. In January 2008, the FDA issued a Public Health Advisory recommending that OTC cough and cold products not be used in infants and children less than 2 years. An official ruling regarding the use of these products in children greater than 2 years has not yet been announced. The FDA recommends that if parents and caregivers use cough and cold products in children greater than 2 years, labels should be read carefully, caution should be used when administering multiple products, and only measuring devices specifically designed for use with medications should be used. While some combination cough/cold products containing these ingredients are available by prescription only and are not necessarily under scrutiny by the FDA, clinicians should thoroughly assess each patient's use of similar products, both prescription and nonprescription, to avoid duplication of therapy and the potential for inadvertent overdose.

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	2, fasting and fed

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:	

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:	

** Please note that the fasted study dosed the subjects at 60 mg (i.e. 10 mL) for the fasted BE study, and apparently 30 mg (i.e. 5 mL) for the fed BE study. However, because there were several places in which it was not clear what the dose was in the fed study, the firm will be asked to clarify.

<table>
<tr><td>Analytes to measure:</td><td>Dextromethorphan and its active metabolite Dextrorphan in plasma</td></tr>
<tr><td>Bioequivalence based on:</td><td>90% CI of Dextromethorphan</td></tr>
<tr><td>Waiver request of in-vivo testing:</td><td>N/A</td></tr>
<tr><td>Source of most recent recommendations:</td><td>There is a finalized Guidance on Dextromethorphan Polistirex posted on the external database (Finalized May 2008).[6]</td></tr>
<tr><td>Summary of OGD or DBE History:</td><td>The following applications were found in DARRTS that reference DELSYM®:
<table>
<tr><th>ANDA #</th><th>Firm</th><th>Current Status</th><th>Status Date</th></tr>
<tr><td>91135</td><td>TRIS PHARMA</td><td>Pending</td><td>6/15/2009</td></tr>
<tr><td colspan="4">(b) (4)</td></tr>
</table>
Highlighted yellow is the current application.

The following are controlled correspondences with regard to Dextromethorphan Polistirex:
<table>
<tr><th>Ctl No</th><th>Status</th><th>Doc Date</th><th>From</th></tr>
<tr><td><>00-381</td><td>Closed</td><td>9/13/2000</td><td>(b) (4)</td></tr>
<tr><td><>04-204</td><td>Closed</td><td>2/25/2004</td><td></td></tr>
<tr><td><>04-700</td><td>Closed</td><td>7/15/2004</td><td></td></tr>
<tr><td><>05-0055</td><td>Closed</td><td>1/7/2005</td><td></td></tr>
<tr><td><>05-0093</td><td>Closed</td><td>1/27/2005</td><td></td></tr>
<tr><td><>05-0143</td><td>Closed</td><td>1/27/2005</td><td></td></tr>
<tr><td><>06-1455</td><td>Closed</td><td>9/26/2006</td><td></td></tr>
<tr><td><>09-0563</td><td>Closed</td><td>10/12/2009</td><td></td></tr>
</table>
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3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	Yes	1
Steady-state	No	-
In vitro dissolution	Yes	1
Waiver requests	No	-
BCS Waivers	No	-
Clinical Endpoints	No	-
Failed Studies	No	-
Amendments	Yes	2

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

3.5 Pre-Study Bioanalytical Method Validation

Dextromethorphan:

Information Requested	Data
Bioanalytical method validation report location	Module 5.3.1.4
Analyte	Dextromethorphan
Internal standard (IS)	(b) (4)
Method description	Liquid/liquid extraction
Limit of quantitation	10.0 pg/mL
Average recovery of drug (%)	58.27%
Average recovery of IS (%)	47.06%
Standard curve concentrations (pg/mL)	10.0, 20.0, 40.0, 100, 200, 500, 1000, 5000, 8500, 10000
QC concentrations (pg/mL)	10.0, 30.0, 750, 4500, 8000
QC Intraday precision range (%)	1.11% – 12.90%
QC Intraday accuracy range (%)	93.85% – 105.83%
QC Interday precision range (%)	3.09% – 8.21%
QC Interday accuracy range (%)	96.42% –101.81%
Bench-top stability (hrs)	23:41 hours–minutes
Stock stability (hrs)	1438:58 hours–minutes @ 4ºC 1438:58 hours–minutes @ room temperature
Processed stability (hrs)	95:44 hours–minutes @ 4ºC
Freeze-thaw stability (cycles)	6 cycles
Long-term storage stability (days)	292 days @ -70ºC
Dilution integrity	50000 pg/mL and 8000 pg/mL diluted 1:9
Selectivity	No interfering peaks noted in blank plasma samples in fourteen out of twenty-four lots

Dextrorphan:

Information Requested	Data
Bioanalytical method validation report location	Module 5.3.1.4
Analyte	Dextrorphan
Internal standard (IS)	(b) (4)
Method description	Liquid/liquid extraction
Limit of quantitation	10.0 pg/mL
Average recovery of drug (%)	57.80%
Average recovery of IS (%)	45.88%
Standard curve concentrations (pg/mL)	10.0, 20.0, 40.0, 100, 200, 500, 1000, 5000, 8500, 10000
QC concentrations (pg/mL)	10.0, 30.0, 750, 4500, 8000
QC Intraday precision range (%)	0.92% – 7.07%
QC Intraday accuracy range (%)	85.67% – 107.05%
QC Interday precision range (%)	2.48% – 11.89%
QC Interday accuracy range (%)	97.22% – 101.23%
Bench-top stability (hrs)	23:41 hours–minutes
Stock stability (days)	1439:14 hours–minutes @ 4ºC

	1439:14 hours–minutes @ room temperature
Processed stability (hrs)	95:44 hours–minutes @ 4°C
Freeze-thaw stability (cycles)	6 cycles
Long-term storage stability (days)	292 days @ -70°C
Dilution integrity	50000 pg/mL and 8000 pg/mL diluted 1:9
Selectivity	No interfering peaks noted in blank plasma samples in twenty-one out of twenty-four lots

SOPs submitted	(b) (4) Assay Validation in Biological Fluids Sample Analysis (Chromatographic) Sample re-analysis and reporting Criteria Reproducibility of Incurred Samples
Bioanalytical method is acceptable	**ACCEPTABLE (ADEQUATE)**

Comments on the Pre-Study Method Validation:

The long term storage stability (LTSS) data supporting the storage of dextromethorphan and dextrorphan for 292 days @ -70°C exceeds the storage duration for both the fasted and fed BE studies (60 and 47 days, respectively).

K2-EDTA was used as anticoagulant in both the pre-study method validation, as well as during the fasted and fed BE studies.

The overall % recovered for dextromethorphan and dextrorphan were only 58.3% and 57.8%, respectively (dextromethorphan = 50.84%=LQC; 58.51%=MQC, 65.47%=HQC; dextrorphan = 48.53%=LQC; 60.66%=MQC, 64.22%=HQC). The reviewer notes that the area response at the LLOQ quality control concentration for both dextromethorphan and dextrorphan was precise, accurate, and reproducible. In addition, the low recovery did not influence the bioanalytical results of the 'full' BE studies. According to Guidance, "recovery need not be 100%, but the extent of recovery should be consistent, precise and reproducible." The low recovery of dextromethorphan and dextrorphan is acceptable.

The reviewer notes that there were a lot of subject samples in the 'full BE' studies which required repeat analysis due to initial measurements above the limit of quantitation (ALQ). The validation report supports measurement up to 12000 pg/mL diluted at 1:4. This apparently did not exceed all of the initial measurements made during the analysis of the fasting and fed BE studies. Therefore, there is a partial validation report supporting the measurement up to 50000 pg/mL diluted at 1:9. The reviewer accepts the partial validation. Nonetheless, the reviewer will ask the firm to acknowledge that for future submissions, a more appropriate standard curve and QC range should be validated, which fully encompasses the expected plasma concentration ranges for all subjects. In addition, specifically with regard to the fasting study, the firm should acknowledge that per the guidance, it is recommended that the study be carried out on subjects dosed with 30 mg, and not 60 mg.

The pre-study method validation is **acceptable (adequate)** at this time.

3.6 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[1] (No. (M/F) Type Age: mean (Range)	Mean Parameters (+/-SD)						Study Report Location
					Cmax (units/mL)	Tmax (hr)	AUC0-t (units)	AUC∞ (units)	T½ (hr)	Kel (hr-1)	
S08-0445	Single Dose, Two-Way Crossover Fasted BE Study of Dextromethorphan Polistirex ER Suspension 30 mg/5 mL in Healthy Volunteers	Randomized single-dose crossover	Dextromethorphan Polistirex ER Oral Suspension 60 mg Dose Oral [TB-023A]	53 (28/25) Healthy volunteers 29.4 yr (18 - 55 yr)	8910.05 (140.58)	6.00 (4.50 - 12.00)	267265.19 (233.45)	119511.47 (196.71)	12.45 (41.28)	0.0636 (33.55)	Module 5.3.1.2
			Delsym® Suspension 60 mg Dose Oral [39469]		9068.78 (141.76)	6.00 (3.00 - 8.00)	273451.72 (249.39)	121441.45 (266.52)	11.19 (37.05)	0.0689 (30.67)	
S08-0446	Single Dose, Two-Way Crossover Fed BE Study of Dextromethorphan Polistirex ER Suspension 30 mg/5 mL in Healthy Volunteers	Randomized single-dose crossover	Dextromethorphan Polistirex ER Oral Suspension 60 mg Dose Oral [TB-023A]	37 (20/17) Healthy volunteers 28.6 yr (18 - 50 yr)	3804.40 (151.69)	5.50 (2.00 - 12.02)	91031.93 (264.58)	56317.97 (134.41)	11.14 (34.72)	0.0679 (26.98)	Module 5.3.1.2
			Delsym® Suspension 60 mg Dose Oral [39469]		4219.79 (148.43)	6.00 (4.00 - 12.00)	106974.22 (282.67)	61904.16 (135.32)	9.94 (29.69)	0.0744 (23.10)	

Dextrorphan:

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects[1] (No. (M/F) Type Age: mean (Range)	Mean Parameters (+/-SD)						Study Report Location
					Cmax (units/mL)	Tmax (hr)	AUC0-t (units)	AUC∞ (units)	T½ (hr)	Kel (hr-1)	
S08-0445	Single Dose, Two-Way Crossover Fasted BE Study of Dextromethorphan Polistirex ER Suspension 30 mg/5 mL in Healthy Volunteers	Randomized single-dose crossover	Dextromethorphan Polistirex ER Oral Suspension 60 mg Dose Oral [TB-023A]	53 (28/25) Healthy volunteers 29.4 yr (18 - 55 yr)	3691.23 (49.25)	5.00 (2.00 - 8.00)	40628.40 (43.27)	43682.40 (40.42)	11.80 (61.57)	0.0771 (45.25)	Module 5.3.1.2
			Delsym® Suspension 60 mg Dose Oral [39469]		4018.34 (58.31)	5.00 (2.00 - 7.00)	40151.39 (45.61)	43511.47 (41.09)	10.24 (57.72)	0.0838 (39.58)	
S08-0446	Single Dose, Two-Way Crossover Fed BE Study of Dextromethorphan Polistirex ER Suspension 30 mg/5 mL in Healthy Volunteers	Randomized single-dose crossover	Dextromethorphan Polistirex ER Oral Suspension 60 mg Dose Oral [TB-023A]	37 (20/17) Healthy volunteers 28.6 yr (18 - 50 yr)	4071.22 (42.02)	5.00 (2.00 - 6.50)	45461.94 (47.65)	47087.48 (45.29)	8.99 (43.96)	0.0893 (33.89)	Module 5.3.1.2
			Delsym® Suspension 60 mg Dose Oral [39469]		4572.57 (52.47)	5.00 (2.00 - 12.00)	49916.68 (44.94)	51512.96 (42.17)	8.01 (41.72)	0.0989 (33.52)	

The reviewer highlighted the 60 mg dose for the fed study because, according to the clinical report, the actual dose was 30 mg for the fed study. In contrast, the fasting study was carried out on subjects dosed with 60 mg. The firm will be asked to clarify.

Table 2. Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer

FASTED – Dextromethorphan (TRT*GRP dropped):

Dextromethorphan Polistirex 30 mg / 5 mL (2 x 30 mg / 5 mL) Fasted Bioequivalence Study (S08-0445) N=53					
	Least Squares Geometric Mean		Ratio	90% Confidence Intervals	
Parameter	Test	Reference	(T/R)	Lower	Upper
AUC0-t (hr *pg/ml)	47984.97	46415.72	1.03	97.43	109.69
AUC∞ (hr *pg/ml)	33050.42	31466.96	1.05	98.28	112.24
Cmax (pg/ml)	2904.86	2929.23	0.99	93.33	105.38

FED - Dextromethorphan:

Dextromethorphan Polistirex 30 mg / 5 mL (1 x 30 mg / 5 mL) Fed Bioequivalence Study (S08-0446) N=37					
	Least Squares Geometric Mean		Ratio	90% Confidence Intervals	
Parameter	Test	Reference	(T/R)	Lower	Upper
AUC0-t (hr *pg/ml)	33667.37	37341.94	0.90	82.15	98.95
AUC∞ (hr *pg/ml)	32574.28	36001.18	0.90	82.21	99.58
Cmax (pg/ml)	2018.75	2259.84	0.89	81.42	98.01

In the BE studies, the pharmacokinetic (PK) parameters of the test and reference for the active metabolite, dextrorphan, were comparable. Therefore the metabolite data are supportive. The reviewer's calculated results for dextrorphan in the fasted and fed BE studies are summarized in the tables below:

FASTED (TRT*GRP dropped) - Dextrorphan:

Dextromethorphan Polistirex 30 mg / 5 mL (2 x 30 mg / 5 mL) Fasted Bioequivalence Study (S08-0445) N=53					
	Least Squares Geometric Mean		Ratio	90% Confidence Intervals	
Parameter	Test	Reference	(T/R)	Lower	Upper
AUC0-t (hr *pg/ml)	35259.36	34403.77	1.02	98.07	107.10
AUC∞ (hr *pg/ml)	39347.92	38498.42	1.02	97.31	107.35
Cmax (pg/ml)	2947.66	3084.91	0.96	90.34	101.07

FED - Dextrorphan:

Dextromethorphan Polistirex 30 mg / 5 mL (1 x 30 mg / 5 mL) Fed Bioequivalence Study (S08-0446) N=37					
	Least Squares Geometric Mean		Ratio	90% Confidence Intervals	
Parameter	Test	Reference	(T/R)	Lower	Upper
AUC0-t (hr *pg/ml)	40656.88	44956.62	0.90	86.39	94.67
AUC∞ (hr *pg/ml)	42917.70	47382.83	0.91	86.44	94.91
Cmax (pg/ml)	3596.29	3903.02	0.92	85.29	99.55

Table 3. Reanalysis of Study Samples

FASTED - Dextromethorphan:

S08-0445 Additional Information in Volume(s), Page(s)								
Reason for Reanalysis	Number of Samples Reanalyzed				Number of Recalculated Values Used After Reanalysis[5]			
	Actual Number		% of Total Assays		Actual Number		% of Total Assays	
	Test N=1018[2]	Reference N=1015[2]	Test N=1018[2]	Reference N=1015[2]	Test N=1018[2]	Reference N=1015[2]	Test N=1018[2]	Reference N=1015[2]
	n[3]	n[3]	%[4]	%[4]	n[3]	n[3]	%[4]	%[4]
Pharmacokinetic[1]	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Above the Limit of Quantitation (ALQ)	164	154	16.1	15.2	164	154	16.1	15.2
ALQ, Low Internal Standard (LIS)	4	1	0.4	0.1	4	1	0.4	0.1
Peak In Pre-Dose	7	7	0.7	0.7	7	7	0.7	0.7
ALQ, ALQ	2	5	0.2	0.5	2	5	0.2	0.5
ALQ, High Internal Standard (HIS)	0	1	0.0	0.1	-	1	-	0.1
LIS	6	3	0.6	0.3	6	3	0.6	0.3
HIS	2	1	0.2	0.1	2	1	0.2	0.1
Total Number of Samples Reanalyzed	185	172	18.2	16.9	185	172	18.2	16.9

[1] If no repeats were performed for pharmacokinetic reasons, insert "0.0" throughout the table
[2] N = Number of samples analyzed for each treatment
[3] n = Number of samples repeated
[4] % = percentage of assays repeated (i.e. 100*(n/N)%)
[5] Reported values that are different from the original value

FASTED - Dextrorphan:

S08-0445 Additional Information in Volume(s), Page(s)								
Reason for Reanalysis	**Number of Samples Reanalyzed**				**Number of Recalculated Values Used After Reanalysis[5]**			
	Actual Number		**% of Total Assays**		**Actual Number**		**% of Total Assays**	
	Test N=1018[2]	**Reference N=1015[2]**	**Test N=1018[2]**	**Reference N=1015[2]**	**Test N=1018[2]**	**Reference N=1015[2]**	**Test N=1018[2]**	**Reference N=1015[2]**
	n[3]	**n[3]**	**%[4]**	**%[4]**	**n[3]**	**n[3]**	**%[4]**	**%[4]**
Pharmacokinetic[1]	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Peak In Pre-Dose	3	1	0.3	0.1	3	1	0.3	0.1
Above the Limit of Quantitation	0	2	0.0	0.2	0	2	0.0	0.2
High Internal Standard	1	3	0.1	0.3	1	3	0.1	0.3
Low Internal Standard	2	7	0.2	0.7	2	6	0.2	0.6
Total Number of Samples Reanalyzed	6	13	0.6	1.3	6	12	0.6	1.2

[1] If no repeats were performed for pharmacokinetic reasons, insert "0.0" throughout the table
[2] N = Number of samples analyzed for each treatment
[3] n = Number of samples repeated
[4] % = percentage of assays repeated (i.e. 100*(n/N)%)
[5] Reported values that are different from the original value

FED - Dextromethorphan:

S08-0446 Additional Information in Volume(s), Page(s)								
Reason for Reanalysis	**Number of Samples Reanalyzed**				**Number of Recalculated Values Used After Reanalysis[5]**			
	Actual Number		**% of Total Assays**		**Actual Number**		**% of Total Assays**	
	Test N=715[2]	**Reference N=716[2]**	**Test N=715[2]**	**Reference N=716[2]**	**Test N=715[2]**	**Reference N=716[2]**	**Test N=715[2]**	**Reference N=716[2]**
	n[3]	**n[3]**	**%[4]**	**%[4]**	**n[3]**	**n[3]**	**%[4]**	**%[4]**
Pharmacokinetic[1]	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
High Internal Standard	3	1	0.4	0.1	3	1	0.4	0.1
Above the Limit of Quantitation	50	47	7.0	6.6	50	47	7.0	6.6
Low Internal Standard	2	4	0.3	0.6	2	2	0.3	0.3
Peak In Pre-Dose	1	2	0.1	0.3	1	1	0.1	0.1
Sample Processing Error	0	1	0.0	0.1	-	1	-	0.1
Total Number of Samples Reanalyzed	56	55	7.8	7.7	56	52	7.8	7.3

[1] If no repeats were performed for pharmacokinetic reasons, insert "0.0" throughout the table
[2] N = Number of samples analyzed for each treatment
[3] n = Number of samples repeated
[4] % = percentage of assays repeated (i.e. 100*(n/N)%)
[5] Reported values that are different from the original value

FED - Dextrorphan:

S08-0446 Additional Information in Volume(s), Page(s)								
Reason for Reanalysis	**Number of Samples Reanalyzed**				**Number of Recalculated Values Used After Reanalysis[5]**			
	Actual Number		**% of Total Assays**		**Actual Number**		**% of Total Assays**	
	Test N=715[2]	**Reference N=716[2]**	**Test N=715[2]**	**Reference N=716[2]**	**Test N=715[2]**	**Reference N=716[2]**	**Test N=715[2]**	**Reference N=716[2]**
	n[3]	**n[3]**	**%[4]**	**%[4]**	**n[3]**	**n[3]**	**%[4]**	**%[4]**
Pharmacokinetic[1]	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
High Internal Standard	2	4	0.3	0.6	2	4	0.3	0.6
Above the Limit of Quantitation	0	3	0.0	0.4	-	3	-	0.4
Low Internal Standard	0	2	0.0	0.3	-	1	-	0.1
Peak In Pre-Dose	1	0	0.1	0.0	1	-	0.1	-
Total Number of Samples Reanalyzed	3	9	0.4	1.3	3	8	0.4	1.1

[1] If no repeats were performed for pharmacokinetic reasons, insert "0.0" throughout the table
[2] N = Number of samples analyzed for each treatment
[3] n = Number of samples repeated
[4] % = percentage of assays repeated (i.e. 100*(n/N)%)
[5] Reported values that are different from the original value

Did use of recalculated plasma concentration data change study outcome?

No. The reviewer agrees with the firm that there is no PK re-assay in any of the studies.

Comments from the Reviewer:

A spot check of the analytical repeats above suggests that the firm did follow its own SOP ((b) (4) : Sample Reanalysis and Reporting Criteria), which was established *a priori*.

The reviewer notes that there were a lot of subject samples re-analyzed because of samples above the limit of quantitation (ALQ). As mentioned in the pre-study method validation section of this review, the firm will be asked to acknowledge that for future submissions, a more appropriate standard curve and QC range should be validated, which fully encompasses the expected plasma concentration ranges for all subjects.

With regard to the repeat analyses, the firm will be asked to submit the following additional information:

1. The firm should submit all appropriate data (for fasting and fed BE studies) supporting repeat analysis of samples for high/low internal standard responses (HIS/LIS). These repeats should meet the objective criterion established in the SOP (b) (4) , page 8 of 19, which says that results are flagged

for repeat when there is a deviation by more than 40% of the mean IS for the entire batch run.

2. Given that this subject sample is at or near Tmax (fed study – dextromethorphan, subject 41, hour 5.5), the firm should submit the analytical procedure sheet defining the reason for the sample processing error, per SOP (b) (4): Sample Reanalysis and Reporting Criteria.

The re-analysis of study samples is incomplete (inadequate) at this time.

3.7 Formulation

Location in appendix	See section 4.2
If a tablet, is the RLD scored?	N/A
If a tablet, is the test product biobatch scored	N/A
Is the formulation acceptable?	**FORMULATION ACCEPTABLE**
If not acceptable, why?	N/A

3.8 In Vitro Dissolution

Location of DBE Dissolution Review	There are 2 'dissolution only' reviews which can be found in DARRTS: 1) PALAMAKULA, ANITHA 06/25/2009 N/A 06/25/2009 REV-BIOEQ-02(Dissolution Review) Original-1 Archive 2) PALAMAKULA, ANITHA 09/03/2009 N/A 09/03/2009 REV-BIOEQ-02(Dissolution Review) Original-1 Archive
Source of Method (USP, FDA or Firm)	Firm Proposed Method[7]
Medium	0.1 N HCl with addition of 400 mL of Phosphate Buffer after 1 hr.
Volume (mL)	500 mL
USP Apparatus type	USP II (Paddle)
Rotation (rpm)	50 rpm
DBE-recommended specifications	1 hr: NMT (b) (4)% 3 hrs: (b) (4)% 6 hrs: (b) (4)% 12 hrs: NLT (b) (4)%.

[7] The firm submitted comparative dissolution testing data for both the firm's proposed method and the FDA-recommended method. The sampling for the dissolution testing conducted using the FDA-recommended method was not taken to the time point of complete dissolution: At 180 minutes, less than (b) (4)% LC of both the test and RLD products was dissolved. The firm's proposed method is accepted.

If a modified-release tablet, was testing done on ½ tablets?	N/A
F2 metric calculated?	No
If no, reason why F2 not calculated	single strength
Is method acceptable?	**METHOD ACCEPTABLE**
If not then why?	N/A

The firm acknowledged the dissolution method and specifications in an amendment dated September 25, 2009. On October 9, 2009, the firm submitted an additional amendment updating the new product dissolution specification, release specification and stability specification, as well as submitted additional stability data.

F2 metric, biostudy strengths compared to other strength(s)			
Biostudy Strength	**Other Strength**	**F2 metric for test**	**F2 metric for RLD**
N/A	N/A	N/A	N/A

3.9 Waiver Request(s)

Strengths for which waivers are requested	N/A
Proportional to strength tested in vivo?	N/A
Is dissolution acceptable?	N/A
Waivers granted?	**N/A**
If not then why?	N/A

3.10 Deficiency Comments

1. The firm should acknowledge that for future submissions, a more appropriate standard curve (SC) and quality control (QC) concentration range should be validated, which fully encompasses the expected plasma concentration ranges for all subjects. Specifically, the Agency recommends the firm avoid situations in which many subject samples have to be re-assayed due to initial measurements determined as being 'above the limit of quantitation (ALOQ)'.

2. In addition, it was not fully clear whether the fed study # S08-0446 was carried out on subjects dosed at 60 mg (like the fasted study), or dosed at the recommended 30 mg. For instance, in the fed study report (page 2 of 547) it lists the dose as 30 mg; however, in the *in vivo* BE summary table, it lists 60 mg as the dose administered. Based on the plasma profiles, the Agency is assuming the dose administered in the fed study was 30 mg. The firm will be asked to clarify if this assumption is correct or not.

3. With regard to the repeat analyses, the firm should submit the following additional information:

- **a.** The firm should submit all appropriate data (for fasting and fed BE studies) supporting repeat analysis of samples for high/low internal standard responses (HIS/LIS). These repeats should meet the objective criterion established in the SOP (b) (4), page 8 of 19, which says that results are flagged for repeat when there is a deviation by more than 40% of the mean IS for the entire batch run.

- **b.** The firm should also submit the analytical procedure sheet defining the reason for the sample processing error, per SOP (b) (4): Sample Reanalysis and Reporting Criteria.

3.11 Recommendations

1. The Division of Bioequivalence finds the fasting BE study # S08-0445 **incomplete (inadequate)** due to the deficiencies listed above. Tris Pharma Inc conducted the fasting BE study on its Dextromethorphan Polistirex Extended Release Oral Suspension, EQ. 30 mg dextromethorphan hydrobromide per 5 mL (lot # TB-0023A), comparing it to the corresponding reference product, DELSYM® ER Suspension, EQ 30 mg dextromethorphan hydrobromide per 5 mL (lot # 39469), manufactured by Reckitt Benckiser.

2. The Division of Bioequivalence finds the fed BE study # S08-0445 **incomplete (inadequate)** due to the deficiencies listed above. Tris Pharma Inc conducted the fed BE study on its Dextromethorphan Polistirex Extended Release Oral Suspension, EQ. 30 mg dextromethorphan hydrobromide per 5 mL (lot # TB-0023A), comparing it to the corresponding reference product, DELSYM® ER Suspension, EQ 30 mg dextromethorphan hydrobromide per 5 mL (lot # 39469), manufactured by Reckitt Benckiser.

3. The firm's *in vitro* dissolution testing is **acceptable (adequate)**. The dissolution testing should be conducted in 500 mL of 0.1 N HCl with addition of 400 mL of Phosphate Buffer after 1 hr sample at 37ºC $\pm$ 0.5ºC using USP apparatus II (Paddle) at 50 rpm. The test product should meet the following specification(s):

   1 hr: NMT (b) (4)%
   3 hrs: (b) (4)%
   6 hrs: (b) (4)%
   12 hrs: NLT (b) (4)%.

The firm should be informed of the above recommendations.

3.12 Comments for Other OGD Disciplines

Discipline	Comment
N/A	--

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	S08-0445
Study Title	A Relative Bioavailability Study of 30 mg / 5 mL Dextromethorphan Polistirex (Equivalent to 30 mg Dextromethorphan HBr) ER Oral Suspension Versus 30 mg / 5 mL Delsym® ER Oral Suspension Under Fasted Conditions
Clinical Site (Name, Address, Phone #)	Cetero Research 400 Fountain Lakes Blvd. St. Charles, MO 63301 (314) 419-6592
Principal Investigator	Jeffrey P. Ciaramita, M.D.
Dosing Dates	Group 1, Period I: 18 October 2008
	Group 1, Period II: 01 November 2008
	Group 2, Period I: 20 November 2008
	Group 2, Period II: 04 December 2008
Analytical Site (Name, Address, Phone #)	(b) (4)
Analysis Dates	November 26, 2008 – December 17, 2008
Analytical Director	(b) (6)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	60 days

Reviewer's comments: Please note that the data analysis began prior to the completion of Group 2 clinical portion of the study, and this raised a concern that the data of one group may also be statistically analyzed prior to the start of the second group and introduced bias to the study data. However, based on the raw data submitted, the reviewer determined that only batches for subject #s 1-21 were analyzed prior to December 4, 2008. All subjects after #21 from Group I were analyzed later. Therefore, the firm could not carry out statistical analysis prior to completion of Group II, and the reviewer finds this acceptable (adequate).

Table 5. Product information

Product	Test	Reference
Treatment ID	A	B
Product Name	Dextromethorphan Polistirex ER Oral Suspension	Delsym® Oral Suspension
Manufacturer	Tris Pharma, Inc.	Adams Respiratory Therapeutics

Batch/Lot No.	TB-0023A	39469
Manufacture Date	09/03/08	N/A
Expiration Date	N/A	Dec 2008
Strength	30 mg per 5 mL (equivalent to 30 mg dextromethorphan HBr)	30 mg per 5 mL (equivalent to 30 mg dextromethorphan HBr)
Dosage Form	Oral Suspension	Oral Suspension
Bio-batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency	100.8%, 102.2%	96.4%, 99.4%
Content Uniformity (mean, %CV)	N/A	N/A
Deliverable Volume (mean, range)	100.8%, 100.0 - 101.7%	N/A
Dose Administered	10 mL, 60 mg	10 mL, 60 mg
Route of Administration	Oral	Oral

The subjects were dosed at 60 mg (i.e. 10 mL)

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

Number of Subjects	61 enrolled / 54 completed / 54 analyzed / 53 used in Final Report
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	2: Period I dosing for Group 1 = October 18, 2008 Period I dosing for Group 2 = November 20, 2008 According to the firm, "Due to an unexpected number of subjects that were either dropped or did not report for Period I check-in on October 17, 2008, an additional 11 alternates were enrolled in a second group (Group 2) so that the total number of healthy adult subjects (male and female) completing the S08-0445 study was 54 as stated in the protocol. Upon approval of the amendment to the protocol on November 10, 2008, analyses of the samples and data from Group 1 commenced; data from Group 2 was included with the analyses of the samples and data of Group 1 in the report." The reviewer verified that the firm specified in the protocol that 54 healthy male and female subjects would be enrolled.
Washout Period	14 days
Randomization Scheme	**GROUP 1** AB: 1, 2, 6, 8, 10, 11, 14, 17, 18, 19, 20, 21, 27, 28, 29, 31, 33, 34, 37, 38, 39, 43, 46, 48, 49, 51, 54 BA: 3, 4, 5, 7, 9, 12, 13, 15, 16, 22, 23, 24, 25, 26, 30, 32, 35, 36, 40, 41, 42, 44, 45, 47, 50, 52, 53 **GROUP 2**

	AB: 56, 57, 59, 61, 65 BA: 55, 58, 60, 62, 63, 64 Highlighted yellow subjects did not complete the study, highlighted pink subject was dropped from the final analysis due to pre-dose concentration greater than 5% respective Cmax.
Blood Sampling Times	During each study period, 19 blood samples (6 mL each) were collected from each subject within 90 minutes prior to administration of study product to the first study participant (Hour 0 only) and post-dose Hours 1, 2, 3, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 10, 12, 16, 24, 36, 48 and 72.
Blood Volume Collected/Sample	During each study period, 19 blood samples were collected (6 mL each) from each subject by direct venipuncture using pre-labeled vacutainers containing K2-EDTA as the anticoagulant. Approximately 228 mL of blood was collected from each subject as pharmacokinetic samples over the course of the study. The actual times at which blood samples were collected are recorded and presented with each subject's Case Report Form.
Blood Sample Processing/Storage	Samples were cooled by an ice bath or Kryorack® until processed, centrifuged at approximately 3000 RPM at 4°C for 10 minutes and then placed into an ice bath or Kryorack®. Plasma was evenly divided and transferred into duplicate 10 mL polypropylene tubes and maintained in the ice bath or Kryorack®. Samples were then stored and frozen at approximately -70°C (±20°C) until shipment to the bioanalytical laboratory. The time between sample collection and placement in freezer did not exceed 1.5 hours. The frozen samples were shipped under dry ice to (b) (4) for assay.
IRB Approval	Yes (Approval dates – October 6 and 13, 2008 and November 10, 2008
Informed Consent	Yes
Length of Fasting	Subjects fasted for 10 hours prior to study drug dosing each period and for four (4) hours after dosing. No fluids were allowed from one (1) hour prior to dosing, until one (1) hour after the 0-hour dosing, except that included with the dose.
Length of Confinement	Subjects meeting all entrance criteria were admitted and sequestered at the clinical facility for at least 10 hours pre-dose until 24 hours post-dose. Subjects returned to the clinic for blood collections at post-dose Hours 36, 48, and 72.
Safety Monitoring	The following assessments were completed within 28 days of Period I dosing: medical and medication history, physical examination, sitting blood pressure and heart rate, oral temperature, ECG, clinical laboratory evaluations, screens for HIV, Hepatitis B, Hepatitis C, drugs of abuse, and serum pregnancy test. All subjects gave written informed consent and were allowed to ask, and have answered, questions concerning the conduct of the study prior to enrollment in the study. Demographic data (including height, weight, age, gender, race, ethnicity and BMI) was collected for each subject.

	At study check-in, the subjects were briefly evaluated to assess if they continued to meet the study inclusion/exclusion criteria. In addition, a urine specimen was collected for drugs of abuse testing and a urine pregnancy test was performed. Blood pressure and pulse measurements were obtained within 90 minutes prior to administration of study product to the first study participant (Hour 0 only), within ±30 minutes of post-dose Hours 5, 12, 24, and at the discretion of the clinical staff. Study exit / early termination procedures were completed with the last blood sample collection. Procedures included general observations, blood pressure, heart rate, selected clinical laboratory measurements, and pregnancy screen.

Comments on Study Design:

The study design is **acceptable (adequate)**. Two groups were used in the fasting study, while a single group was used in the fed study. The firm added the second group in the fasted study after the initiation of period I dosing for group 1, and group 2 subjects were not randomized with group 1 subjects. Please note that the data analysis for Group 1 began prior to the completion of Group 2 clinical portion of the study, and this is generally considered unacceptable. However, based on the raw data submitted, the reviewer determined that only batches for subject #s 1-21 were analyzed prior to December 4, 2008. All subjects after #21 from Group I were analyzed later. Therefore, the firm could not carry out statistical analysis prior to completion of Group II, and the reviewer finds this acceptable.

4.1.1.2 Clinical Results

Table 7. Demographics Profile of Subjects Completing the Bioequivalence Study

S08-0445			
		Treatment Groups	
		Test Product N=53[1]	Reference Product N=53[1]
Age (years)	Mean ± SD	29.4 ± 10.2	29.4 ± 10.2
	Range	18 – 55	18 – 55
Age Groups	< 18	-	-
	18 – 39	42(79.2%)	42(79.2%)
	40 – 64	11(20.8%)	11(20.8%)
	65 – 75	-	-
	> 75	-	-
Sex	Male	28(52.8%)	28(52.8%)
	Female	25(47.2%)	25(47.2%)
Hispanic or Latino	N	1(1.9%)	1(1.9%)
Race	A	1(1.9%)	1(1.9%)

	B	-	-
	I	-	-
	W	1(1.9%)	1(1.9%)
Not Hispanic or Latino	N	-	-
Race	A	-	-
	B	26(49.1%)	26(49.1%)
	I	-	-
	W	24(45.3%)	24(45.3%)
BMI	Mean ± SD	25.2 ± 3.1	25.2 ± 3.1
	Range	17.7 – 30.3	17.7 – 30.3
Other Factors			

[1]Subjects used in final statistical report

RACE:

American Indian or Alaskan Native	N
Asian	A
Black or African American	B
Native Hawaiian or Other Pacific Islander	I
White	W

Table 8. Dropout Information, Fasting Bioequivalence Study

S08-0445				
Subject No	**Reason for dropout/replacement**	**Period**	**Replaced?**	**Replaced with**
04	Withdrew consent for the study at Period II check-in due to work schedule after receiving the reference product	I	No	N/A
06	Withdrew consent for the study due to adverse event (sore throat, fever and cough) experienced after receiving the test product	I	No	N/A
16	Withdrew consent for the study due to personal reasons after receiving the reference product	I	No	N/A
29	Withdrew consent for the study at Period II check-in due to adverse event (fever, headache and intermittent vomiting) experienced after receiving the test product	I	No	N/A
33	Was dropped from the study due to passing away between Period I and Period II after receiving the test product	I	No	N/A
34	Was dropped from the study due to vomiting after receiving the test product	I	No	N/A
43	Withdrew consent for the study due to failure to return to clinic for Period II check-in after receiving the test product	I	No	N/A

Table 9. Study Adverse Events, Fasting Bioequivalence Study

Body System/Adverse Event	Reported Incidence by Treatment Groups	
	S08-0445	
	Test N=59[1]	Reference N=56[1]
	n (%)[2]	n (%)[2]
Body as a whole		
Fatal Gunshot Wound	1 (1.7%)	
Fever	2 (3.4%)	
Headache	4 (6.8%)	2 (3.6%)
Gastrointestinal		
Diarrhea	1 (1.7%)*	
Intermittent Vomiting		1 (1.8%)
Loose Stool		1 (1.8%)
Stomach Ache		1 (1.8%)
Vomiting	1 (1.7%)	
Hemic and Lymphatic		
Abnormal WBC with Differential Blood Level	1 (1.7%)	
Respiratory		
"Scratchy" Throat	1 (1.7%)	
Cough	1 (1.7%)	
Urogenital		
Abnormal Urinalysis	1 (1.7%)	4 (7.1%)
Vaginal Bacterial Infection		1 (1.8%)
Total Subjects Reporting at Least One Adverse Event	9 (15.3%)	8 (14.3%)

* One (1) subject experienced the adverse event two (2) times.

[1] N = Number of subjects dosed for each treatment
[2] n = Number of subjects reporting at least one incidence of respective adverse event;
(%) = percentage of subjects reporting at least one incidence of respective adverse event (i.e. 100*(n/N)%)

Table 10. Protocol Deviations, Fasting Bioequivalence Study

S08-0445		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
Group 1 of the study dosed four (4) subjects less than the 54 subjects called for by the protocol. No subjects were dosed for Subject Nos. 46, 51, 53, and 54. Eleven (11) subjects, numbered 55 - 65 were dosed for Group 2.	01 – 45, 47 – 50, 52, 55 – 65	01 – 45, 47 – 50, 52, 55 – 65
Subject did not have exit procedures obtained	03, 43	
Subject consumed caffeine within the restricted period for caffeine, Period I	01	41, 42
Subject was dosed with out of range BMI	29	07
Subject was confined for less than the required 10 hours prior to Period II dosing	25	
Subject took over-the-counter (OTC) medications subsequent to adverse events experienced Period I	29	
Subjects dosed with out-of-range vitals Period I		30, 50

Subjects dosed with out-of-range vitals Period II	61	
Subjects dosed with out-of-range laboratory values Period I	31	25
Adverse Event Query deviations Period I	29, 38, 48, 49, 61	03, 44, 58, 63
Adverse Event Query deviations Period II	03, 41, 44, 58	27, 38, 48
Blood draw time deviations, Period I	01, 08, 14, 21, 27, 28, 31, 37, 38, 49, 59, 61	03, 05, 07, 23, 30, 35, 36, 40, 42, 44, 45, 55, 58, 60, 62, 63
Blood draw time deviations, Period II	08, 18, 21, 27, 28, 31, 38, 39, 65	03, 12, 23, 26, 35, 40, 41, 42, 50, 58, 60, 62, 63

Comments on Dropouts/Adverse Events/Protocol Deviations:

The firm's handling of dropouts, adverse events and protocol deviations are acceptable.

4.1.1.3 Bioanalytical Results

Table 11. Assay Validation – Within the Fasting Bioequivalence Study

Dextromethorphan:

Bioequivalence Study No. Study No. S08-0445 Dextromethorphan										
Parameter	**Standard Curve Samples**									
Concentration (µg/mL)	10.00	20.00	40.00	100.0	200.0	500.0	1000	5000	8500	10000
Inter day Precision (CV)	7.6	6.7	4.6	3.7	3.6	3.5	3.5	3.1	4.4	3.3
Inter day Accuracy (%Bias)	-0.2	-1.7	-0.2	6.8	4.5	-0.8	4.4	-6.0	-2.8	-4.1
Linearity	0.9908 – 0.9987									
Linearity Range (pg/mL)	10.00 – 10000									
Sensitivity/LOQ (pg/mL)	10.00									

Bioequivalence Study No. Study No. S08-0445 Dextromethorphan				
Parameter	**Quality Control Samples**			
Concentration (pg/mL)	30.00	750.0	4500	8000
Inter day Precision (CV)	14.1	3.8	3.9	4.4
Inter day Accuracy (%Bias)	13.8	4.1	1.0	-4.2

Dextrorphan:

Bioequivalence Study No. Study No. S08-0445 Dextrorphan										
Parameter	**Standard Curve Samples**									
Concentration (µg/mL)	10.00	20.00	40.00	100.0	200.0	500.0	1000	5000	8500	10000
Inter day Precision (CV)	6.8	5.7	6.4	3.6	4.4	3.8	3.4	3.2	4.0	4.2
Inter day Accuracy (%Bias)	0.0	-2.7	1.2	7.4	5.1	0.1	4.3	-6.7	-2.9	-5.7
Linearity	0.9911 – 0.9979									
Linearity Range (pg/mL)	10.00 – 10000									
Sensitivity/LOQ (pg/mL)	10.00									

Bioequivalence Study No. Study No. S08-0445 Dextrorphan				
Parameter	**Quality Control Samples**			
Concentration (pg/mL)	30.00	750.0	4500	8000
Inter day Precision (CV)	7.6	4.6	3.3	4.3
Inter day Accuracy (%Bias)	9.3	3.5	0.2	-4.7

Comments on Study Assay Validation:

Acceptable.

Any interfering peaks in chromatograms?	NO
Were 20% of chromatograms included?	YES
Were chromatograms serially or randomly selected?	Serially after subject 28 (28-42, i.e. batch run 10-13)

Comments on Chromatograms:

Acceptable.

Table 12. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
	(b) (4)	Sample Reanalysis and Reporting Criteria

Table 13. Additional Comments on Repeat Assays

Were all SOPs followed?	See comments below
Did recalculation of PK parameters change the study outcome?	See comments below
Does the reviewer agree with the outcome of the repeat assays?	See comments below
If no, reason for disagreement	N/A

Summary/Conclusions, Study Assays:

The reviewer is requesting from the firm more data to validate that they did follow their SOP with regard to re-analysis of subject samples due to high/low internal standard responses.

4.1.1.4 Pharmacokinetic Results

Table 14. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 18 and Figure 1

Dextromethorphan:

		Test				Reference				Ratio
Parameter	**Unit**	**Mean**	**CV%**	**Min**	**Max**	**Mean**	**CV%**	**Min**	**Max**	**(T/R)**
AUCT	pg hr/mL	267496.6	193.86	3601.26	2083320	274245.8	202.69	3488.06	2401989	0.98
AUCI	pg hr/mL	119415.5	161.90	3829.05	789800.7	122197.8	207.84	3613.77	1572690	0.98
CMAX	pg/mL	8910.049	140.58	302.20	58020.00	9068.785	141.76	283.90	56880.00	0.98
TMAX	hr	6.000	.	4.50	12.00	6.000	.	3.00	8.00	1.00
KE	hr-1	0.066	33.54	0.02	0.12	0.071	29.00	0.03	0.12	0.93
THALF	hr	12.116	44.17	6.02	31.15	10.848	37.97	5.98	27.54	1.12

* Tmax values are presented as median, range

Dextrorphan:

		Test				Reference				Ratio
Parameter	**Unit**	**Mean**	**CV%**	**Min**	**Max**	**Mean**	**CV%**	**Min**	**Max**	**(T/R)**
AUCT	pg hr/mL	40989.37	43.72	7033.90	84830.01	40438.87	45.84	7848.92	83773.18	1.01
AUCI	pg hr/mL	43962.37	41.17	10238.05	85149.33	43794.66	41.05	16790.53	83920.81	1.00
CMAX	pg/mL	3691.234	49.25	255.60	9053.00	4018.338	58.31	212.10	12100.00	0.92
TMAX	hr	5.000	.	2.00	8.00	5.000	.	2.00	7.00	1.00
KE	hr-1	0.075	44.08	0.01	0.13	0.082	37.49	0.01	0.15	0.91
THALF	hr	12.471	74.28	5.17	52.32	10.864	90.24	4.76	70.95	1.15

* Tmax values are presented as median, range

Table 15. Geometric Means and 90% Confidence Intervals - Firm Calculated

Dextromethorphan:

Dextromethorphan Polistirex 30 mg / 5 mL (2 x 30 mg / 5 mL) Geometric Means[1], Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data				
Fasted Bioequivalence Study (S08-0445) N=53[2]				
Parameter	**Test**	**Reference**	**% Ratio**	**90% C.I.**
AUC0-t (hr *pg/ml)	61350.92	59169.10	103.69	(97.77, 109.96)
AUC∞ (hr *pg/ml)	45007.64	42798.30	105.16	(98.82, 111.91)
Cmax (pg/ml)	3685.37	3714.87	99.21	(93.42, 105.35)

Dextrorphan:

Dextromethorphan Polistirex 30 mg / 5 mL (2 x 30 mg / 5 mL) Geometric Means[1], Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data				
Fasted Bioequivalence Study (S08-0445) N=53[2]				
Parameter	**Test**	**Reference**	**% Ratio**	**90% C.I.**
AUC0-t (hr *pg/ml)	36431.34	35431.87	102.82	(98.15, 107.71)
AUC∞ (hr *pg/ml)	40033.71	38898.86	102.92	(98.24, 107.82)
Cmax (pg/ml)	3008.40	3132.54	96.04	(90.84, 101.54)

[1]Geometric means are based on least squares means of ln-transformed values
[2]Subjects used in final statistical report

Table 16. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Dextromethorphan:

Dextromethorphan Polistirex 30 mg / 5 mL (2 x 30 mg / 5 mL) Fasted Bioequivalence Study (S08-0445) N=53					
	Least Squares Geometric Mean		Ratio	90% Confidence Intervals	
Parameter	**Test**	**Reference**	**(T/R)**	**Lower**	**Upper**
AUC0-t (hr *pg/ml)	47984.97	46415.72	1.03	97.43	109.69
AUC∞ (hr *pg/ml)	33050.42	31466.96	1.05	98.28	112.24
Cmax (pg/ml)	2904.86	2929.23	0.99	93.33	105.38

Dextrorphan:

Dextromethorphan Polistirex 30 mg / 5 mL (2 x 30 mg / 5 mL) Fasted Bioequivalence Study (S08-0445) N=53					
	Least Squares Geometric Mean		Ratio	90% Confidence Intervals	
Parameter	Test	Reference	(T/R)	Lower	Upper
AUC0-t (hr *pg/ml)	35259.36	34403.77	1.02	98.07	107.10
AUC∞ (hr *pg/ml)	39347.92	38498.42	1.02	97.31	107.35
Cmax (pg/ml)	2947.66	3084.91	0.96	90.34	101.07

Table 17. Additional Study Information, Fasting Study No.

Dextromethorphan:

Root mean square error, AUC0-t	0.1810	
Root mean square error, AUC∞	0.1909	
Root mean square error, Cmax	0.1855	
	Test	Reference
Kel and AUC∞ determined for how many subjects?	48	48
Do you agree or disagree with firm's decision?	AGREE	AGREE
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	5**	6**
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	Yes	Yes

** Only a single subject (#58) had a pre-dose concentration greater than 5% respective Cmax, and was therefore dropped from the study analysis.

Ratio of AUC0-t/AUC∞				
Treatment	n	Mean	Minimum	Maximum
Test	48	0.96	0.82	1.00
Reference	48	0.97	0.82	1.00

Dextrorphan:

Root mean square error, AUC0-t	0.1346	
Root mean square error, AUC∞	0.1420	
Root mean square error, Cmax	0.1715	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	50	48
Do you agree or disagree with firm's decision?	AGREE	AGREE
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	2**	2**
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	Yes	Yes

** Only a single subject (#58) had a pre-dose concentration greater than 5% respective Cmax, and was therefore dropped from the study analysis.

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	50	0.97	0.69	1.00
Reference	48	0.98	0.67	1.00

Comments on Pharmacokinetic and Statistical Analysis:

The fasted BE study was conducted using two groups. The TRT*GRP parameter was not significant for AUC0-t, AUC∞ or Cmax, and was dropped from the final analysis.

Data from Reviewer's calculations were generated using SAS code "CALCKE".

While the reviewer's arithmetic mean PK values were nearly identical to the firm's calculated values (compare Table 1 versus Table 14), the geometric means from log-transformed data were different (compare Table 15 versus Table 16). However, the plasma concentration data were the same between what the reviewer used and what the firm used to calculate PK parameters (spot-checked). In addition, the Firm/Reviewer ratios were all approximately 1.0 (see pages 119-123). The firm will be asked to clarify.

Blood sampling deviations during the fasted BE study were minor. The sampling time deviations were considered to be insignificant and they did not compromise the outcome of the BE study.

The 90% CI for the least-squares geometric means of lnAUCt, lnAUC∞, and lnCmax calculated by the reviewer (for group 1 only) meet the CI criteria for BE (80.00% - 125.00%).

The median Tmax values for dextromethorphan and dextrorphan for the test product were similar to that for the reference product (dextromethorphan: 5.5 and 6.0 hours respectively; dextrorphan: 5.0 and 5.0 hours, respectively).

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:

Although the 90% CI for the least-squares geometric means of lnAUCt, lnAUC∞, and lnCmax meet the CI criteria for bioequivalence, the fasted study is incomplete (**inadequate)** at this time due to deficiencies listed in Section 3.10 of this review..

Table 18. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Dextromethorphan:

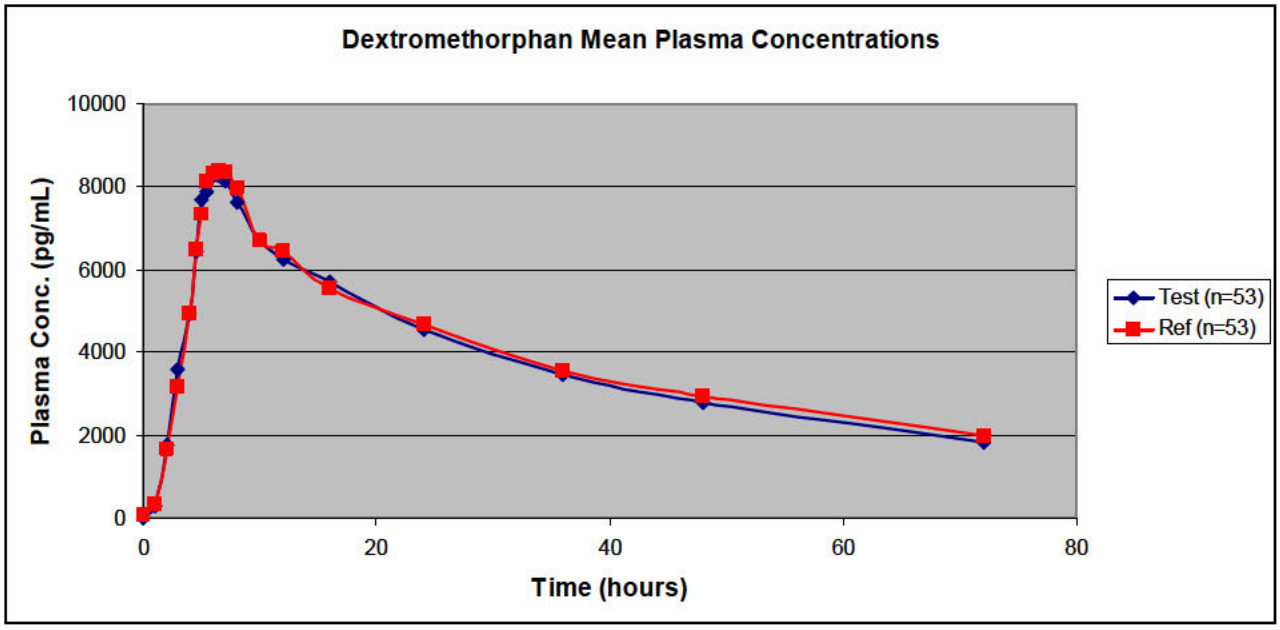
	Test (n=53)		Reference (n=53)		Ratio
Time (hr)	Mean (pg/mL)	CV%	Mean (pg/mL)	CV%	(T/R)
0.00	14.82	486.02	57.58	355.81	0.26
1.00	281.51	93.33	334.06	149.06	0.84
2.00	1768.09	141.69	1655.40	132.81	1.07
3.00	3579.27	139.28	3183.34	120.19	1.12
4.00	4949.78	141.10	4947.49	135.40	1.00
4.50	6437.86	137.94	6468.56	140.21	1.00
5.00	7701.11	137.29	7347.48	135.33	1.05
5.50	7872.28	134.35	8150.13	138.21	0.97
6.00	8271.97	137.32	8329.20	140.92	0.99
6.50	8254.14	140.14	8412.47	143.82	0.98
7.00	8141.29	144.87	8361.77	146.11	0.97
8.00	7633.31	147.22	7968.10	150.08	0.96
10.00	6723.83	154.10	6699.44	156.61	1.00
12.00	6262.44	167.14	6448.94	172.18	0.97
16.00	5711.01	179.49	5559.21	186.43	1.03
24.00	4562.05	195.19	4671.61	206.60	0.98
36.00	3458.83	212.93	3564.10	231.31	0.97
48.00	2788.24	237.37	2942.10	251.64	0.95
72.00	1841.35	272.15	1984.98	263.54	0.93

Dextrorphan:

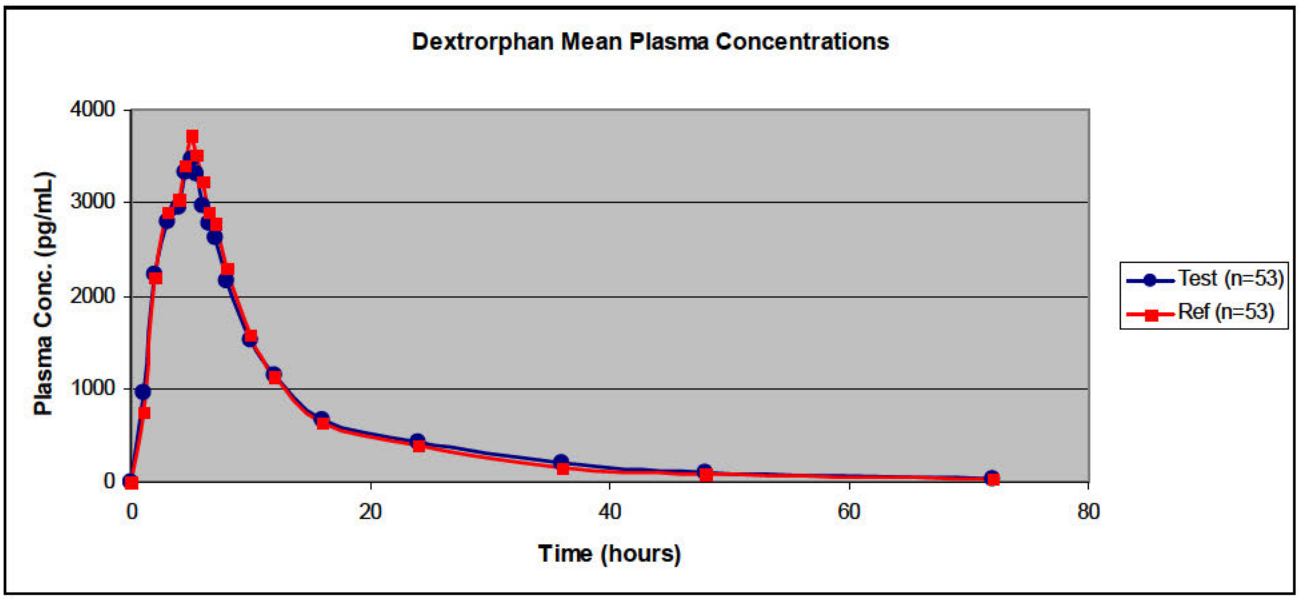
	Test (n=53)		Reference (n=53)		Ratio
Time (hr)	Mean (pg/mL)	CV%	Mean (pg/mL)	CV%	(T/R)
0.00	0.26	728.01	1.23	728.01	0.22
1.00	955.24	103.48	757.32	87.38	1.26
2.00	2234.77	75.73	2195.17	79.25	1.02
3.00	2794.80	62.93	2896.95	69.63	0.96
4.00	2955.92	52.85	3042.63	62.74	0.97
4.50	3330.33	53.70	3396.31	59.76	0.98
5.00	3460.49	48.91	3730.61	59.66	0.93
5.50	3307.64	49.10	3519.17	60.07	0.94
6.00	2966.00	46.37	3223.67	53.92	0.92
6.50	2778.31	48.27	2907.22	53.22	0.96
7.00	2618.75	50.31	2786.32	52.00	0.94
8.00	2169.25	48.44	2296.93	53.04	0.94
10.00	1520.41	46.79	1573.54	52.31	0.97
12.00	1146.45	45.80	1128.32	47.92	1.02
16.00	671.56	47.91	635.85	49.25	1.06
24.00	436.02	61.21	401.65	60.29	1.09
36.00	199.61	92.82	157.92	83.49	1.26
48.00	106.40	110.18	92.74	116.57	1.15
72.00	41.34	138.25	38.58	184.04	1.07

Figure 1. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Dextromethorphan:



Dextrorphan:



4.1.2 Single-dose Fed Bioequivalence Study

4.1.2.1 Study Design

Table 19. Study Information

Study Number	S08-0446
Study Title	A Relative Bioavailability Study of 30 mg / 5 mL Dextromethorphan Polistirex (Equivalent to 30 mg Dextromethorphan HBr) ER Oral Suspension Versus 30 mg / 5 mL Delsym® ER Oral Suspension Under Fed Conditions
Clinical Site (Name, Address, Phone #)	Cetero Research 400 Fountain Lakes Blvd. St. Charles, MO 63301 (314) 419-6592
Principal Investigator	Jeffrey P. Ciaramita, M.D.
Dosing Dates	Period I: 19 October 2008
	Period II: 02 November 2008
Analytical Site (Name, Address, Phone #)	(b) (4)
Analysis Dates	November 15, 2008 – December 05 2008
Analytical Director	(b) (6)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	47 days

Table 20. Product Information

Product	**Test**	**Reference**
Treatment ID	A	B
Product Name	Dextromethorphan Polistirex ER Oral Suspension	Delsym® Oral Suspension
Manufacturer	Tris Pharma, Inc.	Adams Respiratory Therapeutics
Batch/Lot No.	TB-0023A	39469
Manufacture Date	09/03/08	N/A
Expiration Date	N/A	Dec 2008
Strength	30 mg per 5 mL (equivalent to 30 mg dextromethorphan HBr)	30 mg per 5 mL (equivalent to 30 mg dextromethorphan HBr)
Dosage Form	Oral Suspension	Oral Suspension
Bio-batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency	100.8%, 102.2%	96.4%, 99.4%
Content Uniformity (mean, %CV)	N/A	N/A

Deliverable Volume (mean, range)	100.8%, 100.0 - 101.7%	N/A
Dose Administered	10 mL, 60 mg	10 mL, 60 mg
Route of Administration	Oral	Oral

The reviewer assumes that the fed study was actually carried out on subjects dosed at 30 mg, and not at 60 mg.

Table 21. Study Design, Single-Dose Fed Bioequivalence Study

No. of Subjects	42 enrolled / 38 completed / 38 analyzed / 37 in Final Report (1 dropped because of pre-dose concentration)
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	14 days
Randomization Scheme	AB: 1, 2, 4, 9, 10, 11, 15, 16, 18, 19, 20, 21, 27, 28, 29, 31, 35, 36, 38, 39, 42 BA: 3, 5, 6, 7, 8, 12, 13, 14, 17, 22, 23, 24, 25, 26, 30, 32, 33, 34, 37, 40, 41 The firm specified in the protocol that 42 healthy male and female subjects would be enrolled. Highlighted yellow subjects did not complete the study, highlighted pink subject was dropped from the final analysis due to pre-dose concentration greater than 5% respective Cmax.
Blood Sampling Times	During each study period, 19 blood samples were collected (6 mL each) from each subject by direct venipuncture using pre-labeled vacutainers containing K2-EDTA as the anticoagulant. Blood sample collection was obtained within 90 minutes prior to administration of study product to the first study participant (Hour 0 only), and after dose administration at post-dose Hours 1, 2, 3, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 10, 12, 16, 24, 36, 48 and 72.
Blood Volume Collected/Sample	Approximately 228 mL of blood was collected from each subject as pharmacokinetic samples over the course of the study. The actual times at which blood samples were collected are recorded and presented with each subject's Case Report Form.
Blood Sample Processing/Storage	Samples were cooled by an ice bath or Kryorack® until processed, centrifuged at approximately 3000 RPM at 4°C for 10 minutes and then placed into an ice bath or Kryorack®. Plasma was evenly divided and transferred into duplicate 10 mL polypropylene tubes and maintained in the ice bath or Kryorack®. Samples were then stored and frozen at approximately -70°C (±20°C) until shipment to the bioanalytical laboratory. The time between sample collection and placement in freezer did not exceed 1.5 hours. The frozen samples were shipped under dry ice to (b) (4) for assay.

IRB Approval	Yes (Approval dates – October 6 and 13, 2008)
Informed Consent	Yes
Length of Fasting Before Meal	Subjects fasted for at least 10 hours prior to dosing. Subjects consumed the FDA standardized high fat – high calorie meal starting 30 minutes before their assigned dosing time consisting of two (2) eggs cooked in butter, two (2) strips of bacon, two (2) slices of toast with butter, four (4) ounces of hash brown potatoes, and eight (8) fluid ounces of whole milk. Subjects fasted for four (4) hours after dosing.
Length of Confinement	Subjects meeting all entrance criteria were admitted and sequestered at the clinical facility for at least 10 hours pre-dose until 24 hours post-dose. Subjects returned to the clinic for blood collections at post-dose Hours 36, 48, and 72.
Safety Monitoring	The following assessments were completed within 28 days of Period I dosing: medical and medication history, physical examination, sitting blood pressure and heart rate, oral temperature, ECG, clinical laboratory evaluations, screens for HIV, Hepatitis B, Hepatitis C, drugs of abuse, and serum pregnancy test. All subjects gave written informed consent and were allowed to ask, and have answered, questions concerning the conduct of the study prior to enrollment in the study. Demographic data (including height, weight, age, gender, race, ethnicity and BMI) was collected for each subject. At study check-in, the subjects were briefly evaluated to assess if they continued to meet the study inclusion/exclusion criteria. In addition, a urine specimen was collected for drugs of abuse testing and a urine pregnancy test was performed. Blood pressure and pulse measurements were obtained within 90 minutes prior to administration of study product to the first study participant (Hour 0 only), within ±30 minutes of post-dose Hours 5, 12, 24, and at the discretion of the clinical staff. Study exit / early termination procedures were completed with the last blood sample collection. Procedures included general observations, blood pressure, heart rate, selected clinical laboratory measurements, and pregnancy screen.

Standard FDA Meal Used?	YES	
If No, then meal components and composition is listed in the tables below		
Composition of Non-standard FDA Meal Used in Fed Bioequivalence Study		
Composition	**Percent**	**Kcal**
Fat	N/A	
Carbohydrate		
Protein		
Total		

Comments on Study Design:

The study design is acceptable (adequate).

4.1.2.2 Clinical Results

Table 22. Demographics Profile of Subjects Completing the Bioequivalence Study

S08-0446			
		Treatment Groups	
		Test Product N=37[1]	Reference Product N=37[1]
Age (years)	Mean ± SD	28.6 ± 8.9	28.6 ± 8.9
	Range	18 – 50	18 – 50
Age Groups	< 18	-	-
	18 – 39	32(86.5%)	32(86.5%)
	40 – 64	5(13.5%)	5(13.5%)
	65 – 75	-	-
	> 75	-	-
Sex	Male	20(54.1%)	20(54.1%)
	Female	17(47.9%)	17(47.9%)
Hispanic or Latino Race	N	-	-
	A	-	-
	B	-	-
	I	-	-
	W	2(5.4%)	2(5.4%)
Not Hispanic or Latino Race	N	1(2.7%)	1(2.7%)
	A	-	-
	B	6(16.2%)	6(16.2%)
	I	1(2.7%)	1(2.7%)
	W	27(73.0%)	27(73.0%)
BMI	Mean ± SD	24.6 ± 3.0	24.6 ± 3.0
	Range	19.5 – 30.1	19.5 – 30.1
Other Factors			

[1]Subjects used in final statistical report

RACE:

American Indian or Alaskan Native	N
Asian	A
Black or African American	B
Native Hawaiian or Other Pacific Islander	I
White	W

Table 23. Dropout Information, Fed Bioequivalence Study

S08-0446

Subject No	Reason for dropout/replacement	Period	Replaced?	Replaced with
05	Was dropped from the study due to vomiting after receiving the reference product	I	No	N/A
10	Withdrew consent for the study due to personal reasons after receiving the test product	I	No	N/A
23	Withdrew consent for the study due to death in family after receiving the reference product	I	No	N/A
36	Withdrew consent for the study due to personal reasons after receiving the test product	I	No	N/A

Table 24. Study Adverse Events, Fed Bioequivalence Study

Body System/Adverse Event	Reported Incidence by Treatment Groups	
	S08-0446	
	Test N=40[1]	Reference N=40[1]
	n (%)[2]	n (%)[2]
Body as a whole		
Dizziness	1 (2.5%)	
Drowsy		1 (2.5%)
Headache / Head Ache	5 (12.5%)	7 (17.5%)*
Hot Flash	1 (2.5%)	
Lower Left Side Chest Pain	1 (2.5%)	
Menstrual Cramps	1 (2.5%)	
Gastrointestinal		
Constipation		1 (2.5%)
Diarrhea	1 (2.5%)	
Vomiting		1 (2.5%)
Respiratory		
Allergy Symptoms		1 (2.5%)
Skin and Appendages		
Rash		1 (2.5%)
Urogenital		
Abnormal Urinalysis		1 (2.5%)
Total Subjects Reporting at Least One Adverse Event	9 (22.5%)	12 (30.0%)

* One (1) subject experienced the adverse event two (2) times.

[1] N = Number of subjects dosed for each treatment
[2] n = Number of subjects reporting at least one incidence of respective adverse event;
(%) = percentage of subjects reporting at least one incidence of respective adverse event (i.e. 100*(n/N)%)

Table 25. Protocol Deviations, Fed Bioequivalence Study

S08-0446		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
Subject was in confinement less than 10.5 hours prior to Period I dosing		03

Subject took medication subsequent to adverse event experienced Period I	19	05, 07, 40
Subject consumed caffeine containing products within the restricted period prior to Period I dosing	31, 35, 38	40
Subject consumed alcohol within the restricted period prior to Period I dosing	38	40
Subject did not have exit procedures obtained	10, 24, 36	23
Subjects were dosed with out-of-range vital signs Period I		13, 41
Subjects were dosed with out-of-range vital signs Period II	13	
Adverse Event Query deviations Period I	10, 15, 36, 38	24, 40
Adverse Event Query deviations Period II	14, 24, 25	11, 18, 20, 38
Vital sign time deviations, Period I		23
Vital sign time deviations, Period II	33	21, 31, 35
Blood draw time deviations, Period I	01, 02, 09, 15, 18, 20, 21, 27, 29, 38, 39, 42	03, 08, 12, 14, 17, 22, 24, 25, 30, 32, 33, 37, 40, 41
Blood draw time deviations, Period II	03, 07, 08, 14, 17, 22, 24, 25	02, 11, 15, 18, 20, 29, 38, 39, 42

Comments on Adverse Events/Protocol Deviations:

A single subject vomited after dosing with the reference product. This subject (# 05) was dropped from the study. The reviewer agrees with the handling of subject # 05.

The firm's handling of dropouts, adverse events and protocol deviations are acceptable.

4.1.2.3 Bioanalytical Results

Table 26. Assay Validation – Within the Fed Bioequivalence Study

Dextromethorphan:

Bioequivalence Study No. Study No. S08-0446 Dextromethorphan										
Parameter	**Standard Curve Samples**									
Concentration (µg/mL)	10.00	20.00	40.00	100.0	200.0	500.0	1000	5000	8500	10000
Inter day Precision (CV)	6.7	6.9	5.0	3.6	3.8	2.4	3.3	3.0	2.5	3.0
Inter day Accuracy (%Bias)	-0.3	-1.1	-0.2	6.7	5.1	-0.5	3.8	-5.0	-3.4	-5.1
Linearity	0.9923 – 0.9972									
Linearity Range (pg/mL)	10.00 – 10000									
Sensitivity/LOQ (pg/mL)	10.00									

Bioequivalence Study No. Study No. S08-0446 Dextromethorphan				
Parameter	**Quality Control Samples**			
Concentration (pg/mL)	30.00	750.0	4500	8000
Inter day Precision (CV)	10.9	3.6	3.1	2.8
Inter day Accuracy (%Bias)	13.6	3.1	0.5	-5.1

Dextrorphan:

Bioequivalence Study No. Study No. S08-0446 Dextrorphan										
Parameter	**Standard Curve Samples**									
Concentration (µg/mL)	10.00	20.00	40.00	100.0	200.0	500.0	1000	5000	8500	10000
Inter day Precision (CV)	6.7	5.5	4.8	3.2	4.2	3.1	2.9	2.2	2.9	2.7
Inter day Accuracy (%Bias)	-0.6	-1.6	2.1	6.6	5.1	0.1	3.5	-6.0	-3.4	-5.7
Linearity	0.9925 – 0.9976									
Linearity Range (pg/mL)	10.00 – 10000									
Sensitivity/LOQ (pg/mL)	10.00									

Bioequivalence Study No. Study No. S08-0446 Dextrorphan				
Parameter	**Quality Control Samples**			
Concentration (pg/mL)	30.00	750.0	4500	8000
Inter day Precision (CV)	37.9	2.8	3.5	3.0
Inter day Accuracy (%Bias)	18.0	3.5	0.0	-5.2

Comments on Study Assay Validation:

Acceptable.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially (1-11, i.e. batch run 1-3))

Comments on Chromatograms:

Acceptable.

Table 27. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
(b) (4)		Sample Reanalysis and Reporting Criteria

Table 28. Additional Comments on Repeat Assays

Were all SOPs followed?	See comments below
Did recalculation of PK parameters change the study outcome?	See comments below
Does the reviewer agree with the outcome of the repeat assays?	See comments below
If no, reason for disagreement	N/A

Summary/Conclusions, Study Assays:

The reviewer is requesting from the firm more data to validate that they did follow their SOP with regard to re-analysis of subject samples due to high/low internal standard responses.

4.1.2.4 Pharmacokinetic Results

Table 29. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 33 and Figure 2

Dextromethorphan:

		Test				Reference				Ratio
Parameter	**Unit**	**Mean**	**CV%**	**Min**	**Max**	**Mean**	**CV%**	**Min**	**Max**	**(T/R)**
AUCT	pg hr/mL	91146.80	264.19	4296.19	1454090	107042.9	282.46	5929.67	1834938	0.85
AUCI	pg hr/mL	56606.20	133.48	4499.29	370664.5	61976.64	135.07	6702.71	439393.4	0.91
CMAX	pg/mL	3804.403	151.69	222.50	31840.00	4219.795	148.43	224.60	34110.00	0.90
TMAX	hr	5.500	.	2.00	12.00	6.000	.	4.00	12.00	0.92
KE	hr-1	0.068	32.78	0.01	0.10	0.071	26.23	0.03	0.10	0.96
THALF	hr	13.045	98.12	6.73	82.57	10.577	33.54	6.61	22.81	1.23

*** Tmax values are presented as median, range.**

Dextrorphan:

		Test				Reference				Ratio
Parameter	**Unit**	**Mean**	**CV%**	**Min**	**Max**	**Mean**	**CV%**	**Min**	**Max**	**(T/R)**
AUCT	pg hr/mL	45610.46	47.52	8702.30	105573.3	50080.63	44.42	9695.96	104431.1	0.91
AUCI	pg hr/mL	47116.02	45.03	19584.83	105841.7	51595.29	41.62	18966.83	105015.9	0.91
CMAX	pg/mL	4071.224	42.02	223.30	8122.00	4572.573	52.47	209.20	11850.00	0.89
TMAX	hr	5.000	.	2.00	6.50	5.000	.	2.00	12.00	1.00
KE	hr-1	0.096	28.56	0.05	0.17	0.103	21.75	0.06	0.17	0.92
THALF	hr	7.870	29.56	4.05	12.90	6.994	20.74	4.06	11.78	1.13

*** Tmax values are presented as median, range.**

Table 30. Geometric Means and 90% Confidence Intervals - Firm Calculated

Dextromethorphan:

Dextromethorphan Polistirex 30 mg / 5 mL (1 x 30 mg / 5 mL) Geometric Means[1], Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data				
Fed Bioequivalence Study (S08-0446) N=37[2]				
Parameter	**Test**	**Reference**	**% Ratio**	**90% C.I.**
AUC_{0-t}	33274.36	36992.59	89.95	(82.04, 98.62)
AUC_{0-inf}	32201.85	35720.20	90.15	(82.19, 98.88)
C_{max}	2018.75	2259.84	89.33	(81.42, 98.01)

Dextrorphan:

Dextromethorphan Polistirex 30 mg / 5 mL (1 x 30 mg / 5 mL) Geometric Means[1], Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data				
Fed Bioequivalence Study (S08-0446) N=37[2]				
Parameter	**Test**	**Reference**	**% Ratio**	**90% C.I.**
AUC_{0-t}	40523.45	44712.97	90.63	(86.27, 95.21)
AUC_{0-inf}	42867.29	47203.98	90.81	(86.52, 95.32)
C_{max}	3596.29	3903.02	92.14	(85.29, 99.55)

[1]Geometric means are based on least squares means of ln-transformed values
[2]Subjects used in final statistical report

Table 31. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Dextromethorphan:

Dextromethorphan Polistirex 30 mg / 5 mL (1 x 30 mg / 5 mL) Fed Bioequivalence Study (S08-0446) N=37					
	Least Squares Geometric Mean		Ratio	90% Confidence Intervals	
Parameter	Test	Reference	(T/R)	Lower	Upper
AUC0-t (hr *pg/ml)	33667.37	37341.94	0.90	82.15	98.95
AUC∞ (hr *pg/ml)	32574.28	36001.18	0.90	82.21	99.58
Cmax (pg/ml)	2018.75	2259.84	0.89	81.42	98.01

Dextrorphan:

Dextromethorphan Polistirex 30 mg / 5 mL (1 x 30 mg / 5 mL) Fed Bioequivalence Study (S08-0446) N=37					
	Least Squares Geometric Mean		Ratio	90% Confidence Intervals	
Parameter	Test	Reference	(T/R)	Lower	Upper
AUC0-t (hr *pg/ml)	40656.88	44956.62	0.90	86.39	94.67
AUC∞ (hr *pg/ml)	42917.70	47382.83	0.91	86.44	94.91
Cmax (pg/ml)	3596.29	3903.02	0.92	85.29	99.55

The reviewer's calculations are in agreement with the firm's calculations.

Table 32. Additional Study Information

Dextromethorphan:

Root mean square error, AUC0-t	0.2366	
Root mean square error, AUC∞	0.2369	
Root mean square error, Cmax	0.2359	
	Test	Reference
Kel and AUC∞ determined for how many subjects?	35	35
Do you agree or disagree with firm's decision?	Agree	Agree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	1**	1**
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

** Subject #34 was removed from the overall analysis by the firm and this reviewer due to pre-dose concentration of dextromethorphan greater than 5% of respective Cmax. Subject 29 pre-dose concentration was NOT greater than 5% respective Cmax, and was kept in the overall analysis.

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	35	0.97	0.71	1.00
Reference	35	0.98	0.86	1.00

Dextrorphan:

Root mean square error, AUC0-t	0.1164	
Root mean square error, AUC∞	0.1173	
Root mean square error, Cmax	0.1967	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	36	36
Do you agree or disagree with firm's decision?	Agree	Agree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	1**	0
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

** Subject #34 was removed from the overall analysis by the firm and this reviewer due to pre-dose concentration of dextrorphan greater than 5% of respective Cmax during period 2 after dosing with the test product.

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	36	0.99	0.97	1.00
Reference	36	0.99	0.95	1.00

Comments on Pharmacokinetic and Statistical Analysis:

The subjects in the fed BE study were dosed in one group. Data from Reviewer's calculations were generated using SAS code "CALCKE".

Because of several discrepancies between summary tables and the fed study report submitted by the firm to the Agency, the reviewer was unable to definitively state that the fed study was carried out on subjects dosed with 30 mg (i.e. 5 mL), in contrast to the 60 mg in the fasted study. However, based on the plasma profiles (approximately half the Cmax compared to the fasted study), the reviewer is assuming that the concentration was indeed 30 mg dosed. The firm will be asked to clarify if this assumption is correct or not.

Blood sampling deviations during the fed BE study were minor. The sampling time deviations were considered to be insignificant and they did not compromise the outcome of the BE study.

The 90% CI for the least-squares geometric means of lnAUCt, lnAUC∞, and lnCmax calculated by the reviewer agree with the firm's calculations and meet the CI criteria for BE (80.00% - 125.00%).

The median Tmax values for dextromethorphan and dextrorphan for the test product were similar to that for the reference product (dextromethorphan: 5.5 and 6.0 hours respectively; dextrorphan: 5.0 and 5.0 hours, respectively).

Summary/Conclusions, Single-Dose Fed Bioequivalence Study:

Although the 90% CI for the least-squares geometric means of lnAUCt, lnAUC∞, and lnCmax meet the CI criteria for bioequivalence, the fed study is **inadequate** at this time due to deficiencies listed in Section 3.10 of this review.

Table 33. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

Dextromethorphan:

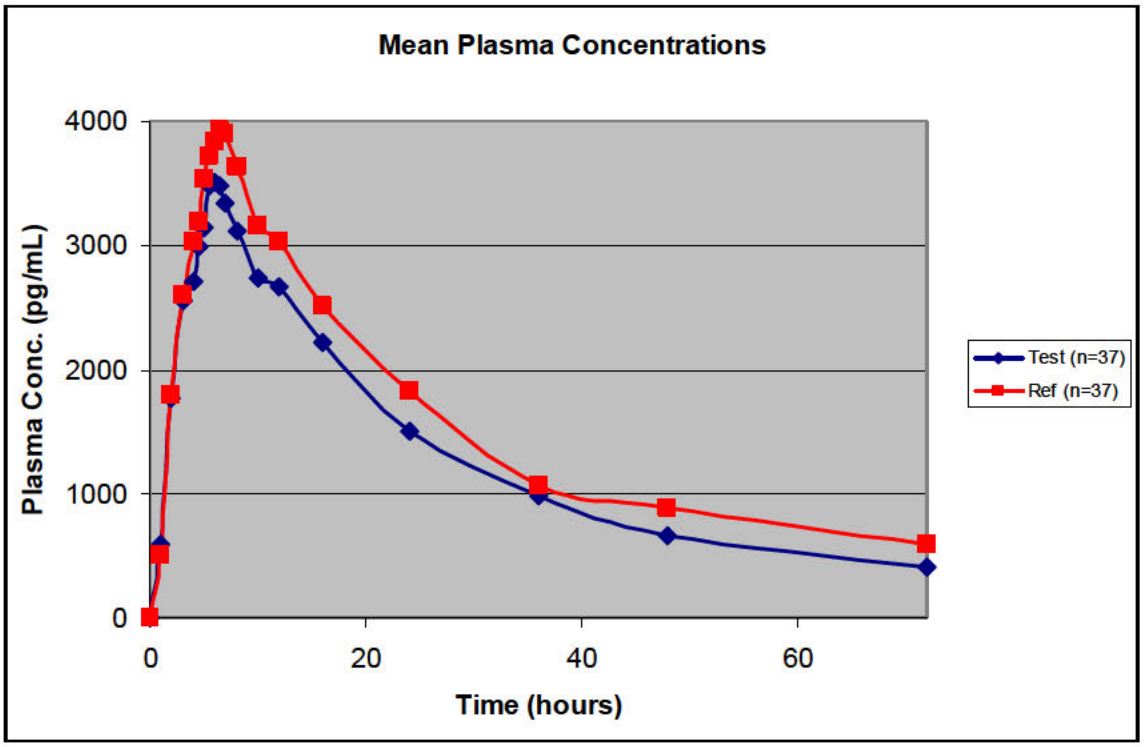
	Test (n=37)		Reference (n=37)		Ratio
Time (hr)	Mean (pg/mL)	CV%	Mean (pg/mL)	CV%	(T/R)
0.00	0.00	.	3.66	608.28	0.00
1.00	588.72	148.54	505.57	120.84	1.16
2.00	1772.16	152.45	1795.37	147.47	0.99
3.00	2551.87	146.20	2601.09	137.24	0.98
4.00	2711.14	136.94	3027.97	141.19	0.90
4.50	2985.08	139.78	3190.98	131.56	0.94
5.00	3141.15	134.31	3530.58	143.60	0.89
5.50	3486.01	142.67	3724.79	133.99	0.94
6.00	3512.83	146.09	3837.56	139.36	0.92
6.50	3484.28	156.35	3932.84	145.91	0.89
7.00	3346.93	153.20	3900.44	152.33	0.86
8.00	3121.39	162.60	3631.11	162.27	0.86
10.00	2730.56	184.76	3154.69	171.65	0.87
12.00	2660.89	206.61	3030.56	193.60	0.88
16.00	2218.93	237.34	2516.19	221.48	0.88
24.00	1506.09	277.62	1822.55	303.01	0.83
36.00	984.97	358.51	1068.24	391.48	0.92
48.00	660.02	408.64	884.06	453.71	0.75
72.00	409.12	498.01	593.54	540.80	0.69

Dextrorphan:

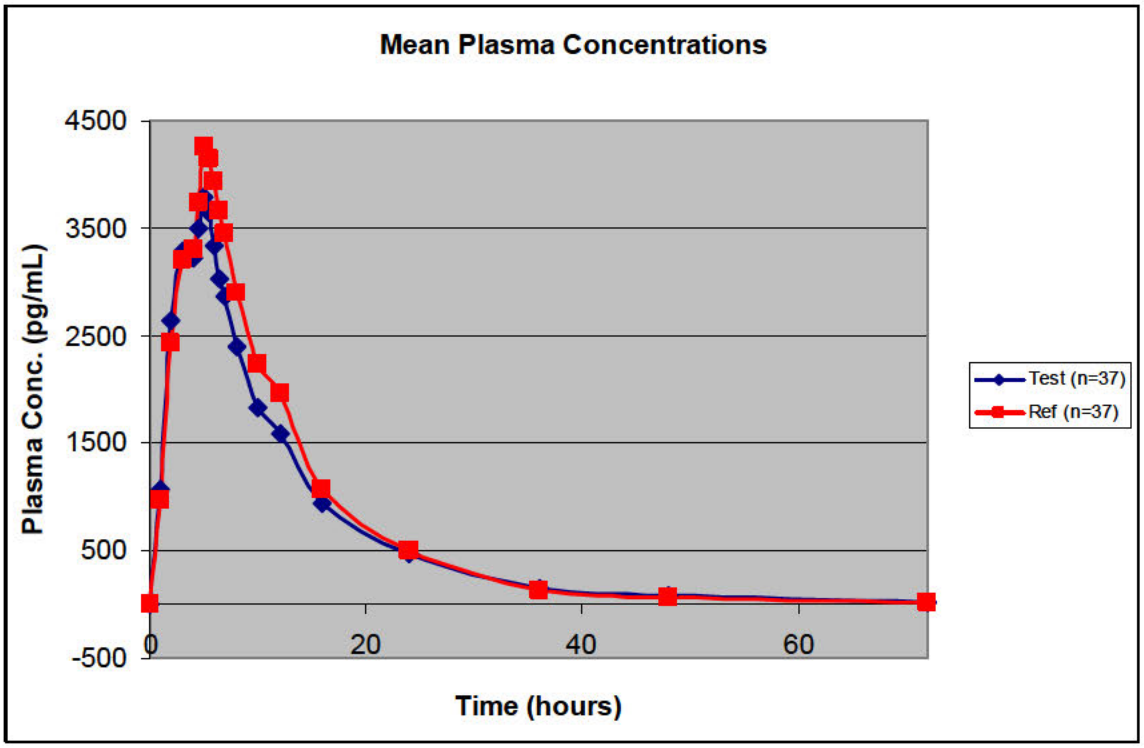
	Test (n=37)		Reference (n=37)		Ratio
Time (hr)	Mean (pg/mL)	CV%	Mean (pg/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
1.00	1076.48	63.98	977.75	75.58	1.10
2.00	2638.15	53.58	2428.61	59.28	1.09
3.00	3290.03	51.97	3205.36	62.81	1.03
4.00	3228.19	50.59	3305.76	50.55	0.98
4.50	3501.74	48.56	3737.36	49.71	0.94
5.00	3786.84	43.37	4263.86	48.53	0.89
5.50	3648.50	43.95	4147.06	49.24	0.88
6.00	3331.94	44.46	3926.36	47.51	0.85
6.50	3029.68	44.01	3660.20	46.48	0.83
7.00	2859.09	44.77	3444.86	44.62	0.83
8.00	2390.78	45.05	2892.74	45.99	0.83
10.00	1823.75	49.88	2236.17	47.81	0.82
12.00	1591.44	54.60	1957.34	50.37	0.81
16.00	947.11	57.78	1065.71	52.03	0.89
24.00	465.55	65.79	496.28	57.73	0.94
36.00	149.21	79.65	128.30	77.07	1.16
48.00	75.06	87.84	59.02	74.93	1.27
72.00	16.02	160.91	12.25	174.52	1.31

Figure 2. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

Dextromethorphan:



Dextrorphan:



4.2 Formulation Data

	TEST		REFERENCE**
Ingredient	**Amount (mg/5mL)**	**Amount w/v (%)**	**Amount (mg/5mL)**
Dextromethorphan Hydrobromide USP			(b) (4)
Sodium Polystyrene Sulfonate (b) (4)			
Povidone USP			
Polyvinyl Acetate (b) (4)			
Triacetin USP			
Purified Water USP			
(b) (4)			
Tartaric Acid NF			
Sodium Metabisulfite NF (b) (4)			
High Fructose Corn Syrup (b) (4)			
Sucrose NF			
D&C Yellow No 10 (b) (4)			
(b) (4)			
D&C Red No 30 (b) (4)			
Glycerin USP			
(b) (4)			
Methylparaben NF			
Propylparaben NF			
Tragacanth Gum NF (b) (4)			
Xanthan Gum NF (b) (4)			
Polysorbate 80 NF (Tween 80K (b) (4))			
(b) (4) Flavor (b) (4)			
(b) (4)			
(b) (4)			
(b) (4)			
(b) (4)			
Total			

(b) (4)

The following inactive ingredients are not validated by the RLD, i.e. they are not present in the RLD *or* they are present in the test formulation at greater amounts than in the RLD.

IIG Limits of Excipients Based on MDD:

Excipient Ingredients	Amount (mg) per 5 mL	IIG limit (mg)	IIG Limit Reference	MDD per RLD labeling	Amount taken based on MDD (mg)	Test formulation Below or exceed FDA IIG
Sodium Polystyrene Sulfonate (b) (4)						(b) (4)
(b) (4)						
Polyvinyl Acetate (b) (4)						
Polyvinyl Acetate						
Povidone						
Sodium Lauryl Sulfate						
Triacetin USP						
Tartaric Acid NF						
Sodium Metabisulfite NF (b) (4)						
Sucrose NF						
D&C Yellow No 10 (b) (4)						
D&C Red No 30 (b) (4)						
Glycerin USP						

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Is there an overage of the active pharmaceutical ingredient (API)?	NO
If the answer is yes, has the appropriate chemistry division been notified?	N/A
If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	N/A
Comments on the drug product formulation:	This reviewer has minor concern with regard to the use of (b) (4) [redacted] Based on MDD, the amount taken in this formulation is much less than the amount of (b) (4) [redacted] This reviewer was unable to determine if the (b) (4) [redacted]

4.3 Dissolution Data

Dissolution Review Path	**2 reviews:** PALAMAKULA, ANITHA 06/25/2009 N/A 06/25/2009 REV-BIOEQ-02(Dissolution Review) Original-1 Archive *and* PALAMAKULA, ANITHA 09/03/2009 N/A 09/03/2009 REV-BIOEQ-02(Dissolution Review) Original-1 Archive

Table 34. Dissolution Data

In-house Method:

Dissolution Conditions	**Apparatus:**	USP II (Paddle)
	Speed of Rotation:	50 rpm
	Medium:	0.1 N HCl, for 1 hr and after sampling add 400 mL of Phosphate Buffer
	Volume:	500 mL
	Temperature:	37 °C ± 0.5 °C
Firm's Proposed Specifications	1 hour NMT (b) (4) %. 3 hour (b) (4) % 6 hour (b) (4) %. 12 hour NLT (b) (4) %	
Dissolution Testing Site (Name, Address)	Tris Pharma, Inc. 3022 Route 130, Monmouth Junction, NJ 08852	

Study Ref No.	Testing Date	Product ID \ Batch No.	Dosage Strength & Form	No. of Dosage Units		Collection Times (hours) 1	3	6	12	Study Report Location
N/A	9/17/08	Dextromethorphan Polistirex ER Oral Suspension TB-023A (Date of Mfr: 09/03/08)	Oral Suspension, eq. to 30 mg/5mL	12	Mean	30.9	58.3	73.7	86.4	Notebook: QC0170
					Range	(b) (4)				
					SD	1.6	2.8	2.8	2.2	Page: 055 and 65
					%CV	5.3	4.7	3.8	2.6	
N/A	8/31/07	Delsym® ER Oral Suspension 39469 (Expiry Date: Dec 08)	Oral Suspension, eq. to 30 mg/5mL	12	Mean	22.8	64.2	77.4	83.6	Notebook: QC0170
					Range	(b) (4)				
					SD	1.0	1.8	1.1	1.0	Page: 001
					%CV	4.4	2.9	1.4	1.2	

FDA-Recommended Method:

Dissolution Conditions	**Apparatus:**	USP II (Paddle)
	Speed of Rotation:	50 rpm
	Medium:	0.1 N HCl
	Volume:	500 mL
	Temperature:	37 °C ± 0.5 °C
Firm's Proposed Specifications	Not applicable	
Dissolution Testing Site (Name, Address)	Tris Pharma, Inc. 3022 Route 130, Monmouth Junction, NJ 08852	

Study Ref No.	Testing Date	Product ID \ Batch No.	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes) 30	60	90	180	Study Report Location
N/A	12/03/08	Dextromethorphan Polistirex ER Oral Suspension TB-023A (Date of Mfr: 09/03/08)	Oral Suspension, eq. to 30 mg/5mL	12	Mean	26.2	30.0	32.7	36.0	Notebook: QC0212
					Range	(b) (4)				
					SD	2.1	2.4	2.4	1.9	Page: 008
					%CV	8.0	7.9	7.4	5.5	
N/A	09/27/07	Delsym® ER Oral Suspension 39469 (Expiry Date: Dec 08)	Oral Suspension, eq. to 30 mg/5mL	12	Mean	21.3	23.3	24.6	27.7	Notebook: QC0151
					Range	(b) (4)				
					SD	1.4	1.8	2.4	3.6	Page: 068
					%CV	6.8	7.9	9.6	12.9	

pH 1.2 Method:

Dissolution Conditions	**Apparatus:**	USP II (Paddle)
	Speed of Rotation:	50 rpm
	Medium:	pH 1.2 Buffer
	Volume:	900 mL
	Temperature:	37 °C ± 0.5 °C
Firm's Proposed Specifications	Not applicable	
Dissolution Testing Site (Name, Address)	Tris Pharma, Inc. 3022 Route 130, Monmouth Junction, NJ 08852	

Study Ref No.	Testing Date	Product ID \ Batch No.	Dosage Strength & Form	No. of Dosage Units		Collection Times (hours) 1	2	4	6	8	10	12	Study Report Location
N/A	12/05/08	Dextromethorphan Polistirex ER Oral Suspension TB-023A (Date of Mfr: 09/03/08)	Oral Suspension, eq. to 30 mg/5mL	12	Mean	56.0	66.5	74.1	77.0	78.3	79.1	78.9	Notebook: QC0212 Page: 013
					Range							(b) (4)	
					SD	1.9	1.7	1.5	1.4	1.4	1.4	1.3	
					%CV	3.4	2.6	2.0	1.8	1.8	1.7	1.7	
N/A	10/02/07	Delsym® ER Oral Suspension 39469 (Expiry Date: Dec 08)	Oral Suspension, eq. to 30 mg/5mL	12	Mean	38.2	47.5	55.6	59.0	60.9	62.2	63.2	Notebook: QC0170 Page: 016
					Range							(b) (4)	
					SD	0.8	1.3	1.8	2.0	2.0	1.8	1.8	
					%CV	2.0	2.7	3.2	3.4	3.3	3.0	2.8	

pH 4.5 buffer:

Dissolution Conditions	**Apparatus:**	USP II (Paddle)
	Speed of Rotation:	50 rpm
	Medium:	pH 4.5 Buffer
	Volume:	900 mL
	Temperature:	37 °C ± 0.5 °C
Firm's Proposed Specifications	Not applicable	
Dissolution Testing Site (Name, Address)	Tris Pharma, Inc. 3022 Route 130, Monmouth Junction, NJ 08852	

Study Ref No.	Testing Date	Product ID \ Batch No.	Dosage Strength & Form	No. of Dosage Units		Collection Times (hours) 1	2	4	6	8	10	12	Study Report Location
N/A	12/03/08	Dextromethorphan Polistirex ER Oral Suspension TB-023A (Date of Mfr: 09/03/08)	Oral Suspension, eq. to 30 mg/5mL	12	Mean	36.5	45.5	54.1	58.0	60.1	61.2	62.0	Notebook: QC0170 Page: 072
					Range	(b) (4)							
					SD	1.5	1.3	1.0	0.8	0.7	0.6	0.6	
					%CV	4.0	2.9	1.9	1.4	1.2	1.0	1.0	
N/A	10/17/07	Delsym® ER Oral Suspension 39469 (Expiry Date: Dec 08)	Oral Suspension, eq. to 30 mg/5mL	12	Mean	17.8	27.3	38.4	44.6	48.3	50.6	52.2	Notebook: QC0151 Page: 080
					Range	(b) (4)							
					SD	1.5	1.9	1.9	1.4	1.1	0.8	0.7	
					%CV	8.7	6.9	5.0	3.2	2.2	1.7	1.3	

pH 6.8 buffer:

Dissolution Conditions	**Apparatus:**	USP II (Paddle)
	Speed of Rotation:	50 rpm
	Medium:	pH 6.8 Buffer
	Volume:	900 mL
	Temperature:	37 °C ± 0.5 °C
Firm's Proposed Specifications	Not applicable	
Dissolution Testing Site (Name, Address)	Tris Pharma, Inc. 3022 Route 130, Monmouth Junction, NJ 08852	

Study Ref No.	Testing Date	Product ID \ Batch No.	Dosage Strength & Form	No. of Dosage Units		Collection Times (hours) 1	2	4	6	8	10	12	Study Report Location
N/A	12/08/08	Dextromethorphan Polistirex ER Oral Suspension TB-023A (Date of Mfr: 09/03/08)	Oral Suspension, eq. to 30 mg/5mL	12	Mean	33.9	43.8	56.4	63.5	68.7	70.9	72.9	Notebook: QC0151 Page: 080
					Range	(b) (4)							
					SD	1.4	2.3	4.9	6.2	7.4	7.1	7.0	
					%CV	1.4	5.3	8.7	9.7	10.8	10.0	9.7	
N/A	11/11/07	Delsym® ER Oral Suspension 39469 (Expiry Date: Dec 08)	Oral Suspension, eq. to 30 mg/5mL	12	Mean	26.5	38.2	52.9	60.6	64.9	67.3	69.0	Notebook: QC0170 Page: 036
					Range	(b) (4)							
					SD	1.8	2.8	3.9	4.4	4.7	4.7	4.4	
					%CV	6.7	7.4	7.4	7.3	7.2	7.0	6.4	

Water:

Dissolution Conditions	**Apparatus:**	USP II (Paddle)
	Speed of Rotation:	50 rpm
	Medium:	Water
	Volume:	900 mL
	Temperature:	37 °C ± 0.5 °C
Firm's Proposed Specifications	Not applicable	
Dissolution Testing Site (Name, Address)	Tris Pharma, Inc. 3022 Route 130, Monmouth Junction, NJ 08852	

Study Ref No.	Testing Date	Product ID \ Batch No.	Dosage Strength & Form	No. of Dosage Units		Collection Times (hours) 1	2	4	6	8	10	12	Study Report Location
N/A	08/06/09	Dextromethorphan Polistirex ER Oral Suspension TB-023A (Date of Mfr: 09/03/08)	Oral Suspension, eq. to 30 mg/5mL	12	Mean	2.5	2.5	2.5	3.0	2.9	3.1	3.1	Notebook: QC0151 Page: 106
					Range							(b) (4)	
					SD	0.2	0.3	0.3	0.4	0.4	0.6	0.4	
					%CV	7.5	11.4	11.2	12.4	14.1	17.9	13.8	
N/A	08/06/09	Delsym® ER Oral Suspension 49775 (Expiry Date: Feb 11)	Oral Suspension, eq. to 30 mg/5mL	12	Mean	0.6	0.7	0.8	0.8	1.0	0.8	0.8	Notebook: QC0153 Page: 046
					Range							(b) (4)	
					SD	0.1	0.1	0.1	0.1	0.1	0.1	0.1	
					%CV	10.4	15.2	13.8	13.0	14.7	15.4	16.2	

Reviewer's comments on dissolution:

The firm submitted comparative dissolution testing data for both the firm's proposed method and the FDA-recommended method. The sampling for the dissolution testing conducted using the FDA-recommended method was not taken to the time point of complete dissolution: At 180 minutes, less than (b)(4)% LC of both the test and RLD products was dissolved.

However, the firm also conducted dissolution with its own proposed method. The firm's method provided faster dissolution at 180 minutes for both the test and RLD product. The firm's method is sufficiently discriminating. For this reason, the firm's proposed method was accepted by the 'dissolution only' reviewer.

On September 25, 2009, the firm has acknowledged the following dissolution method and specifications: 500 mL of 0.1 N HCl with addition of 400 mL of Phosphate Buffer after 1 hr at 37°C, using USP Apparatus II (Paddle) at 50 rpm. Specifications = 1 hr: NMT (b)(4)%, 3 hrs: (b)(4)% - (b)(4)%, 6 hrs: (b)(4)% - (b)(4)% and 12 hrs: NLT (b)(4)%.

On October 9, 2009, the firm submitted an additional amendment updating the new product dissolution specification, release specification and stability specification, as well as submitted additional stability data. With regard to the change in the dissolution specification, this reviewer finds the amendment acceptable (adequate). The chemistry team will need to further review this amendment.

The comparative dissolution testing is acceptable (adequate) at this time.

4.4 Consult Reviews

None.

4.5 SAS Output

4.5.1 Fasting Study Data Dextromethorphan - TRT*GRP in Model

FASTING CONCENTRATION DATASET

Obs	sub	seq	per	grp	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15
1	1	1	1	1	A	0.00	112.30	483.40	989.80	1230.00	1513.0	1792.0	1999.0	1976.0	2046.0	1939.0	1906.0	1188.0	1031.0	805.90
2	1	1	2	1	B	0.00	165.90	781.20	1003.00	1356.00	1520.0	2086.0	2274.0	2568.0	2141.0	1896.0	1960.0	1299.0	1108.0	818.30
3	2	1	1	1	A	0.00	90.37	2190.00	8121.00	13850.00	18510.0	25960.0	25690.0	30730.0	32380.0	32110.0	35890.0	29870.0	30030.0	35210.00
4	2	1	2	1	B	587.80	628.20	2516.00	8842.00	20060.00	25100.0	26980.0	28280.0	32640.0	37490.0	38250.0	40220.0	33510.0	33580.0	29500.00
5	3	2	1	1	B	0.00	142.10	1021.00	1929.00	2737.00	4048.0	6619.0	7035.0	7097.0	6939.0	6741.0	6399.0	4491.0	3316.0	2940.00
6	3	2	2	1	A	0.00	194.30	1573.00	2917.00	3667.00	4433.0	5332.0	7006.0	7377.0	8117.0	7543.0	6581.0	4881.0	3953.0	3350.00
7	5	2	1	1	B	0.00	70.13	374.30	568.90	720.90	876.7	972.2	1116.0	1012.0	886.0	876.9	691.0	552.0	429.7	332.50
8	5	2	2	1	A	0.00	139.20	519.60	975.90	1091.00	1208.0	1432.0	1531.0	1428.0	1509.0	1170.0	1016.0	754.2	571.3	471.10
9	7	2	1	1	B	0.00	227.70	3369.00	6603.00	10730.00	14580.0	19550.0	28810.0	28580.0	32000.0	29820.0	31210.0	30060.0	29750.0	31320.00
10	7	2	2	1	A	0.00	672.60	7303.00	12380.00	19620.00	23570.0	25540.0	26120.0	28560.0	26040.0	24240.0	23560.0	21660.0	21130.0	19510.00
11	8	1	1	1	A	20.67	209.00	460.80	701.40	1431.00	1563.0	2133.0	2557.0	2033.0	1946.0	1831.0	1420.0	1125.0	935.8	753.00
12	8	1	2	1	B	0.00	191.60	865.80	1775.00	1326.00	1486.0	1453.0	1723.0	1683.0	1636.0	1481.0	1253.0	1032.0	730.8	392.20
13	9	2	1	1	B	0.00	59.07	189.10	269.80	429.80	562.4	954.8	1226.0	1116.0	1066.0	988.0	1054.0	755.5	523.6	331.20
14	9	2	2	1	A	0.00	234.50	277.70	483.80	526.50	615.5	720.6	791.1	848.0	834.3	726.5	674.1	497.8	394.4	266.80
15	10	1	1	1	A	0.00	199.90	1117.00	1392.00	1413.00	1658.0	1629.0	1766.0	1867.0	1571.0	1822.0	1260.0	839.1	740.1	565.30
16	10	1	2	1	B	0.00	326.80	997.30	1590.00	1677.00	1781.0	1795.0	1976.0	1969.0	1674.0	1502.0	1306.0	896.6	644.5	494.20
17	11	1	1	1	A	0.00	1365.00	14850.00	28230.00	35540.00	41200.0	47240.0	48690.0	48570.0	53760.0	58020.0	47770.0	43820.0	46220.0	41190.00
18	11	1	2	1	B	664.50	861.80	2995.00	11300.00	28060.00	44340.0	44200.0	48700.0	54830.0	51930.0	56880.0	48550.0	42190.0	49430.0	44980.00
19	12	2	1	1	B	0.00	260.80	819.80	1375.00	1400.00	1520.0	1570.0	1447.0	1532.0	1386.0	1348.0	1209.0	837.4	577.3	395.80

Obs	sub	seq	per	grp	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15
20	12	2	2	1	A	0.00	177.80	564.90	876.30	1001.00	1039.0	1361.0	1343.0	1206.0	1161.0	1251.0	944.7	702.0	540.0	396.80
21	13	2	1	1	B	0.00	53.83	105.70	163.90	239.90	345.6	379.4	433.5	397.1	416.1	378.7	320.4	253.8	187.8	151.50
22	13	2	2	1	A	0.00	68.83	154.70	221.20	268.60	323.5	424.0	424.0	414.6	396.2	411.0	372.5	282.8	224.9	189.70
23	14	1	1	1	A	0.00	298.40	2427.00	4762.00	6525.00	7859.0	11600.0	11110.0	11510.0	10640.0	10570.0	9989.0	8079.0	6337.0	4882.00
24	14	1	2	1	B	0.00	265.00	1629.00	4173.00	5241.00	8039.0	8741.0	7960.0	9307.0	7514.0	8528.0	8202.0	6024.0	5107.0	3742.00
25	15	2	1	1	B	0.00	226.70	5174.00	8182.00	11230.00	14580.0	17110.0	18880.0	18220.0	18990.0	17790.0	14660.0	13970.0	12690.0	9327.00
26	15	2	2	1	A	14.78	381.10	5023.00	11640.00	13550.00	21870.0	20550.0	21000.0	20990.0	19950.0	21230.0	16620.0	14730.0	12430.0	11650.00
27	17	1	1	1	A	0.00	181.90	963.20	1797.00	2182.00	2474.0	3124.0	3366.0	3427.0	3084.0	3000.0	2641.0	1989.0	1690.0	1114.00
28	17	1	2	1	B	0.00	585.60	1392.00	1952.00	1892.00	2391.0	2907.0	3028.0	3174.0	2946.0	2698.0	2322.0	1592.0	1416.0	945.60
29	18	1	1	1	A	0.00	230.00	2399.00	5821.00	8087.00	12710.0	16050.0	14540.0	12980.0	15300.0	15040.0	13070.0	12790.0	12420.0	11110.00
30	18	1	2	1	B	19.21	90.43	811.80	1510.00	3038.00	7120.0	9532.0	11630.0	11210.0	14170.0	12340.0	14060.0	11840.0	11250.0	8255.00
31	19	1	1	1	A	0.00	323.10	1085.00	1332.00	1231.00	1312.0	1668.0	1528.0	1471.0	1400.0	1257.0	1050.0	828.8	514.5	370.30
32	19	1	2	1	B	0.00	476.90	1648.00	1853.00	1768.00	1974.0	2642.0	2507.0	2333.0	2195.0	1964.0	1663.0	1076.0	857.7	554.30
33	20	1	1	1	A	0.00	49.04	2231.00	5569.00	11810.00	12850.0	17430.0	22750.0	32480.0	27950.0	26170.0	30210.0	30950.0	34470.0	33170.00
34	20	1	2	1	B	808.30	1278.00	3277.00	6680.00	12840.00	20420.0	23940.0	32410.0	31250.0	35340.0	33910.0	34400.0	31510.0	34170.0	31420.00
35	21	1	1	1	A	0.00	153.90	367.20	534.30	953.40	948.3	1335.0	1520.0	1700.0	1740.0	1717.0	1614.0	1137.0	927.6	712.40
36	21	1	2	1	B	0.00	138.10	553.40	969.80	1223.00	1398.0	1905.0	1501.0	1789.0	1493.0	1541.0	1464.0	1337.0	891.9	654.50
37	22	2	1	1	B	0.00	252.10	1389.00	2408.00	3631.00	4159.0	4592.0	4527.0	4552.0	4367.0	4396.0	3486.0	2590.0	2112.0	1345.00
38	22	2	2	1	A	0.00	644.70	2239.00	2958.00	3195.00	3733.0	3738.0	3987.0	3388.0	3724.0	3278.0	2656.0	2035.0	1431.0	984.20
39	23	2	1	1	B	0.00	221.00	1263.00	2832.00	3769.00	4771.0	5608.0	5850.0	5383.0	4684.0	5280.0	4128.0	3117.0	2442.0	1678.00
40	23	2	2	1	A	0.00	1065.00	3591.00	4086.00	4456.00	5119.0	5729.0	5917.0	5733.0	5361.0	4799.0	4354.0	3503.0	2626.0	1847.00
41	24	2	1	1	B	0.00	93.74	478.80	990.30	1273.00	1310.0	1278.0	1366.0	1504.0	1230.0	1206.0	1025.0	900.9	584.5	433.10
42	24	2	2	1	A	0.00	185.60	783.50	1279.00	1727.00	2006.0	2071.0	2131.0	2258.0	1832.0	1905.0	1654.0	1174.0	931.2	717.70
43	25	2	1	1	B	0.00	180.70	847.00	1342.00	1475.00	2249.0	2124.0	2304.0	1953.0	2012.0	1859.0	1581.0	1247.0	872.7	585.30
44	25	2	2	1	A	0.00	374.00	749.40	827.20	747.90	912.6	1119.0	1201.0	1046.0	1090.0	991.9	831.5	606.0	462.8	317.00
45	26	2	1	1	B	0.00	52.49	320.50	496.60	1234.00	1454.0	2109.0	2171.0	2353.0	2462.0	2331.0	2284.0	1678.0	1086.0	693.00
46	26	2	2	1	A	0.00	575.20	1038.00	1152.00	1517.00	1642.0	1725.0	1844.0	1805.0	1788.0	1642.0	1377.0	1036.0	660.7	415.00
47	27	1	1	1	A	0.00	123.00	1799.00	4865.00	8251.00	14660.0	18260.0	18700.0	19870.0	18850.0	18710.0	17010.0	15910.0	15430.0	14280.00
48	27	1	2	1	B	0.00	276.00	4418.00	9250.00	14650.00	20070.0	18540.0	20940.0	20970.0	20690.0	19970.0	17450.0	16230.0	15430.0	13610.00

Obs	sub	seq	per	grp	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15
49	28	1	1	1	A	0.00	234.90	653.10	917.30	980.10	935.0	1023.0	917.7	1014.0	887.6	837.9	637.5	528.9	427.9	295.60
50	28	1	2	1	B	0.00	356.40	873.30	1119.00	1074.00	1127.0	1178.0	1242.0	977.1	988.4	995.4	857.6	560.4	516.0	346.00
51	30	2	1	1	B	0.00	3247.00	13900.00	19490.00	26710.00	26770.0	36630.0	39540.0	37880.0	39880.0	35370.0	39240.0	32290.0	34020.0	31960.00
52	30	2	2	1	A	278.10	633.10	8712.00	15480.00	24440.00	31630.0	40830.0	37660.0	39900.0	38770.0	39710.0	40970.0	35100.0	34010.0	32730.00
53	31	1	1	1	A	21.42	667.60	3239.00	9288.00	13320.00	20010.0	20140.0	19820.0	19940.0	19590.0	20810.0	17030.0	16360.0	13230.0	10410.00
54	31	1	2	1	B	14.14	978.90	3914.00	8782.00	12230.00	15710.0	20700.0	19710.0	23830.0	20280.0	20190.0	18750.0	14540.0	12630.0	9642.00
55	32	2	1	1	B	0.00	229.90	754.60	986.20	1131.00	1105.0	1152.0	1160.0	1153.0	1097.0	1167.0	985.7	658.1	623.9	337.20
56	32	2	2	1	A	0.00	153.00	627.60	1157.00	1213.00	1290.0	1326.0	1671.0	1655.0	1577.0	1612.0	1347.0	998.8	915.7	533.70
57	35	2	1	1	B	0.00	98.22	310.90	488.00	656.50	746.3	1118.0	1591.0	1682.0	1796.0	1820.0	1717.0	1492.0	1091.0	730.80
58	35	2	2	1	A	0.00	360.40	1382.00	2054.00	2160.00	2505.0	2715.0	2629.0	2585.0	2572.0	2801.0	2327.0	1620.0	1384.0	842.90
59	36	2	1	1	B	0.00	11.28	27.31	60.23	66.85	107.4	260.6	307.8	369.5	338.3	418.1	376.7	295.8	251.2	182.60
60	36	2	2	1	A	0.00	17.36	40.30	72.80	105.30	130.5	218.1	325.9	392.8	334.1	391.1	317.2	240.5	203.9	244.10
61	37	1	1	1	A	0.00	219.40	1772.00	3376.00	3829.00	5000.0	5531.0	5681.0	5084.0	5280.0	4393.0	4357.0	3542.0	2379.0	1882.00
62	37	1	2	1	B	0.00	61.22	410.70	1035.00	1710.00	3132.0	4718.0	5195.0	5189.0	5757.0	5812.0	4714.0	3602.0	2688.0	1691.00
63	38	1	1	1	A	0.00	83.32	608.70	1270.00	1999.00	3342.0	3891.0	3874.0	4158.0	3855.0	4071.0	3895.0	3234.0	2583.0	1713.00
64	38	1	2	1	B	0.00	741.30	3157.00	4827.00	5049.00	5249.0	5450.0	5269.0	5204.0	4880.0	5094.0	4729.0	2965.0	2762.0	1464.00
65	39	1	1	1	A	0.00	355.60	3573.00	9438.00	9499.00	15080.0	17710.0	20020.0	20120.0	18290.0	19080.0	16190.0	13160.0	9624.0	6818.00
66	39	1	2	1	B	957.70	1192.00	4448.00	9397.00	16470.00	21550.0	22620.0	25360.0	23280.0	19620.0	21740.0	19020.0	14250.0	8865.0	5767.00
67	40	2	1	1	B	0.00	97.90	507.90	798.70	1082.00	1454.0	2016.0	2420.0	2890.0	2425.0	2463.0	2221.0	1589.0	1373.0	967.40
68	40	2	2	1	A	0.00	174.70	681.90	1094.00	1451.00	1649.0	1979.0	2250.0	2248.0	2017.0	1963.0	1488.0	1154.0	1030.0	755.80
69	41	2	1	1	B	0.00	44.52	70.06	112.50	168.00	186.2	255.7	354.0	333.7	305.0	279.6	239.7	175.6	144.6	125.60
70	41	2	2	1	A	0.00	111.90	274.00	218.90	251.50	223.7	293.2	302.2	273.9	239.5	215.1	207.9	138.2	108.4	81.76
71	42	2	1	1	B	0.00	169.30	485.80	569.10	577.00	562.6	562.4	611.4	614.6	582.8	590.1	528.4	452.7	391.6	229.10
72	42	2	2	1	A	0.00	359.40	560.10	595.20	707.20	731.0	728.2	849.5	799.9	762.3	735.8	680.8	519.6	464.9	369.70
73	44	2	1	1	B	0.00	394.10	5175.00	7928.00	9951.00	13020.0	12140.0	12140.0	13500.0	12770.0	13190.0	9703.0	8033.0	7650.0	5801.00
74	44	2	2	1	A	0.00	364.60	2763.00	8448.00	8659.00	12000.0	13740.0	11640.0	14480.0	13770.0	13230.0	13000.0	9464.0	9030.0	7102.00
75	45	2	1	1	B	0.00	202.60	502.50	710.80	830.70	896.3	868.3	893.7	873.8	789.5	819.6	722.0	514.1	407.1	283.30
76	45	2	2	1	A	0.00	156.20	424.80	573.80	709.10	700.0	745.8	965.5	914.0	927.3	827.1	666.8	604.5	464.4	338.70
77	47	2	1	1	B	0.00	217.10	2166.00	6991.00	12200.00	13930.0	14130.0	16940.0	15730.0	16890.0	15860.0	15950.0	12220.0	11670.0	9585.00

Obs	sub	seq	per	grp	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15
78	47	2	2	1	A	0.00	99.36	797.60	4731.00	7813.00	11840.0	14970.0	16700.0	17520.0	18630.0	18140.0	15730.0	14800.0	13100.0	11150.00
79	48	1	1	1	A	0.00	631.50	2733.00	3733.00	4038.00	5334.0	5487.0	5208.0	5012.0	5116.0	4682.0	4312.0	3030.0	2570.0	1575.00
80	48	1	2	1	B	0.00	370.20	1937.00	3168.00	3349.00	3846.0	3608.0	4089.0	4043.0	3487.0	3347.0	3004.0	1936.0	1621.0	1082.00
81	49	1	1	1	A	0.00	125.60	503.10	703.60	1056.00	1652.0	2185.0	2653.0	2559.0	2383.0	2310.0	2028.0	1695.0	1308.0	926.10
82	49	1	2	1	B	0.00	99.58	420.10	835.50	1139.00	1254.0	1697.0	1714.0	1611.0	1540.0	1536.0	1295.0	1207.0	817.2	507.70
83	50	2	1	1	B	0.00	40.39	142.40	329.70	508.20	580.1	1392.0	1282.0	1284.0	1373.0	1359.0	1145.0	749.9	627.4	373.80
84	50	2	2	1	A	0.00	77.49	237.20	484.80	668.40	930.2	2154.0	2082.0	2343.0	1973.0	1919.0	1623.0	1189.0	737.5	577.30
85	52	2	1	1	B	0.00	180.10	1848.00	3675.00	4718.00	5301.0	6010.0	5981.0	6495.0	6617.0	5740.0	5226.0	4378.0	3926.0	2669.00
86	52	2	2	1	A	0.00	158.00	2190.00	3389.00	5093.00	5565.0	6186.0	6190.0	6007.0	6130.0	6110.0	5434.0	4325.0	3353.0	2441.00
87	55	2	1	2	B	0.00	97.12	300.40	529.00	729.30	1058.0	1360.0	1726.0	1559.0	1719.0	1752.0	1552.0	1151.0	831.1	635.20
88	55	2	2	2	A	0.00	158.70	606.20	824.80	955.50	1094.0	1492.0	1434.0	1495.0	1571.0	1376.0	1115.0	881.4	664.9	462.70
89	56	1	1	2	A	0.00	68.81	218.20	359.90	336.60	533.3	904.9	1022.0	1005.0	1122.0	1016.0	790.0	596.1	526.2	446.90
90	56	1	2	2	B	0.00	137.10	436.60	623.40	736.50	786.3	1141.0	1326.0	1429.0	1593.0	1331.0	1302.0	1242.0	978.4	886.80
91	57	1	1	2	A	0.00	185.60	428.10	802.30	835.10	946.2	1134.0	1276.0	1265.0	1121.0	1177.0	1041.0	761.6	593.1	415.00
92	57	1	2	2	B	0.00	262.80	1066.00	1531.00	1832.00	1788.0	1890.0	1707.0	1743.0	1533.0	1398.0	1227.0	919.4	750.6	458.90
93	59	1	1	2	A	0.00	333.20	767.80	1321.00	1555.00	1794.0	1975.0	2194.0	1751.0	1849.0	2007.0	1643.0	1212.0	874.5	619.10
94	59	1	2	2	B	0.00	669.70	1776.00	2366.00	2117.00	2053.0	2336.0	1907.0	1740.0	1525.0	1487.0	1210.0	917.5	594.0	516.50
95	60	2	1	2	B	0.00	110.90	1706.00	7113.00	13720.00	21380.0	22060.0	23460.0	22910.0	25420.0	27570.0	30540.0	28180.0	26260.0	25560.00
96	60	2	2	2	A	450.70	670.90	3275.00	9184.00	17700.00	20710.0	27160.0	25630.0	26220.0	28980.0	26070.0	28160.0	29280.0	26580.0	28540.00
97	61	1	1	2	A	0.00	121.70	335.40	675.20	791.80	897.5	977.2	1032.0	1187.0	1014.0	1059.0	915.9	796.1	653.1	463.70
98	61	1	2	2	B	0.00	77.12	206.40	346.60	464.40	519.8	597.8	614.4	656.1	603.1	668.4	671.7	537.6	454.7	331.30
99	62	2	1	2	B	0.00	78.94	168.10	166.40	206.70	235.3	262.4	263.3	283.9	239.8	277.5	225.8	152.1	126.1	81.51
100	62	2	2	2	A	0.00	57.02	160.30	200.90	279.20	293.7	240.3	313.0	249.8	275.7	224.0	189.3	163.0	134.9	85.87
101	63	2	1	2	B	0.00	180.70	798.70	1817.00	1997.00	2196.0	2203.0	2567.0	2366.0	2144.0	2000.0	1785.0	1185.0	841.9	557.10
102	63	2	2	2	A	0.00	159.60	827.60	1633.00	1829.00	2123.0	2217.0	2470.0	2607.0	2181.0	2083.0	2107.0	1378.0	1035.0	734.70
103	64	2	1	2	B	0.00	72.64	141.70	179.60	200.00	237.9	293.0	371.9	428.6	410.9	444.5	404.1	294.9	277.3	181.90
104	64	2	2	2	A	0.00	47.56	118.40	140.90	181.40	223.4	263.5	290.2	301.5	342.6	294.9	272.2	221.8	182.7	122.70
105	65	1	1	2	A	0.00	84.59	1010.00	3624.00	6013.00	8315.0	11980.0	12620.0	11660.0	13440.0	10970.0	11620.0	8982.0	7640.0	5728.00
106	65	1	2	2	B	0.00	161.70	2850.00	4684.00	8593.00	9958.0	13180.0	14120.0	13970.0	13600.0	14480.0	12070.0	9593.0	9417.0	6786.00

Obs	c16	c17	c18	c19	KE_FIRST	KE_LAST	t1	t2	t3	t4	t5	t6	t7	t8	t9	t10	t11	t12	t13	t14	t15	t16	t17	t18	t19	trt
1	386.00	206.20	.	28.39	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
2	398.20	198.10	116.90	39.96	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
3	31980.00	24590.00	23770.00	19810.00	.	.	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
4	30840.00	25090.00	20690.00	16250.00	.	.	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
5	1572.00	.	.	.	15	16	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
6	1877.00	.	.	.	15	16	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
7	201.20	69.46	25.38	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
8	240.90	156.80	50.68	10.59	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
9	26140.00	18980.00	12890.00	7057.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
10	13430.00	8156.00	5769.00	2185.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
11	347.00	101.00	45.73	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
12	241.90	79.31	38.24	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
13	184.50	82.48	27.36	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
14	144.30	28.04	0.00	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
15	341.00	155.70	71.40	16.12	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
16	329.20	249.30	131.60	20.96	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
17	34370.00	27620.00	23070.00	17790.00	.	.	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
18	38660.00	35300.00	31290.00	21000.00	.	.	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
19	225.00	114.80	41.36	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
20	219.60	93.30	34.39	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
21	97.35	35.64	15.17	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
22	137.30	74.38	59.31	10.08	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
23	3206.00	1008.00	461.10	78.27	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
24	1950.00	746.90	360.70	54.55	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
25	6556.00	3310.00	1705.00	582.30	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
26	7015.00	3997.00	2485.00	914.30	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
27	709.60	258.60	84.79	12.54	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
28	742.20	279.20	105.20	17.66	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2

Obs	c16	c17	c18	c19	KE_FIRST	KE_LAST	t1	t2	t3	t4	t5	t6	t7	t8	t9	t10	t11	t12	t13	t14	t15	t16	t17	t18	t19	trt
29	8034.00	5512.00	3751.00	1216.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
30	6035.00	3134.00	1649.00	586.50	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
31	229.40	188.70	79.73	25.37	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
32	342.00	207.30	108.30	30.48	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
33	31250.00	24340.00	24600.00	19890.00	.	.	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
34	33610.00	26360.00	24280.00	18120.00	.	.	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
35	401.30	199.10	101.50	48.97	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
36	448.10	215.40	138.80	45.11	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
37	740.90	230.80	99.41	20.20	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
38	695.80	197.30	83.50	14.39	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
39	979.20	199.90	69.63	13.37	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
40	961.40	191.00	65.83	15.88	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
41	257.20	56.30	20.37	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
42	453.70	125.10	44.53	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
43	310.10	145.30	85.99	11.62	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
44	204.50	97.66	56.52	14.08	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
45	355.10	159.60	66.90	27.75	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
46	227.50	87.71	31.03	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
47	14150.00	7968.00	5185.00	1659.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
48	9286.00	6198.00	.	1467.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
49	215.30	112.50	45.62	11.91	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
50	186.00	76.02	38.07	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
51	31580.00	26370.00	23960.00	15120.00	.	.	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
52	27240.00	23010.00	21430.00	11500.00	.	.	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
53	7771.00	6249.00	4276.00	2366.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
54	7150.00	4416.00	2874.00	761.10	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
55	282.80	73.84	23.92	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
56	333.40	89.61	42.36	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
57	449.40	171.70	62.66	11.03	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2

Obs	c16	c17	c18	c19	KE_FIRST	KE_LAST	t1	t2	t3	t4	t5	t6	t7	t8	t9	t10	t11	t12	t13	t14	t15	t16	t17	t18	t19	trt
58	526.10	265.70	137.70	53.70	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
59	139.50	57.53	27.11	12.80	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
60	97.04	51.93	37.17	21.16	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
61	1016.00	350.50	96.19	10.52	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
62	1026.00	291.30	107.10	11.79	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
63	865.60	.	26.23	11.17	14	16	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
64	725.60	164.70	.	.	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
65	4392.00	2606.00	1207.00	283.50	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
66	3598.00	1450.00	834.30	312.60	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
67	488.10	170.80	99.25	78.92	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
68	567.00	351.20	242.40	125.50	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
69	73.07	34.92	13.96	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
70	67.50	24.71	0.00	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
71	160.10	45.61	19.86	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
72	213.40	65.51	27.23	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
73	3984.00	1954.00	.	.	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
74	4690.00	2231.00	1212.00	373.80	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
75	158.20	83.37	41.02	12.05	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
76	205.30	78.26	40.45	10.93	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
77	6813.00	4629.00	2664.00	1214.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
78	8251.00	5117.00	3815.00	1616.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
79	845.20	214.60	81.55	10.74	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
80	657.10	260.50	106.80	15.70	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
81	558.80	175.60	87.10	.	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
82	349.50	104.50	52.59	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
83	212.30	91.19	28.90	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
84	326.70	166.60	47.65	10.81	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
85	1644.00	448.30	162.90	39.98	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
86	1352.00	509.00	135.00	33.39	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1

Obs	c16	c17	c18	c19	KE_FIRST	KE_LAST	t1	t2	t3	t4	t5	t6	t7	t8	t9	t10	t11	t12	t13	t14	t15	t16	t17	t18	t19	trt
87	297.60	127.10	95.97	44.34	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
88	260.00	169.40	104.70	41.46	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
89	404.60	289.20	88.98	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
90	483.60	277.80	129.30	41.89	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
91	232.30	97.91	48.88	19.89	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
92	230.60	57.82	20.11	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
93	293.20	163.40	89.38	17.68	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
94	271.80	124.30	71.48	11.13	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
95	20240.00	19660.00	17140.00	13770.00	.	.	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
96	24330.00	22460.00	17510.00	13160.00	.	.	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
97	239.60	.	57.09	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
98	178.20	106.90	56.27	10.37	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
99	48.59	12.16	0.00	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
100	48.20	17.92	0.00	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
101	300.50	56.91	15.51	.	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
102	392.90	160.80	24.17	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
103	104.80	43.30	16.45	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
104	63.31	33.33	16.13	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
105	4980.00	2529.00	1374.00	491.70	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
106	5262.00	2532.00	1546.00	451.70	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2

Reviewer PK Dataset:

Obs	sub	trt	seq	per	grp	auct	auci	CMAX	TMAX	THALFR	KEL
1	1	1	1	1	1	31108.47	31532.84	2046.0	6.5	10.3610	0.06690
2	1	2	1	2	1	32398.32	32969.85	2568.0	6.0	9.9139	0.06992
3	2	1	1	1	1	1806891.37	.	35890.0	8.0	.	.

Obs	sub	trt	seq	per	grp	auct	auci	CMAX	TMAX	THALFR	KEL
4	2	2	1	2	1	1713247.60	.	40220.0	8.0	.	.
5	3	1	2	2	1	122110.80	135071.59	8117.0	6.5	9.5724	0.07241
6	3	2	2	1	1	106822.10	116865.85	7097.0	6.0	8.8572	0.07826
7	5	1	2	2	1	19787.27	19985.26	1531.0	5.5	12.9590	0.05349
8	5	2	2	1	1	13065.53	13386.35	1116.0	5.5	8.7618	0.07911
9	7	1	2	2	1	739509.60	789800.71	28560.0	6.0	15.9538	0.04345
10	7	2	2	1	1	1292341.20	1572689.86	32000.0	6.5	27.5362	0.02517
11	8	1	1	1	1	25605.82	26060.22	2557.0	5.5	6.8876	0.10064
12	8	2	1	2	1	21017.41	21489.82	1775.0	3.0	8.5629	0.08095
13	9	1	2	2	1	10242.49	10487.32	848.0	6.0	6.0522	0.11453
14	9	2	2	1	1	13692.84	14087.55	1226.0	5.5	9.9996	0.06932
15	10	1	1	1	1	25317.99	25567.76	1867.0	6.0	10.7400	0.06454
16	10	2	1	2	1	27450.67	28079.31	1976.0	5.5	20.7890	0.03334
17	11	1	1	1	1	2083320.00	.	58020.0	7.0	.	.
18	11	2	1	2	1	2401989.05	.	56880.0	7.0	.	.
19	12	1	2	2	1	16706.79	17182.46	1361.0	5.0	9.5874	0.07230
20	12	2	2	1	1	19714.86	20388.18	1570.0	5.0	11.2840	0.06143
21	13	1	2	2	1	8336.93	8550.72	424.0	5.5	14.7009	0.04715
22	13	2	2	1	1	5726.03	5933.12	433.5	5.5	9.4622	0.07325
23	14	1	1	1	1	179507.69	180482.84	11600.0	5.0	8.6358	0.08026
24	14	2	1	2	1	134908.25	135585.68	9307.0	6.0	8.6079	0.08052
25	15	1	2	2	1	430712.09	447974.09	21870.0	4.5	13.0866	0.05297
26	15	2	2	1	1	366157.30	377311.36	18990.0	6.5	13.2774	0.05221
27	17	1	1	1	1	46135.50	46305.19	3427.0	6.0	9.3798	0.07390
28	17	2	1	2	1	44061.62	44343.68	3174.0	6.0	11.0706	0.06261

Obs	sub	trt	seq	per	grp	auct	auci	CMAX	TMAX	THALFR	KEL
29	18	1	1	1	1	439284.25	474269.23	16050.0	5.0	19.9422	0.03476
30	18	2	1	2	1	303514.34	315504.93	14170.0	6.5	14.1709	0.04891
31	19	1	1	1	1	21591.48	22376.16	1668.0	5.0	21.4387	0.03233
32	19	2	1	2	1	31370.56	31997.87	2642.0	5.0	14.2657	0.04859
33	20	1	1	1	1	1788769.04	.	34470.0	12.0	.	.
34	20	2	1	2	1	1830931.65	.	35340.0	6.5	.	.
35	21	1	1	1	1	27248.89	28022.26	1740.0	6.5	10.9466	0.06332
36	21	2	1	2	1	29355.52	30161.04	1905.0	5.0	12.3774	0.05600
37	22	1	2	2	1	49234.93	49409.77	3987.0	5.5	8.4219	0.08230
38	22	2	2	1	1	58193.23	58420.59	4592.0	5.0	7.8017	0.08885
39	23	1	2	2	1	75391.25	75529.18	5917.0	5.5	6.0207	0.11513
40	23	2	2	1	1	67675.33	67798.63	5850.0	5.5	6.3924	0.10843
41	24	1	2	2	1	28355.28	28856.03	2258.0	6.0	7.7946	0.08893
42	24	2	2	1	1	17827.31	18023.26	1504.0	6.0	6.6678	0.10395
43	25	1	2	2	1	16092.64	16330.94	1201.0	5.5	11.7313	0.05909
44	25	2	2	1	1	27718.46	27886.49	2304.0	5.5	10.0233	0.06915
45	26	1	2	2	1	21659.75	22058.35	1844.0	5.5	8.9039	0.07785
46	26	2	2	1	1	30019.24	30399.99	2462.0	6.5	9.5104	0.07288
47	27	1	1	1	1	611836.75	665970.20	19870.0	6.0	22.6175	0.03065
48	27	2	1	2	1	545117.00	582844.85	20970.0	6.0	17.8261	0.03888
49	28	1	1	1	1	15095.88	15340.14	1023.0	5.0	14.2156	0.04876
50	28	2	1	2	1	15688.86	16191.92	1242.0	5.5	9.1593	0.07568
51	30	1	2	2	1	1669796.65	.	40970.0	8.0	.	.
52	30	2	2	1	1	1835767.00	.	39880.0	6.5	.	.
53	31	1	1	1	1	507025.81	601905.62	20810.0	7.0	27.7961	0.02494

Obs	sub	trt	seq	per	grp	auct	auci	CMAX	TMAX	THALFR	KEL
54	31	2	1	2	1	426416.17	445865.48	23830.0	6.0	17.7128	0.03913
55	32	1	2	2	1	22446.73	22913.15	1671.0	5.5	7.6322	0.09082
56	32	2	2	1	1	17074.95	17378.59	1167.0	7.0	8.7987	0.07878
57	35	1	2	2	1	41532.45	42463.75	2801.0	7.0	12.0211	0.05766
58	35	2	2	1	1	27253.09	27404.11	1820.0	7.0	9.4910	0.07303
59	36	1	2	2	1	6753.10	7033.78	392.8	6.0	9.1944	0.07539
60	36	2	2	1	1	6887.12	7104.01	418.1	7.0	11.7447	0.05902
61	37	1	1	1	1	73094.06	73218.70	5681.0	5.5	8.2123	0.08440
62	37	2	1	2	1	67453.80	67585.86	5812.0	7.0	7.7640	0.08928
63	38	1	1	1	1	61025.18	61148.91	4158.0	6.0	7.6777	0.09028
64	38	2	1	2	1	69343.25	70338.07	5450.0	5.0	6.2801	0.11037
65	39	1	1	1	1	301115.85	307056.12	20120.0	6.0	14.5237	0.04773
66	39	2	1	2	1	290763.95	295257.99	25360.0	5.5	9.9649	0.06956
67	40	1	2	2	1	37501.00	40765.23	2250.0	5.5	18.0286	0.03845
68	40	2	2	1	1	35762.79	36672.33	2890.0	6.0	7.9884	0.08677
69	41	1	2	2	1	3848.27	4248.65	302.2	5.5	11.2311	0.06172
70	41	2	2	1	1	4411.73	4630.51	354.0	5.5	10.8632	0.06381
71	42	1	2	2	1	13289.20	13600.53	849.5	5.5	7.9250	0.08746
72	42	2	2	1	1	10081.31	10321.77	614.6	6.0	8.3925	0.08259
73	44	1	2	2	1	268910.95	275332.13	14480.0	6.0	11.9070	0.05821
74	44	2	2	1	1	222118.35	245890.01	13500.0	6.0	12.6489	0.05480
75	45	1	2	2	1	13919.23	14067.30	965.5	5.5	9.3902	0.07382
76	45	2	2	1	1	13312.13	13511.14	896.3	4.5	11.4481	0.06055
77	47	1	2	2	1	456293.71	497716.58	18630.0	6.5	17.7674	0.03901
78	47	2	2	1	1	396312.10	429975.87	16940.0	5.5	19.2207	0.03606

Obs	sub	trt	seq	per	grp	auct	auci	CMAX	TMAX	THALFR	KEL
79	48	1	1	1	1	69027.98	69134.51	5487.0	5.0	6.8756	0.10081
80	48	2	1	2	1	51574.50	51793.58	4089.0	5.5	9.6721	0.07166
81	49	1	1	1	1	33703.20	34737.76	2653.0	5.5	8.2331	0.08419
82	49	2	1	2	1	22188.27	22839.63	1714.0	5.5	8.5851	0.08074
83	50	1	2	2	1	24223.56	24398.87	2343.0	6.0	11.2409	0.06166
84	50	2	2	1	1	15601.42	16011.18	1392.0	5.0	9.8278	0.07053
85	52	1	2	2	1	93142.93	93567.61	6190.0	5.5	8.8159	0.07862
86	52	2	2	1	1	98367.16	98807.92	6617.0	6.5	7.6416	0.09071
87	55	1	2	2	2	22102.45	22946.97	1571.0	6.5	14.1191	0.04909
88	55	2	2	1	2	24193.74	24750.11	1752.0	7.0	8.6976	0.07969
89	56	1	1	1	2	18642.44	22641.19	1122.0	6.5	31.1500	0.02225
90	56	2	1	2	2	29578.06	30311.66	1593.0	6.5	12.1389	0.05710
91	57	1	1	1	2	17766.62	18042.12	1276.0	5.5	9.6011	0.07219
92	57	2	1	2	2	21417.80	21610.24	1890.0	5.0	6.6331	0.10450
93	59	1	1	1	2	27815.40	28086.60	2194.0	5.5	10.6325	0.06519
94	59	2	1	2	2	26456.00	26613.33	2366.0	3.0	9.7980	0.07074
95	60	1	2	2	2	1448232.75	.	29280.0	10.0	.	.
96	60	2	2	1	2	1343902.40	.	30540.0	8.0	.	.
97	61	1	1	1	2	17300.48	18326.54	1187.0	6.0	12.4577	0.05564
98	61	2	1	2	2	12612.07	12799.07	671.7	8.0	12.4996	0.05545
99	62	1	2	2	2	3601.26	3829.05	313.0	5.5	8.8108	0.07867
100	62	2	2	1	2	3488.06	3613.77	283.9	6.0	7.1656	0.09673
101	63	1	2	2	2	30786.52	31105.19	2607.0	6.0	9.1389	0.07585
102	63	2	2	1	2	26228.93	26362.63	2567.0	5.5	5.9751	0.11601
103	64	1	2	2	2	4640.73	4891.81	342.6	6.5	10.7899	0.06424

Obs	sub	trt	seq	per	grp	auct	auci	CMAX	TMAX	THALFR	KEL
104	64	2	2	1	2	6534.02	6762.76	444.5	7.0	9.6385	0.07191
105	65	1	1	1	2	249925.74	261602.88	13440.0	6.5	16.4612	0.04211
106	65	2	1	2	2	279924.85	288920.42	14480.0	7.0	13.8040	0.05021

4.5.2 Fasting Study Output Dextromethorphan – TRT*GRP in Model

FASTING STATISTICAL OUTPUT

The GLM Procedure

Class Level Information		
Class	**Levels**	**Values**
sub	53	1 2 3 5 7 8 9 10 11 12 13 14 15 17 18 19 20 21 22 23 24 25 26 27 28 30 31 32 35 36 37 38 39 40 41 42 44 45 47 48 49 50 52 55 56 57 59 60 61 62 63 64 65
trt	2	1 2
per	2	1 2
seq	2	1 2
grp	2	1 2

Data for Analysis of AUCT CMAX LAUCT LCMAX	
Number of Observations Read	106
Number of Observations Used	106

Data for Analysis of AUCI LAUCI	
Number of Observations Read	106
Number of Observations Used	96

Note: Variables in each group are consistent with respect to the presence or absence of missing values.

FASTING STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	56	304.7555078	5.4420626	167.94	<.0001
Error	49	1.5878133	0.0324044		
Corrected Total	105	306.3433211			

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.994817	1.640558	0.180012	10.97261

Source	DF	Type I SS	Mean Square	F Value	Pr > F
grp	1	9.6314360	9.6314360	297.23	<.0001
seq	1	19.0467543	19.0467543	587.78	<.0001
seq*grp	1	2.6332810	2.6332810	81.26	<.0001
sub(seq*grp)	49	273.3630467	5.5788377	172.16	<.0001
per(grp)	2	0.0026539	0.0013270	0.04	0.9599
trt	1	0.0289755	0.0289755	0.89	0.3490
trt*grp	1	0.0493604	0.0493604	1.52	0.2230

Source	DF	Type III SS	Mean Square	F Value	Pr > F
grp	1	11.0958888	11.0958888	342.42	<.0001
seq	1	6.9884827	6.9884827	215.66	<.0001
seq*grp	1	2.6332810	2.6332810	81.26	<.0001
sub(seq*grp)	49	273.3630467	5.5788377	172.16	<.0001
per(grp)	2	0.0036671	0.0018335	0.06	0.9450
trt	1	0.0000132	0.0000132	0.00	0.9839
trt*grp	1	0.0493604	0.0493604	1.52	0.2230

Tests of Hypotheses Using the Type III MS for sub(seq*grp) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	6.98848271	6.98848271	1.25	0.2685
grp	1	11.09588884	11.09588884	1.99	0.1648

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.00090479	0.04474569	-0.02	0.9839


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FASTING STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	56	203.5419849	3.6346783	104.62	<.0001
Error	49	1.7022728	0.0347403		
Corrected Total	105	205.2442577			

R-Square	Coeff Var	Root MSE	LCMAX Mean
0.991706	2.278065	0.186387	8.181831

Source	DF	Type I SS	Mean Square	F Value	Pr > F
grp	1	8.7600057	8.7600057	252.16	<.0001
seq	1	14.9300227	14.9300227	429.76	<.0001
seq*grp	1	1.4245887	1.4245887	41.01	<.0001
sub(seq*grp)	49	178.3962130	3.6407390	104.80	<.0001
per(grp)	2	0.0113776	0.0056888	0.16	0.8494
trt	1	0.0018300	0.0018300	0.05	0.8194
trt*grp	1	0.0179472	0.0179472	0.52	0.4757

Source	DF	Type III SS	Mean Square	F Value	Pr > F
grp	1	9.9614057	9.9614057	286.74	<.0001
seq	1	6.1504522	6.1504522	177.04	<.0001
seq*grp	1	1.4245887	1.4245887	41.01	<.0001
sub(seq*grp)	49	178.3962130	3.6407390	104.80	<.0001
per(grp)	2	0.0107368	0.0053684	0.15	0.8572
trt	1	0.0135649	0.0135649	0.39	0.5350
trt*grp	1	0.0179472	0.0179472	0.52	0.4757

Tests of Hypotheses Using the Type III MS for sub(seq*grp) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	6.15045218	6.15045218	1.69	0.1998
grp	1	9.96140566	9.96140566	2.74	0.1045

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.02895066	0.04633040	-0.62	0.5350

FASTING STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	51	178.9049739	3.5079407	96.56	<.0001
Error	44	1.5984204	0.0363277		
Corrected Total	95	180.5033942			

R-Square	Coeff Var	Root MSE	LAUCI Mean
0.991145	1.789646	0.190598	10.65006

Source	DF	Type I SS	Mean Square	F Value	Pr > F
grp	1	10.4782628	10.4782628	288.44	<.0001
seq	1	12.7936388	12.7936388	352.17	<.0001
seq*grp	1	1.0752145	1.0752145	29.60	<.0001
sub(seq*grp)	44	154.4590961	3.5104340	96.63	<.0001
per(grp)	2	0.0010036	0.0005018	0.01	0.9863
trt	1	0.0562027	0.0562027	1.55	0.2201
trt*grp	1	0.0415553	0.0415553	1.14	0.2907

Source	DF	Type III SS	Mean Square	F Value	Pr > F
grp	1	13.4769579	13.4769579	370.98	<.0001
seq	1	12.4727108	12.4727108	343.34	<.0001
seq*grp	1	1.0752145	1.0752145	29.60	<.0001
sub(seq*grp)	44	154.4590961	3.5104340	96.63	<.0001
per(grp)	2	0.0074200	0.0037100	0.10	0.9031
trt	1	0.0036120	0.0036120	0.10	0.7540
trt*grp	1	0.0415553	0.0415553	1.14	0.2907

Tests of Hypotheses Using the Type III MS for sub(seq*grp) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	12.47271078	12.47271078	3.55	0.0661
grp	1	13.47695793	13.47695793	3.84	0.0564

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	0.01584381	0.05024618	0.32	0.7540

AUCT/AUCI RATIO FOR INDIVIDUAL SUBJECTS

Obs	sub	trt	AUCRATIO
1	1	1	0.99
2	2	1	.
3	3	1	0.90
4	5	1	0.99
5	7	1	0.94
6	8	1	0.98
7	9	1	0.98
8	10	1	0.99
9	11	1	.
10	12	1	0.97
11	13	1	0.97
12	14	1	0.99
13	15	1	0.96
14	17	1	1.00
15	18	1	0.93
16	19	1	0.96
17	20	1	.
18	21	1	0.97
19	22	1	1.00
20	23	1	1.00
21	24	1	0.98
22	25	1	0.99
23	26	1	0.98
24	27	1	0.92
25	28	1	0.98
26	30	1	.
27	31	1	0.84
28	32	1	0.98
29	35	1	0.98
30	36	1	0.96
31	37	1	1.00
32	38	1	1.00
33	39	1	0.98
34	40	1	0.92
35	41	1	0.91
36	42	1	0.98

Obs	sub	trt	AUCRATIO
37	44	1	0.98
38	45	1	0.99
39	47	1	0.92
40	48	1	1.00
41	49	1	0.97
42	50	1	0.99
43	52	1	1.00
44	55	1	0.96
45	56	1	0.82
46	57	1	0.98
47	59	1	0.99
48	60	1	.
49	61	1	0.94
50	62	1	0.94
51	63	1	0.99
52	64	1	0.95
53	65	1	0.96
54	1	2	0.98
55	2	2	.
56	3	2	0.91
57	5	2	0.98
58	7	2	0.82
59	8	2	0.98
60	9	2	0.97
61	10	2	0.98
62	11	2	.
63	12	2	0.97
64	13	2	0.97
65	14	2	1.00
66	15	2	0.97
67	17	2	0.99
68	18	2	0.96
69	19	2	0.98
70	20	2	.
71	21	2	0.97
72	22	2	1.00
73	23	2	1.00
74	24	2	0.99

Obs	sub	trt	AUCRATIO
75	25	2	0.99
76	26	2	0.99
77	27	2	0.94
78	28	2	0.97
79	30	2	.
80	31	2	0.96
81	32	2	0.98
82	35	2	0.99
83	36	2	0.97
84	37	2	1.00
85	38	2	0.99
86	39	2	0.98
87	40	2	0.98
88	41	2	0.95
89	42	2	0.98
90	44	2	0.90
91	45	2	0.99
92	47	2	0.92
93	48	2	1.00
94	49	2	0.97
95	50	2	0.97
96	52	2	1.00
97	55	2	0.98
98	56	2	0.98
99	57	2	0.99
100	59	2	0.99
101	60	2	.
102	61	2	0.99
103	62	2	0.97
104	63	2	0.99
105	64	2	0.97
106	65	2	0.97


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TEST PRODUCT/REFERENCE PRODUCT RATIOS FOR INDIVIDUAL SUBJECTS

sub	seq	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12
1	1	0.96	0.96	0.80	1.08	0.96	1.05
2	1	1.05	.	0.89	1.00	.	.
3	2	1.14	1.16	1.14	1.08	0.93	1.08
5	2	1.51	1.49	1.37	1.00	0.68	1.48
7	2	0.57	0.50	0.89	0.92	1.73	0.58
8	1	1.22	1.21	1.44	1.83	1.24	0.80
9	2	0.75	0.74	0.69	1.09	1.65	0.61
10	1	0.92	0.91	0.94	1.09	1.94	0.52
11	1	0.87	.	1.02	1.00	.	.
12	2	0.85	0.84	0.87	1.00	1.18	0.85
13	2	1.46	1.44	0.98	1.00	0.64	1.55
14	1	1.33	1.33	1.25	0.83	1.00	1.00
15	2	1.18	1.19	1.15	0.69	1.01	0.99
17	1	1.05	1.04	1.08	1.00	1.18	0.85
18	1	1.45	1.50	1.13	0.77	0.71	1.41
19	1	0.69	0.70	0.63	1.00	0.67	1.50
20	1	0.98	.	0.98	1.85	.	.
21	1	0.93	0.93	0.91	1.30	1.13	0.88
22	2	0.85	0.85	0.87	1.10	0.93	1.08
23	2	1.11	1.11	1.01	1.00	1.06	0.94
24	2	1.59	1.60	1.50	1.00	0.86	1.17
25	2	0.58	0.59	0.52	1.00	0.85	1.17
26	2	0.72	0.73	0.75	0.85	1.07	0.94
27	1	1.12	1.14	0.95	1.00	0.79	1.27
28	1	0.96	0.95	0.82	0.91	0.64	1.55
30	2	0.91	.	1.03	1.23	.	.
31	1	1.19	1.35	0.87	1.17	0.64	1.57
32	2	1.31	1.32	1.43	0.79	1.15	0.87
35	2	1.52	1.55	1.54	1.00	0.79	1.27
36	2	0.98	0.99	0.94	0.86	1.28	0.78
37	1	1.08	1.08	0.98	0.79	0.95	1.06
38	1	0.88	0.87	0.76	1.20	0.82	1.22
39	1	1.04	1.04	0.79	1.09	0.69	1.46
40	2	1.05	1.11	0.78	0.92	0.44	2.26
41	2	0.87	0.92	0.85	1.00	0.97	1.03
42	2	1.32	1.32	1.38	0.92	1.06	0.94
44	2	1.21	1.12	1.07	1.00	1.06	0.94
45	2	1.05	1.04	1.08	1.22	1.22	0.82
47	2	1.15	1.16	1.10	1.18	1.08	0.92

sub	seq	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12
48	1	1.34	1.33	1.34	0.91	1.41	0.71
49	1	1.52	1.52	1.55	1.00	1.04	0.96
50	2	1.55	1.52	1.68	1.20	0.87	1.14
52	2	0.95	0.95	0.94	0.85	0.87	1.15
55	2	0.91	0.93	0.90	0.93	0.62	1.62
56	1	0.63	0.75	0.70	1.00	0.39	2.57
57	1	0.83	0.83	0.68	1.10	0.69	1.45
59	1	1.05	1.06	0.93	1.83	0.92	1.09
60	2	1.08	.	0.96	1.25	.	.
61	1	1.37	1.43	1.77	0.75	1.00	1.00
62	2	1.03	1.06	1.10	0.92	0.81	1.23
63	2	1.17	1.18	1.02	1.09	0.65	1.53
64	2	0.71	0.72	0.77	0.93	0.89	1.12
65	1	0.89	0.91	0.93	0.93	0.84	1.19

Firm to Reviewer Ratios:

Obs	sub	seq	per	grp	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
1	1	1	1	1	1	31108.47	31532.84	2046.0	A	31108.47	31629.06	2046.0	1.00000	1.00305	1
2	1	1	2	1	2	32398.32	32969.85	2568.0	B	32398.32	33296.18	2568.0	1.00000	1.00990	1
3	2	1	1	1	1	1806891.37	.	35890.0	A	1806891.37	.	35890.0	1.00000	.	1
4	2	1	2	1	2	1713247.60	.	40220.0	B	1713247.60	.	40220.0	1.00000	.	1
5	3	2	1	1	2	106822.10	116865.85	7097.0	B	78508.94	100902.37	7097.0	0.73495	0.86340	1
6	3	2	2	1	1	122110.80	135071.59	8117.0	A	88324.80	116826.64	8117.0	0.72332	0.86492	1
7	5	2	1	1	2	13065.53	13386.35	1116.0	B	13068.17	13362.37	1116.0	1.00020	0.99821	1
8	5	2	2	1	1	19787.27	19985.26	1531.0	A	19787.27	19944.50	1531.0	1.00000	0.99796	1
9	7	2	1	1	2	1292341.20	1572689.86	32000.0	B	1292253.00	1552844.10	32000.0	0.99993	0.98738	1
10	7	2	2	1	1	739509.60	789800.71	28560.0	A	739509.60	798254.18	28560.0	1.00000	1.01070	1
11	8	1	1	1	1	25605.82	26060.22	2557.0	A	25615.60	26137.89	2557.0	1.00038	1.00298	1
12	8	1	2	1	2	21017.41	21489.82	1775.0	B	21017.41	21526.31	1775.0	1.00000	1.00170	1
13	9	2	1	1	2	13692.84	14087.55	1226.0	B	13692.84	14039.55	1226.0	1.00000	0.99659	1
14	9	2	2	1	1	10242.49	10487.32	848.0	A	10242.49	10498.64	848.0	1.00000	1.00108	1
15	10	1	1	1	1	25317.99	25567.76	1867.0	A	25317.99	25570.06	1867.0	1.00000	1.00009	1
16	10	1	2	1	2	27450.67	28079.31	1976.0	B	27450.67	27750.58	1976.0	1.00000	0.98829	1
17	11	1	1	1	1	2083320.00	.	58020.0	A	2083320.00	.	58020.0	1.00000	.	1
18	11	1	2	1	2	2401989.05	.	56880.0	B	2401989.05	.	56880.0	1.00000	.	1
19	12	2	1	1	2	19714.86	20388.18	1570.0	B	19714.86	20301.66	1570.0	1.00000	0.99576	1
20	12	2	2	1	1	16706.79	17182.46	1361.0	A	16709.57	17163.83	1361.0	1.00017	0.99892	1
21	13	2	1	1	2	5726.03	5933.12	433.5	B	5726.03	5921.88	433.5	1.00000	0.99811	1
22	13	2	2	1	1	8336.93	8550.72	424.0	A	8336.93	8526.75	424.0	1.00000	0.99720	1
23	14	1	1	1	1	179507.69	180482.84	11600.0	A	179644.94	180738.44	11600.0	1.00076	1.00142	1
24	14	1	2	1	2	134908.25	135585.68	9307.0	B	134908.25	135632.23	9307.0	1.00000	1.00034	1

Obs	sub	seq	per	grp	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
25	15	2	1	1	2	366157.30	377311.36	18990.0	B	366157.30	377421.42	18990.0	1.00000	1.00029	1
26	15	2	2	1	1	430712.09	447974.09	21870.0	A	430712.09	452971.91	21870.0	1.00000	1.01116	1
27	17	1	1	1	1	46135.50	46305.19	3427.0	A	46135.50	46284.20	3427.0	1.00000	0.99955	1
28	17	1	2	1	2	44061.62	44343.68	3174.0	B	44061.62	44288.69	3174.0	1.00000	0.99876	1
29	18	1	1	1	1	439284.25	474269.23	16050.0	A	439284.25	472326.38	16050.0	1.00000	0.99590	1
30	18	1	2	1	2	303514.34	315504.93	14170.0	B	303497.39	315408.23	14170.0	0.99994	0.99969	1
31	19	1	1	1	1	21591.48	22376.16	1668.0	A	21591.48	22113.90	1668.0	1.00000	0.98828	1
32	19	1	2	1	2	31370.56	31997.87	2642.0	B	31370.56	31943.58	2642.0	1.00000	0.99830	1
33	20	1	1	1	1	1788769.04	.	34470.0	A	1788769.04	.	34470.0	1.00000	.	1
34	20	1	2	1	2	1830931.65	.	35340.0	B	1830931.65	.	35340.0	1.00000	.	1
35	21	1	1	1	1	27248.89	28022.26	1740.0	A	27259.51	28203.42	1740.0	1.00039	1.00646	1
36	21	1	2	1	2	29355.52	30161.04	1905.0	B	29362.31	30309.13	1905.0	1.00023	1.00491	1
37	22	2	1	1	2	58193.23	58420.59	4592.0	B	58193.23	58492.57	4592.0	1.00000	1.00123	1
38	22	2	2	1	1	49234.93	49409.77	3987.0	A	49234.93	49432.58	3987.0	1.00000	1.00046	1
39	23	2	1	1	2	67675.33	67798.63	5850.0	B	68143.76	68286.59	5850.0	1.00692	1.00720	1
40	23	2	2	1	1	75391.25	75529.18	5917.0	A	75412.19	75581.94	5917.0	1.00028	1.00070	1
41	24	2	1	1	2	17827.31	18023.26	1504.0	B	17827.31	18032.57	1504.0	1.00000	1.00052	1
42	24	2	2	1	1	28355.28	28856.03	2258.0	A	28355.28	28857.22	2258.0	1.00000	1.00004	1
43	25	2	1	1	2	27718.46	27886.49	2304.0	B	27718.46	27886.74	2304.0	1.00000	1.00001	1
44	25	2	2	1	1	16092.64	16330.94	1201.0	A	16092.64	16347.24	1201.0	1.00000	1.00100	1
45	26	2	1	1	2	30019.24	30399.99	2462.0	B	30019.24	30501.33	2462.0	1.00000	1.00333	1
46	26	2	2	1	1	21659.75	22058.35	1844.0	A	21663.16	22037.44	1844.0	1.00016	0.99905	1
47	27	1	1	1	1	611836.75	665970.20	19870.0	A	625422.09	667398.48	19870.0	1.02220	1.00214	1
48	27	1	2	1	2	545117.00	582844.85	20970.0	B	545117.00	582860.83	20970.0	1.00000	1.00003	1
49	28	1	1	1	1	15095.88	15340.14	1023.0	A	15109.25	15310.79	1023.0	1.00089	0.99809	1

Obs	sub	seq	per	grp	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
50	28	1	2	1	2	15688.86	16191.92	1242.0	B	15688.86	16213.29	1242.0	1.00000	1.00132	1
51	30	2	1	1	2	1835767.00	.	39880.0	B	1835879.50	.	39880.0	1.00006	.	1
52	30	2	2	1	1	1669796.65	.	40970.0	A	1669796.65	.	40970.0	1.00000	.	1
53	31	1	1	1	1	507025.81	601905.62	20810.0	A	510275.28	602577.49	20810.0	1.00641	1.00112	1
54	31	1	2	1	2	426416.17	445865.48	23830.0	B	433377.39	451183.00	23830.0	1.01632	1.01193	1
55	32	2	1	1	2	17074.95	17378.59	1167.0	B	17074.95	17307.37	1167.0	1.00000	0.99590	1
56	32	2	2	1	1	22446.73	22913.15	1671.0	A	22446.73	22919.88	1671.0	1.00000	1.00029	1
57	35	2	1	1	2	27253.09	27404.11	1820.0	B	27255.36	27399.12	1820.0	1.00008	0.99982	1
58	35	2	2	1	1	41532.45	42463.75	2801.0	A	41440.36	42514.98	2801.0	0.99778	1.00121	1
59	36	2	1	1	2	6887.12	7104.01	418.1	B	6888.27	7132.80	418.1	1.00017	1.00405	1
60	36	2	2	1	1	6753.10	7033.78	392.8	A	6753.10	7608.76	392.8	1.00000	1.08175	1
61	37	1	1	1	1	73094.06	73218.70	5681.0	A	73129.92	73239.60	5681.0	1.00049	1.00029	1
62	37	1	2	1	2	67453.80	67585.86	5812.0	B	67453.80	67585.54	5812.0	1.00000	1.00000	1
63	38	1	1	1	1	61025.18	61148.91	4158.0	A	65237.55	65357.06	4158.0	1.06903	1.06882	1
64	38	1	2	1	2	69343.25	70338.07	5450.0	B	67696.25	69129.31	5450.0	0.97625	0.98281	1
65	39	1	1	1	1	301115.85	307056.12	20120.0	A	301115.85	305730.02	20120.0	1.00000	0.99568	1
66	39	1	2	1	2	290763.95	295257.99	25360.0	B	290408.41	297647.92	25360.0	0.99878	1.00809	1
67	40	2	1	1	2	35762.79	36672.33	2890.0	B	35769.68	37108.70	2890.0	1.00019	1.01190	1
68	40	2	2	1	1	37501.00	40765.23	2250.0	A	37670.23	42208.77	2250.0	1.00451	1.03541	1
69	41	2	1	1	2	4411.73	4630.51	354.0	B	4411.73	4617.17	354.0	1.00000	0.99712	1
70	41	2	2	1	1	3848.27	4248.65	302.2	A	3848.27	4251.50	302.2	1.00000	1.00067	1
71	42	2	1	1	2	10081.31	10321.77	614.6	B	10083.60	10322.86	614.6	1.00023	1.00011	1
72	42	2	2	1	1	13289.20	13600.53	849.5	A	13297.10	13636.92	849.5	1.00059	1.00268	1
73	44	2	1	1	2	222118.35	245890.01	13500.0	B	202578.35	238233.84	13500.0	0.91203	0.96886	1
74	44	2	2	1	1	268910.95	275332.13	14480.0	A	268910.95	276456.80	14480.0	1.00000	1.00408	1

Obs	sub	seq	per	grp	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
75	45	2	1	1	2	13312.13	13511.14	896.3	B	13316.85	13540.77	896.3	1.00035	1.00219	1
76	45	2	2	1	1	13919.23	14067.30	965.5	A	13919.23	14119.20	965.5	1.00000	1.00369	1
77	47	2	1	1	2	396312.10	429975.87	16940.0	B	396312.10	428448.71	16940.0	1.00000	0.99645	1
78	47	2	2	1	1	456293.71	497716.58	18630.0	A	456293.71	503168.01	18630.0	1.00000	1.01095	1
79	48	1	1	1	1	69027.98	69134.51	5487.0	A	69027.98	69156.80	5487.0	1.00000	1.00032	1
80	48	1	2	1	2	51574.50	51793.58	4089.0	B	51574.50	51776.47	4089.0	1.00000	0.99967	1
81	49	1	1	1	1	33703.20	34737.76	2653.0	A	33703.20	34769.47	2653.0	1.00000	1.00091	1
82	49	1	2	1	2	22188.27	22839.63	1714.0	B	22188.27	22815.39	1714.0	1.00000	0.99894	1
83	50	2	1	1	2	15601.42	16011.18	1392.0	B	15601.42	15949.67	1392.0	1.00000	0.99616	1
84	50	2	2	1	1	24223.56	24398.87	2343.0	A	24257.24	24407.91	2343.0	1.00139	1.00037	1
85	52	2	1	1	2	98367.16	98807.92	6617.0	B	98367.16	98871.54	6617.0	1.00000	1.00064	1
86	52	2	2	1	1	93142.93	93567.61	6190.0	A	93142.93	93549.91	6190.0	1.00000	0.99981	1
87	55	2	1	2	2	24193.74	24750.11	1752.0	B	24211.88	25699.55	1752.0	1.00075	1.03836	1
88	55	2	2	2	1	22102.45	22946.97	1571.0	A	22102.45	23164.79	1571.0	1.00000	1.00949	1
89	56	1	1	2	1	18642.44	22641.19	1122.0	A	18642.44	20499.50	1122.0	1.00000	0.90541	1
90	56	1	2	2	2	29578.06	30311.66	1593.0	B	29578.06	30345.24	1593.0	1.00000	1.00111	1
91	57	1	1	2	1	17766.62	18042.12	1276.0	A	17766.62	18225.96	1276.0	1.00000	1.01019	1
92	57	1	2	2	2	21417.80	21610.24	1890.0	B	21417.80	21615.98	1890.0	1.00000	1.00027	1
93	59	1	1	2	1	27815.40	28086.60	2194.0	A	27820.58	28101.94	2194.0	1.00019	1.00055	1
94	59	1	2	2	2	26456.00	26613.33	2366.0	B	26456.00	26625.04	2366.0	1.00000	1.00044	1
95	60	2	1	2	2	1343902.40	.	30540.0	B	1344120.25	.	30540.0	1.00016	.	1
96	60	2	2	2	1	1448232.75	.	29280.0	A	1448347.35	.	29280.0	1.00008	.	1
97	61	1	1	2	1	17300.48	18326.54	1187.0	A	17300.48	18122.67	1187.0	1.00000	0.98888	1
98	61	1	2	2	2	12612.07	12799.07	671.7	B	12612.07	12780.76	671.7	1.00000	0.99857	1
99	62	2	1	2	2	3488.06	3613.77	283.9	B	3490.63	3618.99	283.9	1.00074	1.00145	1

Obs	sub	seq	per	grp	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
100	62	2	2	2	1	3601.26	3829.05	313.0	A	3601.80	3829.59	313.0	1.00015	1.00014	1
101	63	2	1	2	2	26228.93	26362.63	2567.0	B	26238.90	26370.32	2567.0	1.00038	1.00029	1
102	63	2	2	2	1	30786.52	31105.19	2607.0	A	30790.21	31027.96	2607.0	1.00012	0.99752	1
103	64	2	1	2	2	6534.02	6762.76	444.5	B	6534.02	6747.22	444.5	1.00000	0.99770	1
104	64	2	2	2	1	4640.73	4891.81	342.6	A	4640.73	4923.84	342.6	1.00000	1.00655	1
105	65	1	1	2	1	249925.74	261602.88	13440.0	A	249925.74	260825.80	13440.0	1.00000	0.99703	1
106	65	1	2	2	2	279924.85	288920.42	14480.0	B	279974.79	289094.29	14480.0	1.00018	1.00060	1

4.5.3 Fasting Study Data Dextromethorphan – TRT*GRP Dropped

FASTING CONCENTRATION DATASET

Obs	sub	seq	per	grp	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15
1	1	1	1	1	A	0.00	112.30	483.40	989.80	1230.00	1513.0	1792.0	1999.0	1976.0	2046.0	1939.0	1906.0	1188.0	1031.0	805.90
2	1	1	2	1	B	0.00	165.90	781.20	1003.00	1356.00	1520.0	2086.0	2274.0	2568.0	2141.0	1896.0	1960.0	1299.0	1108.0	818.30
3	2	1	1	1	A	0.00	90.37	2190.00	8121.00	13850.00	18510.0	25960.0	25690.0	30730.0	32380.0	32110.0	35890.0	29870.0	30030.0	35210.00
4	2	1	2	1	B	587.80	628.20	2516.00	8842.00	20060.00	25100.0	26980.0	28280.0	32640.0	37490.0	38250.0	40220.0	33510.0	33580.0	29500.00
5	3	2	1	1	B	0.00	142.10	1021.00	1929.00	2737.00	4048.0	6619.0	7035.0	7097.0	6939.0	6741.0	6399.0	4491.0	3316.0	2940.00
6	3	2	2	1	A	0.00	194.30	1573.00	2917.00	3667.00	4433.0	5332.0	7006.0	7377.0	8117.0	7543.0	6581.0	4881.0	3953.0	3350.00
7	5	2	1	1	B	0.00	70.13	374.30	568.90	720.90	876.7	972.2	1116.0	1012.0	886.0	876.9	691.0	552.0	429.7	332.50
8	5	2	2	1	A	0.00	139.20	519.60	975.90	1091.00	1208.0	1432.0	1531.0	1428.0	1509.0	1170.0	1016.0	754.2	571.3	471.10
9	7	2	1	1	B	0.00	227.70	3369.00	6603.00	10730.00	14580.0	19550.0	28810.0	28580.0	32000.0	29820.0	31210.0	30060.0	29750.0	31320.00
10	7	2	2	1	A	0.00	672.60	7303.00	12380.00	19620.00	23570.0	25540.0	26120.0	28560.0	26040.0	24240.0	23560.0	21660.0	21130.0	19510.00
11	8	1	1	1	A	20.67	209.00	460.80	701.40	1431.00	1563.0	2133.0	2557.0	2033.0	1946.0	1831.0	1420.0	1125.0	935.8	753.00
12	8	1	2	1	B	0.00	191.60	865.80	1775.00	1326.00	1486.0	1453.0	1723.0	1683.0	1636.0	1481.0	1253.0	1032.0	730.8	392.20
13	9	2	1	1	B	0.00	59.07	189.10	269.80	429.80	562.4	954.8	1226.0	1116.0	1066.0	988.0	1054.0	755.5	523.6	331.20
14	9	2	2	1	A	0.00	234.50	277.70	483.80	526.50	615.5	720.6	791.1	848.0	834.3	726.5	674.1	497.8	394.4	266.80
15	10	1	1	1	A	0.00	199.90	1117.00	1392.00	1413.00	1658.0	1629.0	1766.0	1867.0	1571.0	1822.0	1260.0	839.1	740.1	565.30
16	10	1	2	1	B	0.00	326.80	997.30	1590.00	1677.00	1781.0	1795.0	1976.0	1969.0	1674.0	1502.0	1306.0	896.6	644.5	494.20
17	11	1	1	1	A	0.00	1365.00	14850.00	28230.00	35540.00	41200.0	47240.0	48690.0	48570.0	53760.0	58020.0	47770.0	43820.0	46220.0	41190.00
18	11	1	2	1	B	664.50	861.80	2995.00	11300.00	28060.00	44340.0	44200.0	48700.0	54830.0	51930.0	56880.0	48550.0	42190.0	49430.0	44980.00
19	12	2	1	1	B	0.00	260.80	819.80	1375.00	1400.00	1520.0	1570.0	1447.0	1532.0	1386.0	1348.0	1209.0	837.4	577.3	395.80
20	12	2	2	1	A	0.00	177.80	564.90	876.30	1001.00	1039.0	1361.0	1343.0	1206.0	1161.0	1251.0	944.7	702.0	540.0	396.80
21	13	2	1	1	B	0.00	53.83	105.70	163.90	239.90	345.6	379.4	433.5	397.1	416.1	378.7	320.4	253.8	187.8	151.50
22	13	2	2	1	A	0.00	68.83	154.70	221.20	268.60	323.5	424.0	424.0	414.6	396.2	411.0	372.5	282.8	224.9	189.70
23	14	1	1	1	A	0.00	298.40	2427.00	4762.00	6525.00	7859.0	11600.0	11110.0	11510.0	10640.0	10570.0	9989.0	8079.0	6337.0	4882.00
24	14	1	2	1	B	0.00	265.00	1629.00	4173.00	5241.00	8039.0	8741.0	7960.0	9307.0	7514.0	8528.0	8202.0	6024.0	5107.0	3742.00
25	15	2	1	1	B	0.00	226.70	5174.00	8182.00	11230.00	14580.0	17110.0	18880.0	18220.0	18990.0	17790.0	14660.0	13970.0	12690.0	9327.00
26	15	2	2	1	A	14.78	381.10	5023.00	11640.00	13550.00	21870.0	20550.0	21000.0	20990.0	19950.0	21230.0	16620.0	14730.0	12430.0	11650.00

Obs	sub	seq	per	grp	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15
27	17	1	1	1	A	0.00	181.90	963.20	1797.00	2182.00	2474.0	3124.0	3366.0	3427.0	3084.0	3000.0	2641.0	1989.0	1690.0	1114.00
28	17	1	2	1	B	0.00	585.60	1392.00	1952.00	1892.00	2391.0	2907.0	3028.0	3174.0	2946.0	2698.0	2322.0	1592.0	1416.0	945.60
29	18	1	1	1	A	0.00	230.00	2399.00	5821.00	8087.00	12710.0	16050.0	14540.0	12980.0	15300.0	15040.0	13070.0	12790.0	12420.0	11110.00
30	18	1	2	1	B	19.21	90.43	811.80	1510.00	3038.00	7120.0	9532.0	11630.0	11210.0	14170.0	12340.0	14060.0	11840.0	11250.0	8255.00
31	19	1	1	1	A	0.00	323.10	1085.00	1332.00	1231.00	1312.0	1668.0	1528.0	1471.0	1400.0	1257.0	1050.0	828.8	514.5	370.30
32	19	1	2	1	B	0.00	476.90	1648.00	1853.00	1768.00	1974.0	2642.0	2507.0	2333.0	2195.0	1964.0	1663.0	1076.0	857.7	554.30
33	20	1	1	1	A	0.00	49.04	2231.00	5569.00	11810.00	12850.0	17430.0	22750.0	32480.0	27950.0	26170.0	30210.0	30950.0	34470.0	33170.00
34	20	1	2	1	B	808.30	1278.00	3277.00	6680.00	12840.00	20420.0	23940.0	32410.0	31250.0	35340.0	33910.0	34400.0	31510.0	34170.0	31420.00
35	21	1	1	1	A	0.00	153.90	367.20	534.30	953.40	948.3	1335.0	1520.0	1700.0	1740.0	1717.0	1614.0	1137.0	927.6	712.40
36	21	1	2	1	B	0.00	138.10	553.40	969.80	1223.00	1398.0	1905.0	1501.0	1789.0	1493.0	1541.0	1464.0	1337.0	891.9	654.50
37	22	2	1	1	B	0.00	252.10	1389.00	2408.00	3631.00	4159.0	4592.0	4527.0	4552.0	4367.0	4396.0	3486.0	2590.0	2112.0	1345.00
38	22	2	2	1	A	0.00	644.70	2239.00	2958.00	3195.00	3733.0	3738.0	3987.0	3388.0	3724.0	3278.0	2656.0	2035.0	1431.0	984.20
39	23	2	1	1	B	0.00	221.00	1263.00	2832.00	3769.00	4771.0	5608.0	5850.0	5383.0	4684.0	5280.0	4128.0	3117.0	2442.0	1678.00
40	23	2	2	1	A	0.00	1065.00	3591.00	4086.00	4456.00	5119.0	5729.0	5917.0	5733.0	5361.0	4799.0	4354.0	3503.0	2626.0	1847.00
41	24	2	1	1	B	0.00	93.74	478.80	990.30	1273.00	1310.0	1278.0	1366.0	1504.0	1230.0	1206.0	1025.0	900.9	584.5	433.10
42	24	2	2	1	A	0.00	185.60	783.50	1279.00	1727.00	2006.0	2071.0	2131.0	2258.0	1832.0	1905.0	1654.0	1174.0	931.2	717.70
43	25	2	1	1	B	0.00	180.70	847.00	1342.00	1475.00	2249.0	2124.0	2304.0	1953.0	2012.0	1859.0	1581.0	1247.0	872.7	585.30
44	25	2	2	1	A	0.00	374.00	749.40	827.20	747.90	912.6	1119.0	1201.0	1046.0	1090.0	991.9	831.5	606.0	462.8	317.00
45	26	2	1	1	B	0.00	52.49	320.50	496.60	1234.00	1454.0	2109.0	2171.0	2353.0	2462.0	2331.0	2284.0	1678.0	1086.0	693.00
46	26	2	2	1	A	0.00	575.20	1038.00	1152.00	1517.00	1642.0	1725.0	1844.0	1805.0	1788.0	1642.0	1377.0	1036.0	660.7	415.00
47	27	1	1	1	A	0.00	123.00	1799.00	4865.00	8251.00	14660.0	18260.0	18700.0	19870.0	18850.0	18710.0	17010.0	15910.0	15430.0	14280.00
48	27	1	2	1	B	0.00	276.00	4418.00	9250.00	14650.00	20070.0	18540.0	20940.0	20970.0	20690.0	19970.0	17450.0	16230.0	15430.0	13610.00
49	28	1	1	1	A	0.00	234.90	653.10	917.30	980.10	935.0	1023.0	917.7	1014.0	887.6	837.9	637.5	528.9	427.9	295.60
50	28	1	2	1	B	0.00	356.40	873.30	1119.00	1074.00	1127.0	1178.0	1242.0	977.1	988.4	995.4	857.6	560.4	516.0	346.00
51	30	2	1	1	B	0.00	3247.00	13900.00	19490.00	26710.00	26770.0	36630.0	39540.0	37880.0	39880.0	35370.0	39240.0	32290.0	34020.0	31960.00
52	30	2	2	1	A	278.10	633.10	8712.00	15480.00	24440.00	31630.0	40830.0	37660.0	39900.0	38770.0	39710.0	40970.0	35100.0	34010.0	32730.00
53	31	1	1	1	A	21.42	667.60	3239.00	9288.00	13320.00	20010.0	20140.0	19820.0	19940.0	19590.0	20810.0	17030.0	16360.0	13230.0	10410.00
54	31	1	2	1	B	14.14	978.90	3914.00	8782.00	12230.00	15710.0	20700.0	19710.0	23830.0	20280.0	20190.0	18750.0	14540.0	12630.0	9642.00
55	32	2	1	1	B	0.00	229.90	754.60	986.20	1131.00	1105.0	1152.0	1160.0	1153.0	1097.0	1167.0	985.7	658.1	623.9	337.20

Obs	sub	seq	per	grp	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15
56	32	2	2	1	A	0.00	153.00	627.60	1157.00	1213.00	1290.0	1326.0	1671.0	1655.0	1577.0	1612.0	1347.0	998.8	915.7	533.70
57	35	2	1	1	B	0.00	98.22	310.90	488.00	656.50	746.3	1118.0	1591.0	1682.0	1796.0	1820.0	1717.0	1492.0	1091.0	730.80
58	35	2	2	1	A	0.00	360.40	1382.00	2054.00	2160.00	2505.0	2715.0	2629.0	2585.0	2572.0	2801.0	2327.0	1620.0	1384.0	842.90
59	36	2	1	1	B	0.00	11.28	27.31	60.23	66.85	107.4	260.6	307.8	369.5	338.3	418.1	376.7	295.8	251.2	182.60
60	36	2	2	1	A	0.00	17.36	40.30	72.80	105.30	130.5	218.1	325.9	392.8	334.1	391.1	317.2	240.5	203.9	244.10
61	37	1	1	1	A	0.00	219.40	1772.00	3376.00	3829.00	5000.0	5531.0	5681.0	5084.0	5280.0	4393.0	4357.0	3542.0	2379.0	1882.00
62	37	1	2	1	B	0.00	61.22	410.70	1035.00	1710.00	3132.0	4718.0	5195.0	5189.0	5757.0	5812.0	4714.0	3602.0	2688.0	1691.00
63	38	1	1	1	A	0.00	83.32	608.70	1270.00	1999.00	3342.0	3891.0	3874.0	4158.0	3855.0	4071.0	3895.0	3234.0	2583.0	1713.00
64	38	1	2	1	B	0.00	741.30	3157.00	4827.00	5049.00	5249.0	5450.0	5269.0	5204.0	4880.0	5094.0	4729.0	2965.0	2762.0	1464.00
65	39	1	1	1	A	0.00	355.60	3573.00	9438.00	9499.00	15080.0	17710.0	20020.0	20120.0	18290.0	19080.0	16190.0	13160.0	9624.0	6818.00
66	39	1	2	1	B	957.70	1192.00	4448.00	9397.00	16470.00	21550.0	22620.0	25360.0	23280.0	19620.0	21740.0	19020.0	14250.0	8865.0	5767.00
67	40	2	1	1	B	0.00	97.90	507.90	798.70	1082.00	1454.0	2016.0	2420.0	2890.0	2425.0	2463.0	2221.0	1589.0	1373.0	967.40
68	40	2	2	1	A	0.00	174.70	681.90	1094.00	1451.00	1649.0	1979.0	2250.0	2248.0	2017.0	1963.0	1488.0	1154.0	1030.0	755.80
69	41	2	1	1	B	0.00	44.52	70.06	112.50	168.00	186.2	255.7	354.0	333.7	305.0	279.6	239.7	175.6	144.6	125.60
70	41	2	2	1	A	0.00	111.90	274.00	218.90	251.50	223.7	293.2	302.2	273.9	239.5	215.1	207.9	138.2	108.4	81.76
71	42	2	1	1	B	0.00	169.30	485.80	569.10	577.00	562.6	562.4	611.4	614.6	582.8	590.1	528.4	452.7	391.6	229.10
72	42	2	2	1	A	0.00	359.40	560.10	595.20	707.20	731.0	728.2	849.5	799.9	762.3	735.8	680.8	519.6	464.9	369.70
73	44	2	1	1	B	0.00	394.10	5175.00	7928.00	9951.00	13020.0	12140.0	12140.0	13500.0	12770.0	13190.0	9703.0	8033.0	7650.0	5801.00
74	44	2	2	1	A	0.00	364.60	2763.00	8448.00	8659.00	12000.0	13740.0	11640.0	14480.0	13770.0	13230.0	13000.0	9464.0	9030.0	7102.00
75	45	2	1	1	B	0.00	202.60	502.50	710.80	830.70	896.3	868.3	893.7	873.8	789.5	819.6	722.0	514.1	407.1	283.30
76	45	2	2	1	A	0.00	156.20	424.80	573.80	709.10	700.0	745.8	965.5	914.0	927.3	827.1	666.8	604.5	464.4	338.70
77	47	2	1	1	B	0.00	217.10	2166.00	6991.00	12200.00	13930.0	14130.0	16940.0	15730.0	16890.0	15860.0	15950.0	12220.0	11670.0	9585.00
78	47	2	2	1	A	0.00	99.36	797.60	4731.00	7813.00	11840.0	14970.0	16700.0	17520.0	18630.0	18140.0	15730.0	14800.0	13100.0	11150.00
79	48	1	1	1	A	0.00	631.50	2733.00	3733.00	4038.00	5334.0	5487.0	5208.0	5012.0	5116.0	4682.0	4312.0	3030.0	2570.0	1575.00
80	48	1	2	1	B	0.00	370.20	1937.00	3168.00	3349.00	3846.0	3608.0	4089.0	4043.0	3487.0	3347.0	3004.0	1936.0	1621.0	1082.00
81	49	1	1	1	A	0.00	125.60	503.10	703.60	1056.00	1652.0	2185.0	2653.0	2559.0	2383.0	2310.0	2028.0	1695.0	1308.0	926.10
82	49	1	2	1	B	0.00	99.58	420.10	835.50	1139.00	1254.0	1697.0	1714.0	1611.0	1540.0	1536.0	1295.0	1207.0	817.2	507.70
83	50	2	1	1	B	0.00	40.39	142.40	329.70	508.20	580.1	1392.0	1282.0	1284.0	1373.0	1359.0	1145.0	749.9	627.4	373.80
84	50	2	2	1	A	0.00	77.49	237.20	484.80	668.40	930.2	2154.0	2082.0	2343.0	1973.0	1919.0	1623.0	1189.0	737.5	577.30

Obs	sub	seq	per	grp	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15
85	52	2	1	1	B	0.00	180.10	1848.00	3675.00	4718.00	5301.0	6010.0	5981.0	6495.0	6617.0	5740.0	5226.0	4378.0	3926.0	2669.00
86	52	2	2	1	A	0.00	158.00	2190.00	3389.00	5093.00	5565.0	6186.0	6190.0	6007.0	6130.0	6110.0	5434.0	4325.0	3353.0	2441.00
87	55	2	1	2	B	0.00	97.12	300.40	529.00	729.30	1058.0	1360.0	1726.0	1559.0	1719.0	1752.0	1552.0	1151.0	831.1	635.20
88	55	2	2	2	A	0.00	158.70	606.20	824.80	955.50	1094.0	1492.0	1434.0	1495.0	1571.0	1376.0	1115.0	881.4	664.9	462.70
89	56	1	1	2	A	0.00	68.81	218.20	359.90	336.60	533.3	904.9	1022.0	1005.0	1122.0	1016.0	790.0	596.1	526.2	446.90
90	56	1	2	2	B	0.00	137.10	436.60	623.40	736.50	786.3	1141.0	1326.0	1429.0	1593.0	1331.0	1302.0	1242.0	978.4	886.80
91	57	1	1	2	A	0.00	185.60	428.10	802.30	835.10	946.2	1134.0	1276.0	1265.0	1121.0	1177.0	1041.0	761.6	593.1	415.00
92	57	1	2	2	B	0.00	262.80	1066.00	1531.00	1832.00	1788.0	1890.0	1707.0	1743.0	1533.0	1398.0	1227.0	919.4	750.6	458.90
93	59	1	1	2	A	0.00	333.20	767.80	1321.00	1555.00	1794.0	1975.0	2194.0	1751.0	1849.0	2007.0	1643.0	1212.0	874.5	619.10
94	59	1	2	2	B	0.00	669.70	1776.00	2366.00	2117.00	2053.0	2336.0	1907.0	1740.0	1525.0	1487.0	1210.0	917.5	594.0	516.50
95	60	2	1	2	B	0.00	110.90	1706.00	7113.00	13720.00	21380.0	22060.0	23460.0	22910.0	25420.0	27570.0	30540.0	28180.0	26260.0	25560.00
96	60	2	2	2	A	450.70	670.90	3275.00	9184.00	17700.00	20710.0	27160.0	25630.0	26220.0	28980.0	26070.0	28160.0	29280.0	26580.0	28540.00
97	61	1	1	2	A	0.00	121.70	335.40	675.20	791.80	897.5	977.2	1032.0	1187.0	1014.0	1059.0	915.9	796.1	653.1	463.70
98	61	1	2	2	B	0.00	77.12	206.40	346.60	464.40	519.8	597.8	614.4	656.1	603.1	668.4	671.7	537.6	454.7	331.30
99	62	2	1	2	B	0.00	78.94	168.10	166.40	206.70	235.3	262.4	263.3	283.9	239.8	277.5	225.8	152.1	126.1	81.51
100	62	2	2	2	A	0.00	57.02	160.30	200.90	279.20	293.7	240.3	313.0	249.8	275.7	224.0	189.3	163.0	134.9	85.87
101	63	2	1	2	B	0.00	180.70	798.70	1817.00	1997.00	2196.0	2203.0	2567.0	2366.0	2144.0	2000.0	1785.0	1185.0	841.9	557.10
102	63	2	2	2	A	0.00	159.60	827.60	1633.00	1829.00	2123.0	2217.0	2470.0	2607.0	2181.0	2083.0	2107.0	1378.0	1035.0	734.70
103	64	2	1	2	B	0.00	72.64	141.70	179.60	200.00	237.9	293.0	371.9	428.6	410.9	444.5	404.1	294.9	277.3	181.90
104	64	2	2	2	A	0.00	47.56	118.40	140.90	181.40	223.4	263.5	290.2	301.5	342.6	294.9	272.2	221.8	182.7	122.70
105	65	1	1	2	A	0.00	84.59	1010.00	3624.00	6013.00	8315.0	11980.0	12620.0	11660.0	13440.0	10970.0	11620.0	8982.0	7640.0	5728.00
106	65	1	2	2	B	0.00	161.70	2850.00	4684.00	8593.00	9958.0	13180.0	14120.0	13970.0	13600.0	14480.0	12070.0	9593.0	9417.0	6786.00

Obs	c16	c17	c18	c19	KE_FIRST	KE_LAST	t1	t2	t3	t4	t5	t6	t7	t8	t9	t10	t11	t12	t13	t14	t15	t16	t17	t18	t19	trt
1	386.00	206.20	.	28.39	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
2	398.20	198.10	116.90	39.96	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
3	31980.00	24590.00	23770.00	19810.00	.	.	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
4	30840.00	25090.00	20690.00	16250.00	.	.	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
5	1572.00	.	.	.	15	16	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2

Obs	c16	c17	c18	c19	KE_FIRST	KE_LAST	t1	t2	t3	t4	t5	t6	t7	t8	t9	t10	t11	t12	t13	t14	t15	t16	t17	t18	t19	trt
6	1877.00	.	.	.	15	16	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
7	201.20	69.46	25.38	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
8	240.90	156.80	50.68	10.59	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
9	26140.00	18980.00	12890.00	7057.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
10	13430.00	8156.00	5769.00	2185.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
11	347.00	101.00	45.73	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
12	241.90	79.31	38.24	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
13	184.50	82.48	27.36	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
14	144.30	28.04	0.00	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
15	341.00	155.70	71.40	16.12	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
16	329.20	249.30	131.60	20.96	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
17	34370.00	27620.00	23070.00	17790.00	.	.	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
18	38660.00	35300.00	31290.00	21000.00	.	.	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
19	225.00	114.80	41.36	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
20	219.60	93.30	34.39	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
21	97.35	35.64	15.17	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
22	137.30	74.38	59.31	10.08	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
23	3206.00	1008.00	461.10	78.27	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
24	1950.00	746.90	360.70	54.55	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
25	6556.00	3310.00	1705.00	582.30	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
26	7015.00	3997.00	2485.00	914.30	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
27	709.60	258.60	84.79	12.54	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
28	742.20	279.20	105.20	17.66	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
29	8034.00	5512.00	3751.00	1216.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
30	6035.00	3134.00	1649.00	586.50	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
31	229.40	188.70	79.73	25.37	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
32	342.00	207.30	108.30	30.48	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
33	31250.00	24340.00	24600.00	19890.00	.	.	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
34	33610.00	26360.00	24280.00	18120.00	.	.	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2

Obs	c16	c17	c18	c19	KE_FIRST	KE_LAST	t1	t2	t3	t4	t5	t6	t7	t8	t9	t10	t11	t12	t13	t14	t15	t16	t17	t18	t19	trt
35	401.30	199.10	101.50	48.97	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
36	448.10	215.40	138.80	45.11	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
37	740.90	230.80	99.41	20.20	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
38	695.80	197.30	83.50	14.39	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
39	979.20	199.90	69.63	13.37	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
40	961.40	191.00	65.83	15.88	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
41	257.20	56.30	20.37	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
42	453.70	125.10	44.53	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
43	310.10	145.30	85.99	11.62	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
44	204.50	97.66	56.52	14.08	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
45	355.10	159.60	66.90	27.75	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
46	227.50	87.71	31.03	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
47	14150.00	7968.00	5185.00	1659.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
48	9286.00	6198.00	.	1467.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
49	215.30	112.50	45.62	11.91	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
50	186.00	76.02	38.07	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
51	31580.00	26370.00	23960.00	15120.00	.	.	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
52	27240.00	23010.00	21430.00	11500.00	.	.	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
53	7771.00	6249.00	4276.00	2366.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
54	7150.00	4416.00	2874.00	761.10	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
55	282.80	73.84	23.92	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
56	333.40	89.61	42.36	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
57	449.40	171.70	62.66	11.03	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
58	526.10	265.70	137.70	53.70	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
59	139.50	57.53	27.11	12.80	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
60	97.04	51.93	37.17	21.16	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
61	1016.00	350.50	96.19	10.52	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
62	1026.00	291.30	107.10	11.79	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
63	865.60	.	26.23	11.17	14	16	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1

Obs	c16	c17	c18	c19	KE_FIRST	KE_LAST	t1	t2	t3	t4	t5	t6	t7	t8	t9	t10	t11	t12	t13	t14	t15	t16	t17	t18	t19	trt
64	725.60	164.70	.	.	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
65	4392.00	2606.00	1207.00	283.50	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
66	3598.00	1450.00	834.30	312.60	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
67	488.10	170.80	99.25	78.92	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
68	567.00	351.20	242.40	125.50	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
69	73.07	34.92	13.96	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
70	67.50	24.71	0.00	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
71	160.10	45.61	19.86	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
72	213.40	65.51	27.23	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
73	3984.00	1954.00	.	.	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
74	4690.00	2231.00	1212.00	373.80	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
75	158.20	83.37	41.02	12.05	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
76	205.30	78.26	40.45	10.93	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
77	6813.00	4629.00	2664.00	1214.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
78	8251.00	5117.00	3815.00	1616.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
79	845.20	214.60	81.55	10.74	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
80	657.10	260.50	106.80	15.70	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
81	558.80	175.60	87.10	.	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
82	349.50	104.50	52.59	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
83	212.30	91.19	28.90	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
84	326.70	166.60	47.65	10.81	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
85	1644.00	448.30	162.90	39.98	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
86	1352.00	509.00	135.00	33.39	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
87	297.60	127.10	95.97	44.34	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
88	260.00	169.40	104.70	41.46	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
89	404.60	289.20	88.98	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
90	483.60	277.80	129.30	41.89	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
91	232.30	97.91	48.88	19.89	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
92	230.60	57.82	20.11	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2

Obs	c16	c17	c18	c19	KE_FIRST	KE_LAST	t1	t2	t3	t4	t5	t6	t7	t8	t9	t10	t11	t12	t13	t14	t15	t16	t17	t18	t19	trt
93	293.20	163.40	89.38	17.68	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
94	271.80	124.30	71.48	11.13	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
95	20240.00	19660.00	17140.00	13770.00	.	.	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
96	24330.00	22460.00	17510.00	13160.00	.	.	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
97	239.60	.	57.09	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
98	178.20	106.90	56.27	10.37	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
99	48.59	12.16	0.00	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
100	48.20	17.92	0.00	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
101	300.50	56.91	15.51	.	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
102	392.90	160.80	24.17	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
103	104.80	43.30	16.45	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
104	63.31	33.33	16.13	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
105	4980.00	2529.00	1374.00	491.70	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
106	5262.00	2532.00	1546.00	451.70	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2

Reviewer PK Dataset:

Obs	sub	trt	seq	per	grp	auct	auci	CMAX	TMAX	THALFR	KEL
1	1	1	1	1	1	31108.47	31532.84	2046.0	6.5	10.3610	0.06690
2	1	2	1	2	1	32398.32	32969.85	2568.0	6.0	9.9139	0.06992
3	2	1	1	1	1	1806891.37	.	35890.0	8.0	.	.
4	2	2	1	2	1	1713247.60	.	40220.0	8.0	.	.
5	3	1	2	2	1	122110.80	135071.59	8117.0	6.5	9.5724	0.07241
6	3	2	2	1	1	106822.10	116865.85	7097.0	6.0	8.8572	0.07826
7	5	1	2	2	1	19787.27	19985.26	1531.0	5.5	12.9590	0.05349
8	5	2	2	1	1	13065.53	13386.35	1116.0	5.5	8.7618	0.07911

Obs	sub	trt	seq	per	grp	auct	auci	CMAX	TMAX	THALFR	KEL
9	7	1	2	2	1	739509.60	789800.71	28560.0	6.0	15.9538	0.04345
10	7	2	2	1	1	1292341.20	1572689.86	32000.0	6.5	27.5362	0.02517
11	8	1	1	1	1	25605.82	26060.22	2557.0	5.5	6.8876	0.10064
12	8	2	1	2	1	21017.41	21489.82	1775.0	3.0	8.5629	0.08095
13	9	1	2	2	1	10242.49	10487.32	848.0	6.0	6.0522	0.11453
14	9	2	2	1	1	13692.84	14087.55	1226.0	5.5	9.9996	0.06932
15	10	1	1	1	1	25317.99	25567.76	1867.0	6.0	10.7400	0.06454
16	10	2	1	2	1	27450.67	28079.31	1976.0	5.5	20.7890	0.03334
17	11	1	1	1	1	2083320.00	.	58020.0	7.0	.	.
18	11	2	1	2	1	2401989.05	.	56880.0	7.0	.	.
19	12	1	2	2	1	16706.79	17182.46	1361.0	5.0	9.5874	0.07230
20	12	2	2	1	1	19714.86	20388.18	1570.0	5.0	11.2840	0.06143
21	13	1	2	2	1	8336.93	8550.72	424.0	5.5	14.7009	0.04715
22	13	2	2	1	1	5726.03	5933.12	433.5	5.5	9.4622	0.07325
23	14	1	1	1	1	179507.69	180482.84	11600.0	5.0	8.6358	0.08026
24	14	2	1	2	1	134908.25	135585.68	9307.0	6.0	8.6079	0.08052
25	15	1	2	2	1	430712.09	447974.09	21870.0	4.5	13.0866	0.05297
26	15	2	2	1	1	366157.30	377311.36	18990.0	6.5	13.2774	0.05221
27	17	1	1	1	1	46135.50	46305.19	3427.0	6.0	9.3798	0.07390
28	17	2	1	2	1	44061.62	44343.68	3174.0	6.0	11.0706	0.06261
29	18	1	1	1	1	439284.25	474269.23	16050.0	5.0	19.9422	0.03476
30	18	2	1	2	1	303514.34	315504.93	14170.0	6.5	14.1709	0.04891
31	19	1	1	1	1	21591.48	22376.16	1668.0	5.0	21.4387	0.03233
32	19	2	1	2	1	31370.56	31997.87	2642.0	5.0	14.2657	0.04859
33	20	1	1	1	1	1788769.04	.	34470.0	12.0	.	.

Obs	sub	trt	seq	per	grp	auct	auci	CMAX	TMAX	THALFR	KEL
34	20	2	1	2	1	1830931.65	.	35340.0	6.5	.	.
35	21	1	1	1	1	27248.89	28022.26	1740.0	6.5	10.9466	0.06332
36	21	2	1	2	1	29355.52	30161.04	1905.0	5.0	12.3774	0.05600
37	22	1	2	2	1	49234.93	49409.77	3987.0	5.5	8.4219	0.08230
38	22	2	2	1	1	58193.23	58420.59	4592.0	5.0	7.8017	0.08885
39	23	1	2	2	1	75391.25	75529.18	5917.0	5.5	6.0207	0.11513
40	23	2	2	1	1	67675.33	67798.63	5850.0	5.5	6.3924	0.10843
41	24	1	2	2	1	28355.28	28856.03	2258.0	6.0	7.7946	0.08893
42	24	2	2	1	1	17827.31	18023.26	1504.0	6.0	6.6678	0.10395
43	25	1	2	2	1	16092.64	16330.94	1201.0	5.5	11.7313	0.05909
44	25	2	2	1	1	27718.46	27886.49	2304.0	5.5	10.0233	0.06915
45	26	1	2	2	1	21659.75	22058.35	1844.0	5.5	8.9039	0.07785
46	26	2	2	1	1	30019.24	30399.99	2462.0	6.5	9.5104	0.07288
47	27	1	1	1	1	611836.75	665970.20	19870.0	6.0	22.6175	0.03065
48	27	2	1	2	1	545117.00	582844.85	20970.0	6.0	17.8261	0.03888
49	28	1	1	1	1	15095.88	15340.14	1023.0	5.0	14.2156	0.04876
50	28	2	1	2	1	15688.86	16191.92	1242.0	5.5	9.1593	0.07568
51	30	1	2	2	1	1669796.65	.	40970.0	8.0	.	.
52	30	2	2	1	1	1835767.00	.	39880.0	6.5	.	.
53	31	1	1	1	1	507025.81	601905.62	20810.0	7.0	27.7961	0.02494
54	31	2	1	2	1	426416.17	445865.48	23830.0	6.0	17.7128	0.03913
55	32	1	2	2	1	22446.73	22913.15	1671.0	5.5	7.6322	0.09082
56	32	2	2	1	1	17074.95	17378.59	1167.0	7.0	8.7987	0.07878
57	35	1	2	2	1	41532.45	42463.75	2801.0	7.0	12.0211	0.05766
58	35	2	2	1	1	27253.09	27404.11	1820.0	7.0	9.4910	0.07303

Obs	sub	trt	seq	per	grp	auct	auci	CMAX	TMAX	THALFR	KEL
59	36	1	2	2	1	6753.10	7033.78	392.8	6.0	9.1944	0.07539
60	36	2	2	1	1	6887.12	7104.01	418.1	7.0	11.7447	0.05902
61	37	1	1	1	1	73094.06	73218.70	5681.0	5.5	8.2123	0.08440
62	37	2	1	2	1	67453.80	67585.86	5812.0	7.0	7.7640	0.08928
63	38	1	1	1	1	61025.18	61148.91	4158.0	6.0	7.6777	0.09028
64	38	2	1	2	1	69343.25	70338.07	5450.0	5.0	6.2801	0.11037
65	39	1	1	1	1	301115.85	307056.12	20120.0	6.0	14.5237	0.04773
66	39	2	1	2	1	290763.95	295257.99	25360.0	5.5	9.9649	0.06956
67	40	1	2	2	1	37501.00	40765.23	2250.0	5.5	18.0286	0.03845
68	40	2	2	1	1	35762.79	36672.33	2890.0	6.0	7.9884	0.08677
69	41	1	2	2	1	3848.27	4248.65	302.2	5.5	11.2311	0.06172
70	41	2	2	1	1	4411.73	4630.51	354.0	5.5	10.8632	0.06381
71	42	1	2	2	1	13289.20	13600.53	849.5	5.5	7.9250	0.08746
72	42	2	2	1	1	10081.31	10321.77	614.6	6.0	8.3925	0.08259
73	44	1	2	2	1	268910.95	275332.13	14480.0	6.0	11.9070	0.05821
74	44	2	2	1	1	222118.35	245890.01	13500.0	6.0	12.6489	0.05480
75	45	1	2	2	1	13919.23	14067.30	965.5	5.5	9.3902	0.07382
76	45	2	2	1	1	13312.13	13511.14	896.3	4.5	11.4481	0.06055
77	47	1	2	2	1	456293.71	497716.58	18630.0	6.5	17.7674	0.03901
78	47	2	2	1	1	396312.10	429975.87	16940.0	5.5	19.2207	0.03606
79	48	1	1	1	1	69027.98	69134.51	5487.0	5.0	6.8756	0.10081
80	48	2	1	2	1	51574.50	51793.58	4089.0	5.5	9.6721	0.07166
81	49	1	1	1	1	33703.20	34737.76	2653.0	5.5	8.2331	0.08419
82	49	2	1	2	1	22188.27	22839.63	1714.0	5.5	8.5851	0.08074
83	50	1	2	2	1	24223.56	24398.87	2343.0	6.0	11.2409	0.06166

Obs	sub	trt	seq	per	grp	auct	auci	CMAX	TMAX	THALFR	KEL
84	50	2	2	1	1	15601.42	16011.18	1392.0	5.0	9.8278	0.07053
85	52	1	2	2	1	93142.93	93567.61	6190.0	5.5	8.8159	0.07862
86	52	2	2	1	1	98367.16	98807.92	6617.0	6.5	7.6416	0.09071
87	55	1	2	2	2	22102.45	22946.97	1571.0	6.5	14.1191	0.04909
88	55	2	2	1	2	24193.74	24750.11	1752.0	7.0	8.6976	0.07969
89	56	1	1	1	2	18642.44	22641.19	1122.0	6.5	31.1500	0.02225
90	56	2	1	2	2	29578.06	30311.66	1593.0	6.5	12.1389	0.05710
91	57	1	1	1	2	17766.62	18042.12	1276.0	5.5	9.6011	0.07219
92	57	2	1	2	2	21417.80	21610.24	1890.0	5.0	6.6331	0.10450
93	59	1	1	1	2	27815.40	28086.60	2194.0	5.5	10.6325	0.06519
94	59	2	1	2	2	26456.00	26613.33	2366.0	3.0	9.7980	0.07074
95	60	1	2	2	2	1448232.75	.	29280.0	10.0	.	.
96	60	2	2	1	2	1343902.40	.	30540.0	8.0	.	.
97	61	1	1	1	2	17300.48	18326.54	1187.0	6.0	12.4577	0.05564
98	61	2	1	2	2	12612.07	12799.07	671.7	8.0	12.4996	0.05545
99	62	1	2	2	2	3601.26	3829.05	313.0	5.5	8.8108	0.07867
100	62	2	2	1	2	3488.06	3613.77	283.9	6.0	7.1656	0.09673
101	63	1	2	2	2	30786.52	31105.19	2607.0	6.0	9.1389	0.07585
102	63	2	2	1	2	26228.93	26362.63	2567.0	5.5	5.9751	0.11601
103	64	1	2	2	2	4640.73	4891.81	342.6	6.5	10.7899	0.06424
104	64	2	2	1	2	6534.02	6762.76	444.5	7.0	9.6385	0.07191
105	65	1	1	1	2	249925.74	261602.88	13440.0	6.5	16.4612	0.04211
106	65	2	1	2	2	279924.85	288920.42	14480.0	7.0	13.8040	0.05021

4.5.4 Fasting Study Output Dextromethorphan – TRT*GRP Dropped

FASTING STATISTICAL OUTPUT

The GLM Procedure

Class Level Information		
Class	**Levels**	**Values**
sub	53	1 2 3 5 7 8 9 10 11 12 13 14 15 17 18 19 20 21 22 23 24 25 26 27 28 30 31 32 35 36 37 38 39 40 41 42 44 45 47 48 49 50 52 55 56 57 59 60 61 62 63 64 65
trt	2	1 2
per	2	1 2
seq	2	1 2
grp	2	1 2

Data for Analysis of AUCT CMAX LAUCT LCMAX	
Number of Observations Read	106
Number of Observations Used	106

Data for Analysis of AUCI LAUCI	
Number of Observations Read	106
Number of Observations Used	96

Note: Variables in each group are consistent with respect to the presence or absence of missing values.

FASTING STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	55	304.7061474	5.5401118	169.20	<.0001
Error	50	1.6371737	0.0327435		
Corrected Total	105	306.3433211			

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.994656	1.649120	0.180952	10.97261

Source	DF	Type I SS	Mean Square	F Value	Pr > F
grp	1	9.6314360	9.6314360	294.15	<.0001
seq	1	19.0467543	19.0467543	581.70	<.0001
seq*grp	1	2.6332810	2.6332810	80.42	<.0001
sub(seq*grp)	49	273.3630467	5.5788377	170.38	<.0001
per(grp)	2	0.0026539	0.0013270	0.04	0.9603
trt	1	0.0289755	0.0289755	0.88	0.3514

Source	DF	Type III SS	Mean Square	F Value	Pr > F
grp	1	11.0958888	11.0958888	338.87	<.0001
seq	1	6.9884827	6.9884827	213.43	<.0001
seq*grp	1	2.6332810	2.6332810	80.42	<.0001
sub(seq*grp)	49	273.3630467	5.5788377	170.38	<.0001
per(grp)	2	0.0030742	0.0015371	0.05	0.9542
trt	1	0.0289755	0.0289755	0.88	0.3514

Tests of Hypotheses Using the Type III MS for sub(seq*grp) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	6.98848271	6.98848271	1.25	0.2685
grp	1	11.09588884	11.09588884	1.99	0.1648

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	0.03324969	0.03534554	0.94	0.3514

FASTING STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	55	203.5240377	3.7004370	107.56	<.0001
Error	50	1.7202199	0.0344044		
Corrected Total	105	205.2442577			

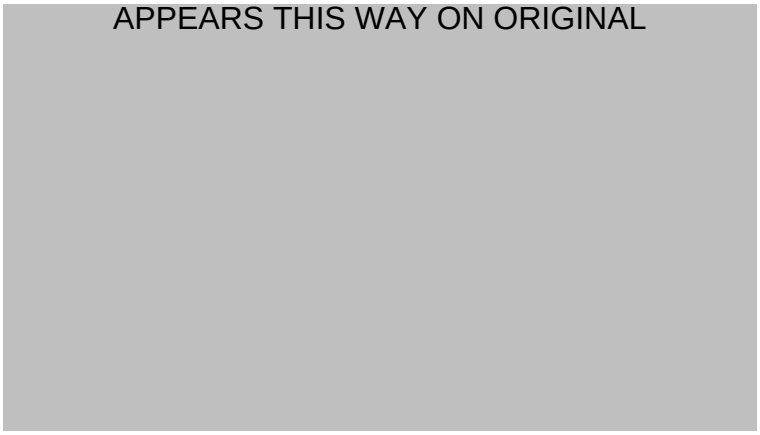
R-Square	Coeff Var	Root MSE	LCMAX Mean
0.991619	2.267026	0.185484	8.181831

Source	DF	Type I SS	Mean Square	F Value	Pr > F
grp	1	8.7600057	8.7600057	254.62	<.0001
seq	1	14.9300227	14.9300227	433.96	<.0001
seq*grp	1	1.4245887	1.4245887	41.41	<.0001
sub(seq*grp)	49	178.3962130	3.6407390	105.82	<.0001
per(grp)	2	0.0113776	0.0056888	0.17	0.8481
trt	1	0.0018300	0.0018300	0.05	0.8185

Source	DF	Type III SS	Mean Square	F Value	Pr > F
grp	1	9.9614057	9.9614057	289.54	<.0001
seq	1	6.1504522	6.1504522	178.77	<.0001
seq*grp	1	1.4245887	1.4245887	41.41	<.0001
sub(seq*grp)	49	178.3962130	3.6407390	105.82	<.0001
per(grp)	2	0.0122224	0.0061112	0.18	0.8378
trt	1	0.0018300	0.0018300	0.05	0.8185

Tests of Hypotheses Using the Type III MS for sub(seq*grp) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	6.15045218	6.15045218	1.69	0.1998
grp	1	9.96140566	9.96140566	2.74	0.1045

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.00835593	0.03623091	-0.23	0.8185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FASTING STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	50	178.8634186	3.5772684	98.16	<.0001
Error	45	1.6399756	0.0364439		
Corrected Total	95	180.5033942			

R-Square	Coeff Var	Root MSE	LAUCI Mean
0.990914	1.792505	0.190903	10.65006

Source	DF	Type I SS	Mean Square	F Value	Pr > F
grp	1	10.4782628	10.4782628	287.52	<.0001
seq	1	12.7936388	12.7936388	351.05	<.0001
seq*grp	1	1.0752145	1.0752145	29.50	<.0001
sub(seq*grp)	44	154.4590961	3.5104340	96.32	<.0001
per(grp)	2	0.0010036	0.0005018	0.01	0.9863
trt	1	0.0562027	0.0562027	1.54	0.2207

Source	DF	Type III SS	Mean Square	F Value	Pr > F
grp	1	13.4769579	13.4769579	369.80	<.0001
seq	1	12.4727108	12.4727108	342.24	<.0001
seq*grp	1	1.0752145	1.0752145	29.50	<.0001
sub(seq*grp)	44	154.4590961	3.5104340	96.32	<.0001
per(grp)	2	0.0048629	0.0024315	0.07	0.9356
trt	1	0.0562027	0.0562027	1.54	0.2207

Tests of Hypotheses Using the Type III MS for sub(seq*grp) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	12.47271078	12.47271078	3.55	0.0661
grp	1	13.47695793	13.47695793	3.84	0.0564

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	0.04909637	0.03953513	1.24	0.2207

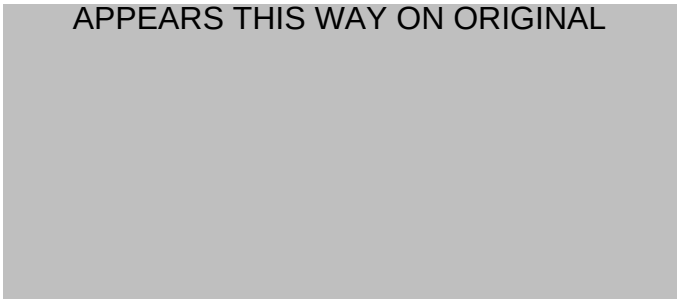

APPEARS THIS WAY ON ORIGINAL

AUCT/AUCI RATIO FOR INDIVIDUAL SUBJECTS

Obs	sub	trt	AUCRATIO
1	1	1	0.99
2	2	1	.
3	3	1	0.90
4	5	1	0.99
5	7	1	0.94
6	8	1	0.98
7	9	1	0.98
8	10	1	0.99
9	11	1	.
10	12	1	0.97
11	13	1	0.97
12	14	1	0.99
13	15	1	0.96
14	17	1	1.00
15	18	1	0.93
16	19	1	0.96
17	20	1	.
18	21	1	0.97
19	22	1	1.00
20	23	1	1.00
21	24	1	0.98
22	25	1	0.99
23	26	1	0.98
24	27	1	0.92
25	28	1	0.98
26	30	1	.
27	31	1	0.84
28	32	1	0.98
29	35	1	0.98
30	36	1	0.96
31	37	1	1.00
32	38	1	1.00
33	39	1	0.98
34	40	1	0.92
35	41	1	0.91
36	42	1	0.98

Obs	sub	trt	AUCRATIO
37	44	1	0.98
38	45	1	0.99
39	47	1	0.92
40	48	1	1.00
41	49	1	0.97
42	50	1	0.99
43	52	1	1.00
44	55	1	0.96
45	56	1	0.82
46	57	1	0.98
47	59	1	0.99
48	60	1	.
49	61	1	0.94
50	62	1	0.94
51	63	1	0.99
52	64	1	0.95
53	65	1	0.96
54	1	2	0.98
55	2	2	.
56	3	2	0.91
57	5	2	0.98
58	7	2	0.82
59	8	2	0.98
60	9	2	0.97
61	10	2	0.98
62	11	2	.
63	12	2	0.97
64	13	2	0.97
65	14	2	1.00
66	15	2	0.97
67	17	2	0.99
68	18	2	0.96
69	19	2	0.98
70	20	2	.
71	21	2	0.97
72	22	2	1.00
73	23	2	1.00
74	24	2	0.99

Obs	sub	trt	AUCRATIO
75	25	2	0.99
76	26	2	0.99
77	27	2	0.94
78	28	2	0.97
79	30	2	.
80	31	2	0.96
81	32	2	0.98
82	35	2	0.99
83	36	2	0.97
84	37	2	1.00
85	38	2	0.99
86	39	2	0.98
87	40	2	0.98
88	41	2	0.95
89	42	2	0.98
90	44	2	0.90
91	45	2	0.99
92	47	2	0.92
93	48	2	1.00
94	49	2	0.97
95	50	2	0.97
96	52	2	1.00
97	55	2	0.98
98	56	2	0.98
99	57	2	0.99
100	59	2	0.99
101	60	2	.
102	61	2	0.99
103	62	2	0.97
104	63	2	0.99
105	64	2	0.97
106	65	2	0.97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TEST PRODUCT/REFERENCE PRODUCT RATIOS FOR INDIVIDUAL SUBJECTS

sub	seq	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12
1	1	0.96	0.96	0.80	1.08	0.96	1.05
2	1	1.05	.	0.89	1.00	.	.
3	2	1.14	1.16	1.14	1.08	0.93	1.08
5	2	1.51	1.49	1.37	1.00	0.68	1.48
7	2	0.57	0.50	0.89	0.92	1.73	0.58
8	1	1.22	1.21	1.44	1.83	1.24	0.80
9	2	0.75	0.74	0.69	1.09	1.65	0.61
10	1	0.92	0.91	0.94	1.09	1.94	0.52
11	1	0.87	.	1.02	1.00	.	.
12	2	0.85	0.84	0.87	1.00	1.18	0.85
13	2	1.46	1.44	0.98	1.00	0.64	1.55
14	1	1.33	1.33	1.25	0.83	1.00	1.00
15	2	1.18	1.19	1.15	0.69	1.01	0.99
17	1	1.05	1.04	1.08	1.00	1.18	0.85
18	1	1.45	1.50	1.13	0.77	0.71	1.41
19	1	0.69	0.70	0.63	1.00	0.67	1.50
20	1	0.98	.	0.98	1.85	.	.
21	1	0.93	0.93	0.91	1.30	1.13	0.88
22	2	0.85	0.85	0.87	1.10	0.93	1.08
23	2	1.11	1.11	1.01	1.00	1.06	0.94
24	2	1.59	1.60	1.50	1.00	0.86	1.17
25	2	0.58	0.59	0.52	1.00	0.85	1.17
26	2	0.72	0.73	0.75	0.85	1.07	0.94
27	1	1.12	1.14	0.95	1.00	0.79	1.27
28	1	0.96	0.95	0.82	0.91	0.64	1.55
30	2	0.91	.	1.03	1.23	.	.
31	1	1.19	1.35	0.87	1.17	0.64	1.57
32	2	1.31	1.32	1.43	0.79	1.15	0.87
35	2	1.52	1.55	1.54	1.00	0.79	1.27
36	2	0.98	0.99	0.94	0.86	1.28	0.78
37	1	1.08	1.08	0.98	0.79	0.95	1.06
38	1	0.88	0.87	0.76	1.20	0.82	1.22
39	1	1.04	1.04	0.79	1.09	0.69	1.46
40	2	1.05	1.11	0.78	0.92	0.44	2.26
41	2	0.87	0.92	0.85	1.00	0.97	1.03
42	2	1.32	1.32	1.38	0.92	1.06	0.94
44	2	1.21	1.12	1.07	1.00	1.06	0.94
45	2	1.05	1.04	1.08	1.22	1.22	0.82
47	2	1.15	1.16	1.10	1.18	1.08	0.92

sub	seq	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12
48	1	1.34	1.33	1.34	0.91	1.41	0.71
49	1	1.52	1.52	1.55	1.00	1.04	0.96
50	2	1.55	1.52	1.68	1.20	0.87	1.14
52	2	0.95	0.95	0.94	0.85	0.87	1.15
55	2	0.91	0.93	0.90	0.93	0.62	1.62
56	1	0.63	0.75	0.70	1.00	0.39	2.57
57	1	0.83	0.83	0.68	1.10	0.69	1.45
59	1	1.05	1.06	0.93	1.83	0.92	1.09
60	2	1.08	.	0.96	1.25	.	.
61	1	1.37	1.43	1.77	0.75	1.00	1.00
62	2	1.03	1.06	1.10	0.92	0.81	1.23
63	2	1.17	1.18	1.02	1.09	0.65	1.53
64	2	0.71	0.72	0.77	0.93	0.89	1.12
65	1	0.89	0.91	0.93	0.93	0.84	1.19

Firm to Reviewer Ratios:

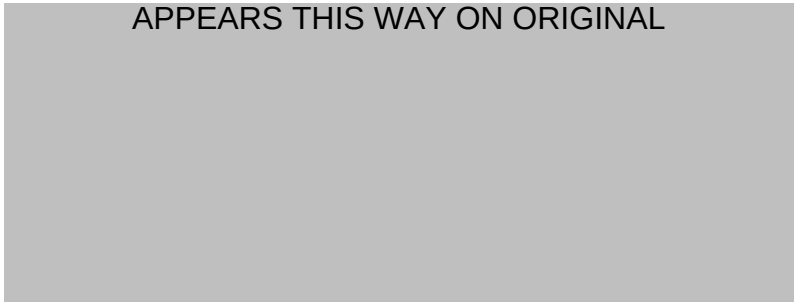
Obs	sub	seq	per	grp	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
1	1	1	1	1	1	31108.47	31532.84	2046.0	A	31108.47	31629.06	2046.0	1.00000	1.00305	1
2	1	1	2	1	2	32398.32	32969.85	2568.0	B	32398.32	33296.18	2568.0	1.00000	1.00990	1
3	2	1	1	1	1	1806891.37	.	35890.0	A	1806891.37	.	35890.0	1.00000	.	1
4	2	1	2	1	2	1713247.60	.	40220.0	B	1713247.60	.	40220.0	1.00000	.	1
5	3	2	1	1	2	106822.10	116865.85	7097.0	B	78508.94	100902.37	7097.0	0.73495	0.86340	1
6	3	2	2	1	1	122110.80	135071.59	8117.0	A	88324.80	116826.64	8117.0	0.72332	0.86492	1
7	5	2	1	1	2	13065.53	13386.35	1116.0	B	13068.17	13362.37	1116.0	1.00020	0.99821	1
8	5	2	2	1	1	19787.27	19985.26	1531.0	A	19787.27	19944.50	1531.0	1.00000	0.99796	1
9	7	2	1	1	2	1292341.20	1572689.86	32000.0	B	1292253.00	1552844.10	32000.0	0.99993	0.98738	1
10	7	2	2	1	1	739509.60	789800.71	28560.0	A	739509.60	798254.18	28560.0	1.00000	1.01070	1
11	8	1	1	1	1	25605.82	26060.22	2557.0	A	25615.60	26137.89	2557.0	1.00038	1.00298	1
12	8	1	2	1	2	21017.41	21489.82	1775.0	B	21017.41	21526.31	1775.0	1.00000	1.00170	1
13	9	2	1	1	2	13692.84	14087.55	1226.0	B	13692.84	14039.55	1226.0	1.00000	0.99659	1
14	9	2	2	1	1	10242.49	10487.32	848.0	A	10242.49	10498.64	848.0	1.00000	1.00108	1
15	10	1	1	1	1	25317.99	25567.76	1867.0	A	25317.99	25570.06	1867.0	1.00000	1.00009	1
16	10	1	2	1	2	27450.67	28079.31	1976.0	B	27450.67	27750.58	1976.0	1.00000	0.98829	1
17	11	1	1	1	1	2083320.00	.	58020.0	A	2083320.00	.	58020.0	1.00000	.	1
18	11	1	2	1	2	2401989.05	.	56880.0	B	2401989.05	.	56880.0	1.00000	.	1
19	12	2	1	1	2	19714.86	20388.18	1570.0	B	19714.86	20301.66	1570.0	1.00000	0.99576	1
20	12	2	2	1	1	16706.79	17182.46	1361.0	A	16709.57	17163.83	1361.0	1.00017	0.99892	1
21	13	2	1	1	2	5726.03	5933.12	433.5	B	5726.03	5921.88	433.5	1.00000	0.99811	1
22	13	2	2	1	1	8336.93	8550.72	424.0	A	8336.93	8526.75	424.0	1.00000	0.99720	1
23	14	1	1	1	1	179507.69	180482.84	11600.0	A	179644.94	180738.44	11600.0	1.00076	1.00142	1
24	14	1	2	1	2	134908.25	135585.68	9307.0	B	134908.25	135632.23	9307.0	1.00000	1.00034	1

Obs	sub	seq	per	grp	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
25	15	2	1	1	2	366157.30	377311.36	18990.0	B	366157.30	377421.42	18990.0	1.00000	1.00029	1
26	15	2	2	1	1	430712.09	447974.09	21870.0	A	430712.09	452971.91	21870.0	1.00000	1.01116	1
27	17	1	1	1	1	46135.50	46305.19	3427.0	A	46135.50	46284.20	3427.0	1.00000	0.99955	1
28	17	1	2	1	2	44061.62	44343.68	3174.0	B	44061.62	44288.69	3174.0	1.00000	0.99876	1
29	18	1	1	1	1	439284.25	474269.23	16050.0	A	439284.25	472326.38	16050.0	1.00000	0.99590	1
30	18	1	2	1	2	303514.34	315504.93	14170.0	B	303497.39	315408.23	14170.0	0.99994	0.99969	1
31	19	1	1	1	1	21591.48	22376.16	1668.0	A	21591.48	22113.90	1668.0	1.00000	0.98828	1
32	19	1	2	1	2	31370.56	31997.87	2642.0	B	31370.56	31943.58	2642.0	1.00000	0.99830	1
33	20	1	1	1	1	1788769.04	.	34470.0	A	1788769.04	.	34470.0	1.00000	.	1
34	20	1	2	1	2	1830931.65	.	35340.0	B	1830931.65	.	35340.0	1.00000	.	1
35	21	1	1	1	1	27248.89	28022.26	1740.0	A	27259.51	28203.42	1740.0	1.00039	1.00646	1
36	21	1	2	1	2	29355.52	30161.04	1905.0	B	29362.31	30309.13	1905.0	1.00023	1.00491	1
37	22	2	1	1	2	58193.23	58420.59	4592.0	B	58193.23	58492.57	4592.0	1.00000	1.00123	1
38	22	2	2	1	1	49234.93	49409.77	3987.0	A	49234.93	49432.58	3987.0	1.00000	1.00046	1
39	23	2	1	1	2	67675.33	67798.63	5850.0	B	68143.76	68286.59	5850.0	1.00692	1.00720	1
40	23	2	2	1	1	75391.25	75529.18	5917.0	A	75412.19	75581.94	5917.0	1.00028	1.00070	1
41	24	2	1	1	2	17827.31	18023.26	1504.0	B	17827.31	18032.57	1504.0	1.00000	1.00052	1
42	24	2	2	1	1	28355.28	28856.03	2258.0	A	28355.28	28857.22	2258.0	1.00000	1.00004	1
43	25	2	1	1	2	27718.46	27886.49	2304.0	B	27718.46	27886.74	2304.0	1.00000	1.00001	1
44	25	2	2	1	1	16092.64	16330.94	1201.0	A	16092.64	16347.24	1201.0	1.00000	1.00100	1
45	26	2	1	1	2	30019.24	30399.99	2462.0	B	30019.24	30501.33	2462.0	1.00000	1.00333	1
46	26	2	2	1	1	21659.75	22058.35	1844.0	A	21663.16	22037.44	1844.0	1.00016	0.99905	1
47	27	1	1	1	1	611836.75	665970.20	19870.0	A	625422.09	667398.48	19870.0	1.02220	1.00214	1
48	27	1	2	1	2	545117.00	582844.85	20970.0	B	545117.00	582860.83	20970.0	1.00000	1.00003	1
49	28	1	1	1	1	15095.88	15340.14	1023.0	A	15109.25	15310.79	1023.0	1.00089	0.99809	1

Obs	sub	seq	per	grp	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
50	28	1	2	1	2	15688.86	16191.92	1242.0	B	15688.86	16213.29	1242.0	1.00000	1.00132	1
51	30	2	1	1	2	1835767.00	.	39880.0	B	1835879.50	.	39880.0	1.00006	.	1
52	30	2	2	1	1	1669796.65	.	40970.0	A	1669796.65	.	40970.0	1.00000	.	1
53	31	1	1	1	1	507025.81	601905.62	20810.0	A	510275.28	602577.49	20810.0	1.00641	1.00112	1
54	31	1	2	1	2	426416.17	445865.48	23830.0	B	433377.39	451183.00	23830.0	1.01632	1.01193	1
55	32	2	1	1	2	17074.95	17378.59	1167.0	B	17074.95	17307.37	1167.0	1.00000	0.99590	1
56	32	2	2	1	1	22446.73	22913.15	1671.0	A	22446.73	22919.88	1671.0	1.00000	1.00029	1
57	35	2	1	1	2	27253.09	27404.11	1820.0	B	27255.36	27399.12	1820.0	1.00008	0.99982	1
58	35	2	2	1	1	41532.45	42463.75	2801.0	A	41440.36	42514.98	2801.0	0.99778	1.00121	1
59	36	2	1	1	2	6887.12	7104.01	418.1	B	6888.27	7132.80	418.1	1.00017	1.00405	1
60	36	2	2	1	1	6753.10	7033.78	392.8	A	6753.10	7608.76	392.8	1.00000	1.08175	1
61	37	1	1	1	1	73094.06	73218.70	5681.0	A	73129.92	73239.60	5681.0	1.00049	1.00029	1
62	37	1	2	1	2	67453.80	67585.86	5812.0	B	67453.80	67585.54	5812.0	1.00000	1.00000	1
63	38	1	1	1	1	61025.18	61148.91	4158.0	A	65237.55	65357.06	4158.0	1.06903	1.06882	1
64	38	1	2	1	2	69343.25	70338.07	5450.0	B	67696.25	69129.31	5450.0	0.97625	0.98281	1
65	39	1	1	1	1	301115.85	307056.12	20120.0	A	301115.85	305730.02	20120.0	1.00000	0.99568	1
66	39	1	2	1	2	290763.95	295257.99	25360.0	B	290408.41	297647.92	25360.0	0.99878	1.00809	1
67	40	2	1	1	2	35762.79	36672.33	2890.0	B	35769.68	37108.70	2890.0	1.00019	1.01190	1
68	40	2	2	1	1	37501.00	40765.23	2250.0	A	37670.23	42208.77	2250.0	1.00451	1.03541	1
69	41	2	1	1	2	4411.73	4630.51	354.0	B	4411.73	4617.17	354.0	1.00000	0.99712	1
70	41	2	2	1	1	3848.27	4248.65	302.2	A	3848.27	4251.50	302.2	1.00000	1.00067	1
71	42	2	1	1	2	10081.31	10321.77	614.6	B	10083.60	10322.86	614.6	1.00023	1.00011	1
72	42	2	2	1	1	13289.20	13600.53	849.5	A	13297.10	13636.92	849.5	1.00059	1.00268	1
73	44	2	1	1	2	222118.35	245890.01	13500.0	B	202578.35	238233.84	13500.0	0.91203	0.96886	1
74	44	2	2	1	1	268910.95	275332.13	14480.0	A	268910.95	276456.80	14480.0	1.00000	1.00408	1

Obs	sub	seq	per	grp	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
75	45	2	1	1	2	13312.13	13511.14	896.3	B	13316.85	13540.77	896.3	1.00035	1.00219	1
76	45	2	2	1	1	13919.23	14067.30	965.5	A	13919.23	14119.20	965.5	1.00000	1.00369	1
77	47	2	1	1	2	396312.10	429975.87	16940.0	B	396312.10	428448.71	16940.0	1.00000	0.99645	1
78	47	2	2	1	1	456293.71	497716.58	18630.0	A	456293.71	503168.01	18630.0	1.00000	1.01095	1
79	48	1	1	1	1	69027.98	69134.51	5487.0	A	69027.98	69156.80	5487.0	1.00000	1.00032	1
80	48	1	2	1	2	51574.50	51793.58	4089.0	B	51574.50	51776.47	4089.0	1.00000	0.99967	1
81	49	1	1	1	1	33703.20	34737.76	2653.0	A	33703.20	34769.47	2653.0	1.00000	1.00091	1
82	49	1	2	1	2	22188.27	22839.63	1714.0	B	22188.27	22815.39	1714.0	1.00000	0.99894	1
83	50	2	1	1	2	15601.42	16011.18	1392.0	B	15601.42	15949.67	1392.0	1.00000	0.99616	1
84	50	2	2	1	1	24223.56	24398.87	2343.0	A	24257.24	24407.91	2343.0	1.00139	1.00037	1
85	52	2	1	1	2	98367.16	98807.92	6617.0	B	98367.16	98871.54	6617.0	1.00000	1.00064	1
86	52	2	2	1	1	93142.93	93567.61	6190.0	A	93142.93	93549.91	6190.0	1.00000	0.99981	1
87	55	2	1	2	2	24193.74	24750.11	1752.0	B	24211.88	25699.55	1752.0	1.00075	1.03836	1
88	55	2	2	2	1	22102.45	22946.97	1571.0	A	22102.45	23164.79	1571.0	1.00000	1.00949	1
89	56	1	1	2	1	18642.44	22641.19	1122.0	A	18642.44	20499.50	1122.0	1.00000	0.90541	1
90	56	1	2	2	2	29578.06	30311.66	1593.0	B	29578.06	30345.24	1593.0	1.00000	1.00111	1
91	57	1	1	2	1	17766.62	18042.12	1276.0	A	17766.62	18225.96	1276.0	1.00000	1.01019	1
92	57	1	2	2	2	21417.80	21610.24	1890.0	B	21417.80	21615.98	1890.0	1.00000	1.00027	1
93	59	1	1	2	1	27815.40	28086.60	2194.0	A	27820.58	28101.94	2194.0	1.00019	1.00055	1
94	59	1	2	2	2	26456.00	26613.33	2366.0	B	26456.00	26625.04	2366.0	1.00000	1.00044	1
95	60	2	1	2	2	1343902.40	.	30540.0	B	1344120.25	.	30540.0	1.00016	.	1
96	60	2	2	2	1	1448232.75	.	29280.0	A	1448347.35	.	29280.0	1.00008	.	1
97	61	1	1	2	1	17300.48	18326.54	1187.0	A	17300.48	18122.67	1187.0	1.00000	0.98888	1
98	61	1	2	2	2	12612.07	12799.07	671.7	B	12612.07	12780.76	671.7	1.00000	0.99857	1
99	62	2	1	2	2	3488.06	3613.77	283.9	B	3490.63	3618.99	283.9	1.00074	1.00145	1

Obs	sub	seq	per	grp	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
100	62	2	2	2	1	3601.26	3829.05	313.0	A	3601.80	3829.59	313.0	1.00015	1.00014	1
101	63	2	1	2	2	26228.93	26362.63	2567.0	B	26238.90	26370.32	2567.0	1.00038	1.00029	1
102	63	2	2	2	1	30786.52	31105.19	2607.0	A	30790.21	31027.96	2607.0	1.00012	0.99752	1
103	64	2	1	2	2	6534.02	6762.76	444.5	B	6534.02	6747.22	444.5	1.00000	0.99770	1
104	64	2	2	2	1	4640.73	4891.81	342.6	A	4640.73	4923.84	342.6	1.00000	1.00655	1
105	65	1	1	2	1	249925.74	261602.88	13440.0	A	249925.74	260825.80	13440.0	1.00000	0.99703	1
106	65	1	2	2	2	279924.85	288920.42	14480.0	B	279974.79	289094.29	14480.0	1.00018	1.00060	1


APPEARS THIS WAY ON ORIGINAL

4.5.5 Fed Study Data Dextromethorphan

FED CONCENTRATION DATASET

Obs	sub	seq	per	grp	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15
1	1	1	1	1	A	0.0	154.30	812.40	1257.0	1514.0	1682.0	1875.0	1925.0	1792.0	1786.0	1732.0	1562.0	1281.0	1054.0	665.1
2	1	1	2	1	B	0.0	92.35	1435.00	1748.0	2061.0	2635.0	2900.0	3176.0	3651.0	3293.0	3600.0	3349.0	2876.0	2645.0	1721.0
3	2	1	1	1	A	0.0	154.00	551.30	1095.0	1156.0	1556.0	1399.0	1473.0	1447.0	1460.0	1282.0	1147.0	1069.0	787.7	573.3
4	2	1	2	1	B	0.0	155.80	486.00	800.2	1038.0	1193.0	1249.0	1449.0	1432.0	1482.0	1587.0	1408.0	1186.0	996.3	738.4
5	3	2	1	1	B	0.0	901.40	4881.00	5532.0	7380.0	7771.0	7909.0	8791.0	7995.0	8026.0	7235.0	6316.0	6033.0	6220.0	4942.0
6	3	2	2	1	A	0.0	1577.00	4046.00	4561.0	4843.0	4944.0	4943.0	5271.0	5421.0	5167.0	4936.0	4200.0	3679.0	3443.0	2967.0
7	4	1	1	1	A	0.0	157.90	262.30	572.6	514.1	550.6	713.3	662.1	648.3	648.5	638.2	612.8	508.2	412.0	371.3
8	4	1	2	1	B	0.0	388.30	287.00	532.6	485.7	497.7	558.8	576.0	652.2	632.9	619.4	559.3	511.1	464.0	372.9
9	6	2	1	1	B	0.0	275.60	828.00	1152.0	1390.0	1545.0	1537.0	1594.0	1540.0	1450.0	1517.0	1428.0	1196.0	1157.0	955.1
10	6	2	2	1	A	0.0	342.30	789.30	1135.0	1182.0	1249.0	1413.0	1339.0	1304.0	1269.0	1265.0	1142.0	896.0	772.1	555.7
11	7	2	1	1	B	0.0	204.90	527.20	950.2	894.2	952.8	951.9	1082.0	1150.0	1094.0	1121.0	923.6	688.8	599.8	442.7
12	7	2	2	1	A	0.0	262.90	635.30	746.1	728.7	738.4	730.0	738.7	798.7	748.9	692.5	581.7	486.7	354.6	307.4
13	8	2	1	1	B	0.0	259.50	1273.00	2534.0	3071.0	3601.0	4224.0	5207.0	5316.0	5261.0	5226.0	4911.0	4206.0	3764.0	3397.0
14	8	2	2	1	A	0.0	206.30	1746.00	3661.0	4815.0	5261.0	6359.0	8283.0	7267.0	7239.0	7125.0	6765.0	5671.0	4543.0	3982.0
15	9	1	1	1	A	0.0	534.70	1504.00	1992.0	2046.0	2264.0	2354.0	2417.0	2230.0	2144.0	2063.0	2016.0	1645.0	1628.0	1168.0
16	9	1	2	1	B	0.0	454.30	1544.00	2097.0	2291.0	2348.0	2452.0	2239.0	2335.0	2266.0	2158.0	1951.0	1561.0	1443.0	926.8
17	11	1	1	1	A	0.0	674.80	1581.00	2135.0	2153.0	2100.0	1957.0	2009.0	1750.0	1809.0	1684.0	1364.0	1085.0	960.1	792.9
18	11	1	2	1	B	0.0	211.80	1047.00	1605.0	2140.0	2298.0	2522.0	2879.0	2616.0	2647.0	2571.0	2000.0	1513.0	1217.0	961.1
19	12	2	1	1	B	0.0	545.10	1728.00	2351.0	2432.0	2415.0	2791.0	2607.0	2496.0	2578.0	2278.0	1996.0	1806.0	1649.0	1484.0
20	12	2	2	1	A	0.0	658.70	2086.00	3338.0	3376.0	3740.0	3748.0	4086.0	3959.0	3471.0	3412.0	2826.0	1975.0	1807.0	1323.0
21	13	2	1	1	B	0.0	1168.00	5825.00	12470.0	13190.0	15010.0	14110.0	16700.0	16590.0	17990.0	17590.0	17820.0	14920.0	11840.0	11740.0
22	13	2	2	1	A	0.0	499.50	2632.00	5653.0	7357.0	9785.0	11090.0	12240.0	14540.0	13510.0	13020.0	12820.0	10680.0	11350.0	9238.0
23	14	2	1	1	B	0.0	198.20	606.20	793.8	802.3	850.6	1092.0	1128.0	1076.0	1162.0	1094.0	941.4	630.5	581.0	453.2
24	14	2	2	1	A	0.0	321.40	623.40	681.1	705.7	931.6	995.3	1163.0	1087.0	1008.0	870.7	835.5	602.9	555.5	321.2
25	15	1	1	1	A	0.0	589.70	2087.00	2181.0	2364.0	2298.0	2386.0	2450.0	2493.0	2327.0	2446.0	1964.0	1684.0	1724.0	1258.0
26	15	1	2	1	B	0.0	692.30	2350.00	3106.0	3741.0	3660.0	3973.0	4077.0	3761.0	3679.0	3812.0	2889.0	2930.0	3288.0	2320.0

Obs	sub	seq	per	grp	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15
27	16	1	1	1	A	0.0	613.50	1960.00	2142.0	2088.0	2027.0	1833.0	1873.0	1936.0	1750.0	1842.0	1444.0	1156.0	949.5	803.5
28	16	1	2	1	B	0.0	397.00	1718.00	2122.0	2608.0	2701.0	2633.0	2966.0	3521.0	3481.0	3321.0	2939.0	2409.0	2162.0	1687.0
29	17	2	1	1	B	0.0	151.50	512.10	701.6	706.5	895.1	1204.0	1522.0	1687.0	1692.0	1452.0	1302.0	903.1	659.3	420.4
30	17	2	2	1	A	0.0	130.30	581.40	1079.0	1159.0	1497.0	1939.0	2403.0	2206.0	1991.0	1904.0	1763.0	1206.0	1122.0	720.3
31	18	1	1	1	A	0.0	458.60	1940.00	2639.0	2738.0	2810.0	2891.0	3145.0	3143.0	2603.0	2731.0	2372.0	2236.0	1800.0	1392.0
32	18	1	2	1	B	0.0	652.00	1647.00	1996.0	2229.0	2777.0	2508.0	2828.0	2420.0	2326.0	2470.0	2058.0	1890.0	1293.0	904.1
33	19	1	1	1	A	0.0	485.20	1575.00	1497.0	1321.0	1275.0	1110.0	1103.0	1046.0	1048.0	969.6	866.6	658.6	567.5	371.1
34	19	1	2	1	B	0.0	623.40	1134.00	1362.0	1377.0	1284.0	1216.0	1149.0	1077.0	1079.0	1114.0	908.2	791.8	514.9	356.8
35	20	1	1	1	A	0.0	258.50	369.60	410.4	397.8	416.6	474.5	517.0	510.4	459.9	423.3	359.9	271.5	228.2	183.4
36	20	1	2	1	B	0.0	290.10	451.00	509.1	500.8	522.4	622.5	607.1	575.6	590.6	563.2	516.3	427.7	323.3	215.8
37	21	1	1	1	A	0.0	859.10	1827.00	2528.0	2686.0	3125.0	3277.0	3271.0	3062.0	2810.0	2542.0	1993.0	1646.0	1180.0	803.8
38	21	1	2	1	B	0.0	630.30	1680.00	2481.0	2674.0	2907.0	3502.0	3678.0	4102.0	3404.0	3348.0	2620.0	1966.0	1584.0	885.1
39	22	2	1	1	B	0.0	231.40	614.80	999.5	1323.0	1412.0	1687.0	1647.0	2140.0	2069.0	2042.0	1901.0	1529.0	1333.0	1018.0
40	22	2	2	1	A	0.0	130.60	558.60	1023.0	1606.0	1577.0	2350.0	2477.0	2669.0	2960.0	3151.0	2447.0	2241.0	2287.0	1474.0
41	24	2	1	1	B	0.0	218.10	506.10	642.9	705.7	856.3	923.7	1036.0	1147.0	1096.0	1014.0	918.7	578.7	498.1	406.7
42	24	2	2	1	A	0.0	191.50	494.40	851.3	853.6	851.8	897.8	868.9	798.5	811.9	839.6	740.5	591.1	473.5	359.4
43	25	2	1	1	B	0.0	199.80	1089.00	2631.0	2994.0	3890.0	4578.0	4775.0	5181.0	5393.0	5318.0	4532.0	4180.0	3743.0	2497.0
44	25	2	2	1	A	0.0	327.40	1451.00	3487.0	3779.0	4549.0	5157.0	5924.0	5710.0	6066.0	5705.0	5400.0	4118.0	3620.0	2418.0
45	26	2	1	1	B	0.0	87.20	367.80	458.1	387.7	492.9	608.4	978.8	936.5	973.1	859.0	723.0	519.5	539.7	355.2
46	26	2	2	1	A	0.0	78.35	172.10	193.0	188.0	246.9	317.5	335.3	314.5	296.4	276.9	248.8	185.0	146.5	120.8
47	27	1	1	1	A	0.0	707.40	2157.00	2777.0	2949.0	2615.0	2493.0	2388.0	2512.0	2412.0	2208.0	1946.0	1512.0	1491.0	1210.0
48	27	1	2	1	B	0.0	1075.00	3503.00	5695.0	5731.0	5806.0	6089.0	5861.0	5547.0	4957.0	4678.0	4493.0	3741.0	3337.0	2563.0
49	28	1	1	1	A	0.0	57.72	361.90	726.9	747.8	800.4	859.8	1016.0	1032.0	985.7	955.3	914.3	776.0	739.7	544.4
50	28	1	2	1	B	0.0	41.53	281.80	459.3	650.6	647.4	771.7	977.5	1316.0	1315.0	1463.0	1250.0	1092.0	1007.0	772.7
51	29	1	1	1	A	0.0	4920.00	15770.00	21510.0	19820.0	22390.0	21780.0	26550.0	27060.0	29870.0	27840.0	27560.0	28690.0	31840.0	31220.0
52	29	1	2	1	B	135.5	3305.00	15180.00	17390.0	21990.0	20250.0	27790.0	25230.0	28380.0	30210.0	32010.0	31730.0	29900.0	34110.0	32580.0
53	30	2	1	1	B	0.0	909.50	2174.00	1879.0	2180.0	2725.0	2947.0	3285.0	3253.0	3169.0	2907.0	2688.0	1857.0	1744.0	1161.0
54	30	2	2	1	A	0.0	510.60	1822.00	1895.0	1832.0	1959.0	2227.0	2460.0	2592.0	2361.0	2404.0	2188.0	1632.0	1436.0	974.6
55	31	1	1	1	A	0.0	357.60	766.20	1456.0	1490.0	1852.0	2581.0	2748.0	3287.0	3191.0	2656.0	2518.0	1883.0	1763.0	1283.0

Obs	sub	seq	per	grp	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15
56	31	1	2	1	B	0.0	487.40	1247.00	1362.0	2352.0	2704.0	3356.0	3415.0	3635.0	4247.0	3876.0	3674.0	3049.0	2910.0	1825.0
57	32	2	1	1	B	0.0	570.80	2384.00	5415.0	7514.0	8053.0	9138.0	11240.0	11460.0	12870.0	12810.0	11540.0	9416.0	8626.0	6180.0
58	32	2	2	1	A	0.0	829.00	2778.00	6338.0	6614.0	7957.0	8236.0	9747.0	9376.0	8732.0	9685.0	8943.0	7782.0	7716.0	5551.0
59	33	2	1	1	B	0.0	358.00	1299.00	2015.0	2117.0	2303.0	2152.0	2382.0	2325.0	2372.0	2141.0	1997.0	1703.0	1301.0	847.2
60	33	2	2	1	A	0.0	1004.00	1911.00	1869.0	1814.0	1598.0	1587.0	1612.0	1603.0	1659.0	1635.0	1456.0	1145.0	1056.0	910.5
61	35	1	1	1	A	0.0	98.37	332.80	480.3	486.4	511.1	456.9	576.3	552.1	505.8	508.3	446.7	361.3	338.5	259.2
62	35	1	2	1	B	0.0	101.90	268.90	400.7	422.6	430.8	551.4	534.1	594.5	544.4	530.7	431.9	340.5	388.6	255.7
63	37	2	1	1	B	0.0	23.30	97.01	137.1	161.4	185.7	197.9	220.8	206.3	215.4	203.7	224.6	174.2	172.8	157.6
64	37	2	2	1	A	0.0	36.14	126.10	213.0	230.6	270.8	254.0	255.4	281.5	309.5	301.5	307.0	230.2	202.1	180.4
65	38	1	1	1	A	0.0	152.10	222.50	222.4	202.0	211.6	211.4	188.2	179.1	194.3	182.4	162.7	138.6	165.5	191.9
66	38	1	2	1	B	0.0	112.10	199.00	222.5	220.5	232.4	222.6	209.9	225.6	190.0	212.0	182.6	178.1	179.1	159.6
67	39	1	1	1	A	0.0	2610.00	7054.00	9309.0	11700.0	11610.0	12300.0	12260.0	12250.0	12440.0	11170.0	11140.0	9377.0	8133.0	6337.0
68	39	1	2	1	B	0.0	1963.00	5107.00	9236.0	9853.0	9676.0	9026.0	9013.0	8895.0	9006.0	9138.0	9068.0	8255.0	8268.0	6242.0
69	40	2	1	1	B	0.0	233.90	645.60	665.1	689.8	816.3	867.4	952.3	983.6	945.3	833.3	839.1	659.9	606.2	485.0
70	40	2	2	1	A	0.0	260.30	558.10	701.9	844.3	980.6	1073.0	1103.0	1055.0	967.4	911.0	880.5	590.4	521.1	310.3
71	41	2	1	1	B	0.0	278.50	1051.00	1321.0	1296.0	1336.0	1287.0	1236.0	1225.0	1244.0	1093.0	921.5	809.9	704.9	485.2
72	41	2	2	1	A	0.0	339.40	931.80	1590.0	1593.0	1789.0	1578.0	1690.0	1675.0	1538.0	1477.0	1318.0	1151.0	1116.0	840.9
73	42	1	1	1	A	0.0	233.30	493.50	473.3	418.2	428.4	376.2	414.4	387.5	368.9	352.1	240.5	190.1	169.8	118.1
74	42	1	2	1	B	0.0	217.70	454.30	467.8	435.2	386.0	483.0	568.8	546.4	565.3	511.0	400.9	295.7	261.9	184.6

Obs	c16	c17	c18	c19	KE_FIRST	KE_LAST	t1	t2	t3	t4	t5	t6	t7	t8	t9	t10	t11	t12	t13	t14	t15	t16	t17	t18	t19	trt
1	390.80	159.60	74.39	28.03	17	19	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
2	938.60	297.70	138.20	39.70	17	19	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
3	340.70	205.60	124.30	21.21	17	19	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
4	417.90	203.40	79.96	16.15	17	19	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
5	2155.00	1110.00	520.80	148.80	17	19	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
6	1483.00	743.20	402.80	152.80	17	19	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
7	235.00	127.40	52.85	0.00	16	18	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
8	231.80	80.94	39.54	0.00	16	18	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2

Obs	c16	c17	c18	c19	KE_FIRST	KE_LAST	t1	t2	t3	t4	t5	t6	t7	t8	t9	t10	t11	t12	t13	t14	t15	t16	t17	t18	t19	trt
9	528.00	167.50	102.00	28.48	17	19	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
10	306.20	113.80	77.78	79.54	17	19	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
11	248.10	80.73	41.30	0.00	16	18	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
12	176.00	61.02	33.86	0.00	16	18	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
13	1951.00	687.90	399.60	66.34	17	19	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
14	2375.00	821.50	428.20	95.07	17	19	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
15	557.40	198.30	77.70	0.00	16	18	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
16	383.90	87.01	30.96	0.00	16	18	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
17	477.10	297.10	240.40	123.10	17	19	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
18	491.00	261.30	169.20	40.45	17	19	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
19	900.10	302.30	120.50	21.78	17	19	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
20	856.40	250.70	123.50	24.95	17	19	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
21	7593.00	3515.00	2324.00	895.60	17	19	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
22	6579.00	3501.00	2302.00	936.30	17	19	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
23	177.50	59.67	28.79	0.00	17	19	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
24	174.40	.	40.80	22.84	14	16	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
25	616.90	337.10	131.10	.	16	18	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
26	1424.00	592.00	259.60	.	16	18	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
27	424.10	189.80	67.42	11.96	17	19	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
28	891.00	329.90	158.20	31.45	17	19	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
29	195.50	75.86	26.54	0.00	16	18	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
30	300.20	118.00	43.34	0.00	16	18	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
31	887.50	485.40	152.00	25.77	17	19	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
32	460.70	150.20	56.88	13.32	17	19	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
33	187.40	56.90	17.09	0.00	16	18	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
34	159.20	44.51	21.66	0.00	16	18	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
35	106.80	50.38	11.83	0.00	16	18	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
36	131.00	.	.	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
37	518.80	163.60	64.82	0.00	16	18	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1

Obs	c16	c17	c18	c19	KE_FIRST	KE_LAST	t1	t2	t3	t4	t5	t6	t7	t8	t9	t10	t11	t12	t13	t14	t15	t16	t17	t18	t19	trt
38	483.20	133.40	48.64	0.00	16	18	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
39	529.90	170.70	71.48	0.00	16	18	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
40	918.10	255.70	113.60	17.90	17	19	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
41	179.30	64.09	25.70	.	16	18	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
42	203.60	.	.	.	14	16	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
43	1451.00	486.90	182.80	36.48	17	19	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
44	1196.00	.	111.90	16.00	17	19	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
45	171.20	48.27	15.86	0.00	16	18	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
46	72.69	19.06	0.00	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
47	572.50	380.50	194.70	48.12	17	19	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
48	1374.00	547.70	216.20	55.42	17	19	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
49	295.80	136.30	87.13	15.70	17	19	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
50	395.30	144.60	52.04	0.00	16	18	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
51	25060.00	20630.00	15980.00	12080.00	.	.	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
52	33450.00	25180.00	23470.00	19020.00	.	.	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
53	750.00	218.50	88.31	21.91	17	19	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
54	570.20	206.00	126.30	20.00	17	19	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
55	693.70	236.50	80.72	0.00	16	18	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
56	778.60	281.70	100.70	11.13	17	19	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
57	3550.00	1571.00	505.80	97.11	17	19	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
58	3658.00	1552.00	935.00	310.00	17	19	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
59	590.60	212.70	106.90	14.04	17	19	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
60	589.80	306.00	155.60	41.15	17	19	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
61	142.60	47.03	14.96	0.00	16	18	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
62	150.30	40.24	15.47	0.00	16	18	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
63	105.00	67.77	37.38	21.67	17	19	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
64	105.60	98.61	49.04	20.39	17	19	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
65	203.10	104.60	.	0.00	.	.	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
66	172.10	42.84	.	0.00	.	.	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2

Obs	c16	c17	c18	c19	KE_FIRST	KE_LAST	t1	t2	t3	t4	t5	t6	t7	t8	t9	t10	t11	t12	t13	t14	t15	t16	t17	t18	t19	trt
67	3594.00	1325.00	630.80	196.80	17	19	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
68	3301.00	985.40	529.10	178.80	17	19	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
69	267.00	66.46	.	0.00	15	17	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
70	157.20	47.27	13.29	0.00	16	18	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
71	359.00	124.40	63.96	15.25	17	19	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2
72	613.10	229.10	130.00	31.69	17	19	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
73	86.67	34.88	11.58	0.00	16	18	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	1
74	99.45	24.00	10.13	0.00	16	18	0	1	2	3	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	2

Reviewer PK Datasets:

Obs	sub	trt	seq	per	grp	auct	auci	CMAX	TMAX	THALFR	KEL
1	1	1	1	1	1	28744.38	29337.93	1925.0	5.5	14.6779	0.04722
2	1	2	1	2	1	60307.50	61024.18	3651.0	6.0	12.5129	0.05539
3	2	1	1	1	1	25323.82	25652.11	1556.0	4.5	10.7286	0.06461
4	2	2	1	2	1	26969.43	27200.68	1587.0	7.0	9.9252	0.06984
5	3	1	2	2	1	105012.65	108530.76	5421.0	6.0	15.9592	0.04343
6	3	2	2	1	1	158403.65	161094.31	8791.0	5.5	12.5338	0.05530
7	4	1	1	1	1	13063.73	13913.79	713.3	5.0	11.1489	0.06217
8	4	2	1	2	1	12512.60	13049.17	652.2	6.0	9.4062	0.07369
9	6	1	2	2	1	23326.47	32801.20	1413.0	5.0	82.5670	0.00839
10	6	2	2	1	1	31472.21	32044.34	1594.0	5.5	13.9245	0.04978
11	7	1	2	2	1	12037.10	12530.13	798.7	6.0	10.0928	0.06868
12	7	2	2	1	1	16725.21	17278.04	1150.0	6.0	9.2782	0.07471
13	8	1	2	2	1	133239.74	134816.26	8283.0	5.5	11.4942	0.06030

Obs	sub	trt	seq	per	grp	auct	auci	CMAX	TMAX	THALFR	KEL
14	8	2	2	1	1	105299.93	106299.40	5316.0	6.0	10.4428	0.06638
15	9	1	1	1	1	39442.75	40389.14	2417.0	5.5	8.4426	0.08210
16	9	2	1	2	1	34259.23	34554.36	2452.0	5.0	6.6075	0.10490
17	11	1	1	1	1	38075.35	43006.87	2153.0	4.0	27.7682	0.02496
18	11	2	1	2	1	39898.25	40662.37	2879.0	5.5	13.0938	0.05294
19	12	1	2	2	1	56318.50	56705.58	4086.0	5.5	10.7535	0.06446
20	12	2	2	1	1	50116.06	50415.19	2791.0	5.0	9.5197	0.07281
21	13	1	2	2	1	345191.35	370664.49	14540.0	6.0	18.8579	0.03676
22	13	2	2	1	1	415967.20	439393.41	17990.0	6.5	18.1307	0.03823
23	14	1	2	2	1	15497.08	15740.95	1163.0	5.5	7.4009	0.09366
24	14	2	2	1	1	15473.81	15947.84	1162.0	6.5	11.4129	0.06073
25	15	1	1	1	1	44477.00	46508.58	2493.0	6.0	10.7413	0.06453
26	15	2	1	2	1	78267.15	81927.61	4077.0	5.5	9.7736	0.07092
27	16	1	1	1	1	32395.68	32552.81	2142.0	3.0	9.1068	0.07611
28	16	2	1	2	1	58263.05	58742.64	3521.0	6.0	10.5699	0.06558
29	17	1	2	2	1	26528.29	27065.74	2403.0	5.5	8.5955	0.08064
30	17	2	2	1	1	17768.19	18087.16	1692.0	6.5	8.3306	0.08320
31	18	1	1	1	1	55962.39	56282.66	3145.0	5.5	8.6145	0.08046
32	18	2	1	2	1	38012.43	38213.26	2828.0	5.5	10.4509	0.06632
33	19	1	1	1	1	17271.69	17442.96	1575.0	2.0	6.9467	0.09978
34	19	2	1	2	1	16777.63	17038.24	1377.0	4.0	8.3399	0.08311
35	20	1	1	1	1	7454.92	7583.95	517.0	5.5	7.5605	0.09168
36	20	2	1	2	1	10283.85	12001.72	622.5	5.0	18.1792	0.03813
37	21	1	1	1	1	39092.02	39839.98	3277.0	5.0	7.9982	0.08666
38	21	2	1	2	1	42753.54	43261.98	4102.0	6.0	7.2455	0.09567

Obs	sub	trt	seq	per	grp	auct	auci	CMAX	TMAX	THALFR	KEL
39	22	1	2	2	1	49662.95	49903.82	3151.0	7.0	9.3273	0.07431
40	22	2	2	1	1	32639.73	33496.09	2140.0	6.0	8.3042	0.08347
41	24	1	2	2	1	15270.60	16715.94	897.8	5.0	9.8412	0.07043
42	24	2	2	1	1	14372.61	14690.12	1147.0	6.0	8.5637	0.08094
43	25	1	2	2	1	89799.00	89959.13	6066.0	6.5	6.9369	0.09992
44	25	2	2	1	1	87512.26	88023.97	5393.0	6.5	9.7229	0.07129
45	26	1	2	2	1	4296.19	4499.29	335.3	5.5	7.3861	0.09384
46	26	2	2	1	1	12103.18	12263.17	978.8	5.5	6.9926	0.09913
47	27	1	1	1	1	47768.19	48604.29	2949.0	4.0	12.0436	0.05755
48	27	2	1	2	1	96689.29	97573.95	6089.0	5.0	11.0646	0.06265
49	28	1	1	1	1	19530.09	19784.72	1032.0	6.0	11.2418	0.06166
50	28	2	1	2	1	22598.27	23214.24	1463.0	7.0	8.2044	0.08448
51	29	1	1	1	1	1454090.00	.	31840.0	12.0	.	.
52	29	2	1	2	1	1834937.75	.	34110.0	12.0	.	.
53	30	1	2	2	1	40593.10	40893.87	2592.0	6.0	10.4237	0.06650
54	30	2	2	1	1	48385.75	48733.22	3285.0	5.5	10.9927	0.06306
55	31	1	1	1	1	43308.12	44208.74	3287.0	6.0	7.7337	0.08963
56	31	2	1	2	1	60847.46	60971.07	4247.0	6.5	7.6979	0.09004
57	32	1	2	2	1	205379.75	212280.61	9747.0	5.5	15.4300	0.04492
58	32	2	2	1	1	213715.02	214991.11	12870.0	6.5	9.1084	0.07610
59	33	1	2	2	1	37369.85	38108.79	1911.0	2.0	12.4471	0.05569
60	33	2	2	1	1	38571.28	38754.10	2382.0	5.5	9.0257	0.07680
61	35	1	1	1	1	9002.07	9161.31	576.3	5.5	7.3783	0.09394
62	35	2	1	2	1	8921.63	9084.92	594.5	6.0	7.3164	0.09474
63	37	1	2	2	1	7436.24	7913.19	309.5	6.5	16.2137	0.04275

Obs	sub	trt	seq	per	grp	auct	auci	CMAX	TMAX	THALFR	KEL
64	37	2	2	1	1	5989.71	6702.71	224.6	8.0	22.8064	0.03039
65	38	1	1	1	1	7251.35	.	222.5	2.0	.	.
66	38	2	1	2	1	5929.67	.	232.4	4.5	.	.
67	39	1	1	1	1	229996.50	233756.70	12440.0	6.5	13.2438	0.05234
68	39	2	1	2	1	202229.45	206026.00	9853.0	4.0	14.7179	0.04710
69	40	1	2	2	1	13571.91	13701.01	1103.0	5.5	6.7337	0.10294
70	40	2	2	1	1	16009.79	16449.86	983.6	6.0	6.8846	0.10068
71	41	1	2	2	1	33571.58	34142.56	1789.0	4.5	12.4889	0.05550
72	41	2	2	1	1	22051.28	22311.93	1336.0	4.5	11.8470	0.05851
73	42	1	1	1	1	6079.22	6217.29	493.5	2.0	8.2648	0.08387
74	42	2	1	2	1	7553.53	7659.97	568.8	5.5	7.2830	0.09517

4.5.6 Fed Study Output Dextromethorphan

FED STATISTICAL OUTPUT

The GLM Procedure

Class Level Information		
Class	**Levels**	**Values**
sub	37	1 2 3 4 6 7 8 9 11 12 13 14 15 16 17 18 19 20 21 22 24 25 26 27 28 29 30 31 32 33 35 37 38 39 40 41 42
trt	2	1 2
per	2	1 2
seq	2	1 2

Data for Analysis of AUCT CMAX LAUCT LCMAX	
Number of Observations Read	74
Number of Observations Used	74

Data for Analysis of AUCI LAUCI	
Number of Observations Read	74
Number of Observations Used	70

Note: Variables in each group are consistent with respect to the presence or absence of missing values.

FED STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	38	104.3255994	2.7454105	49.03	<.0001
Error	35	1.9597111	0.0559917		
Corrected Total	73	106.2853105			

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.981562	2.258919	0.236626	10.47518

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.0822419	0.0822419	1.47	0.2337
sub(seq)	35	103.9710323	2.9706009	53.05	<.0001
per	1	0.0739559	0.0739559	1.32	0.2582
trt	1	0.1983693	0.1983693	3.54	0.0681

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.0822419	0.0822419	1.47	0.2337
sub(seq)	35	103.9710323	2.9706009	53.05	<.0001
per	1	0.0675020	0.0675020	1.21	0.2797
trt	1	0.1983693	0.1983693	3.54	0.0681

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.08224195	0.08224195	0.03	0.8688

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.10358813	0.05503447	-1.88	0.0681

FED STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	38	86.66576998	2.28067816	40.99	<.0001
Error	35	1.94746085	0.05564174		
Corrected Total	73	88.61323084			

R-Square	Coeff Var	Root MSE	LCMAX Mean
0.978023	3.077328	0.235885	7.665255

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.19480207	0.19480207	3.50	0.0697
sub(seq)	35	86.14492527	2.46128358	44.23	<.0001
per	1	0.09075403	0.09075403	1.63	0.2100
trt	1	0.23528861	0.23528861	4.23	0.0473

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.19480207	0.19480207	3.50	0.0697
sub(seq)	35	86.14492527	2.46128358	44.23	<.0001
per	1	0.08296368	0.08296368	1.49	0.2302
trt	1	0.23528861	0.23528861	4.23	0.0473

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.19480207	0.19480207	0.08	0.7801

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.11281667	0.05486219	-2.06	0.0473

FED STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	36	68.16126905	1.89336858	33.75	<.0001
Error	33	1.85131681	0.05610051		
Corrected Total	69	70.01258587			

R-Square	Coeff Var	Root MSE	LAUCI Mean
0.973557	2.267811	0.236855	10.44423

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.74102368	0.74102368	13.21	0.0009
sub(seq)	33	67.14213418	2.03461013	36.27	<.0001
per	1	0.10315372	0.10315372	1.84	0.1843
trt	1	0.17495747	0.17495747	3.12	0.0867

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.74102368	0.74102368	13.21	0.0009
sub(seq)	33	67.14213418	2.03461013	36.27	<.0001
per	1	0.11088583	0.11088583	1.98	0.1691
trt	1	0.17495747	0.17495747	3.12	0.0867

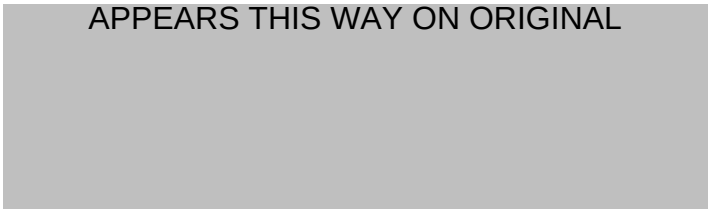
Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.74102368	0.74102368	0.36	0.5503

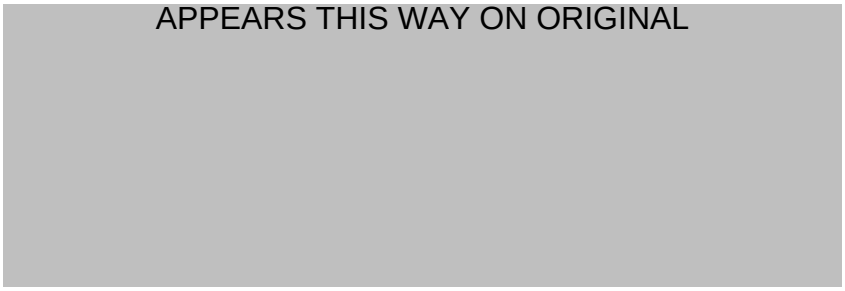
Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.10002868	0.05664241	-1.77	0.0867

AUCT/AUCI RATIO FOR INDIVIDUAL SUBJECTS

Obs	sub	trt	AUCRATIO
1	1	1	0.98
2	2	1	0.99
3	3	1	0.97
4	4	1	0.94
5	6	1	0.71
6	7	1	0.96
7	8	1	0.99
8	9	1	0.98
9	11	1	0.89
10	12	1	0.99
11	13	1	0.93
12	14	1	0.98
13	15	1	0.96
14	16	1	1.00
15	17	1	0.98
16	18	1	0.99
17	19	1	0.99
18	20	1	0.98
19	21	1	0.98
20	22	1	1.00
21	24	1	0.91
22	25	1	1.00
23	26	1	0.95
24	27	1	0.98
25	28	1	0.99
26	29	1	.
27	30	1	0.99
28	31	1	0.98
29	32	1	0.97
30	33	1	0.98
31	35	1	0.98
32	37	1	0.94
33	38	1	.
34	39	1	0.98
35	40	1	0.99
36	41	1	0.98

Obs	sub	trt	AUCRATIO
37	42	1	0.98
38	1	2	0.99
39	2	2	0.99
40	3	2	0.98
41	4	2	0.96
42	6	2	0.98
43	7	2	0.97
44	8	2	0.99
45	9	2	0.99
46	11	2	0.98
47	12	2	0.99
48	13	2	0.95
49	14	2	0.97
50	15	2	0.96
51	16	2	0.99
52	17	2	0.98
53	18	2	0.99
54	19	2	0.98
55	20	2	0.86
56	21	2	0.99
57	22	2	0.97
58	24	2	0.98
59	25	2	0.99
60	26	2	0.99
61	27	2	0.99
62	28	2	0.97
63	29	2	.
64	30	2	0.99
65	31	2	1.00
66	32	2	0.99
67	33	2	1.00
68	35	2	0.98
69	37	2	0.89
70	38	2	.
71	39	2	0.98
72	40	2	0.97
73	41	2	0.99
74	42	2	0.99


APPEARS THIS WAY ON ORIGINAL


APPEARS THIS WAY ON ORIGINAL

TEST PRODUCT/REFERENCE PRODUCT RATIOS FOR INDIVIDUAL SUBJECTS

sub	seq	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12
1	1	0.48	0.48	0.53	0.92	0.85	1.17
2	1	0.94	0.94	0.98	0.64	0.93	1.08
3	2	0.66	0.67	0.62	1.09	0.79	1.27
4	1	1.04	1.07	1.09	0.83	0.84	1.19
6	2	0.74	1.02	0.89	0.91	0.17	5.93
7	2	0.72	0.73	0.69	1.00	0.92	1.09
8	2	1.27	1.27	1.56	0.92	0.91	1.10
9	1	1.15	1.17	0.99	1.10	0.78	1.28
11	1	0.95	1.06	0.75	0.73	0.47	2.12
12	2	1.12	1.12	1.46	1.10	0.89	1.13
13	2	0.83	0.84	0.81	0.92	0.96	1.04
14	2	1.00	0.99	1.00	0.85	1.54	0.65
15	1	0.57	0.57	0.61	1.09	0.91	1.10
16	1	0.56	0.55	0.61	0.50	1.16	0.86
17	2	1.49	1.50	1.42	0.85	0.97	1.03
18	1	1.47	1.47	1.11	1.00	1.21	0.82
19	1	1.03	1.02	1.14	0.50	1.20	0.83
20	1	0.72	0.63	0.83	1.10	2.40	0.42
21	1	0.91	0.92	0.80	0.83	0.91	1.10
22	2	1.52	1.49	1.47	1.17	0.89	1.12
24	2	1.06	1.14	0.78	0.83	0.87	1.15
25	2	1.03	1.02	1.12	1.00	1.40	0.71
26	2	0.35	0.37	0.34	1.00	0.95	1.06
27	1	0.49	0.50	0.48	0.80	0.92	1.09
28	1	0.86	0.85	0.71	0.86	0.73	1.37
29	1	0.79	.	0.93	1.00	.	.
30	2	0.84	0.84	0.79	1.09	1.05	0.95
31	1	0.71	0.73	0.77	0.92	1.00	1.00
32	2	0.96	0.99	0.76	0.85	0.59	1.69
33	2	0.97	0.98	0.80	0.36	0.73	1.38
35	1	1.01	1.01	0.97	0.92	0.99	1.01
37	2	1.24	1.18	1.38	0.81	1.41	0.71
38	1	1.22	.	0.96	0.44	.	.
39	1	1.14	1.13	1.26	1.63	1.11	0.90
40	2	0.85	0.83	1.12	0.92	1.02	0.98
41	2	1.52	1.53	1.34	1.00	0.95	1.05
42	1	0.80	0.81	0.87	0.36	0.88	1.13

Firm to Reviewer Ratios:

Obs	sub	seq	per	grp	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
1	1	1	1	1	1	28744.38	29337.93	1925.0	A	28746.62	29166.07	1925.0	1.00008	0.99414	1
2	1	1	2	1	2	60307.50	61024.18	3651.0	B	60307.50	61024.18	3651.0	1.00000	1.00000	1
3	2	1	1	1	1	25323.82	25652.11	1556.0	A	25325.28	25668.58	1556.0	1.00006	1.00064	1
4	2	1	2	1	2	26969.43	27200.68	1587.0	B	26974.78	27209.14	1587.0	1.00020	1.00031	1
5	3	2	1	1	2	158403.65	161094.31	8791.0	B	158491.96	161157.50	8791.0	1.00056	1.00039	1
6	3	2	2	1	1	105012.65	108530.76	5421.0	A	105132.63	108666.38	5421.0	1.00114	1.00125	1
7	4	1	1	1	1	13063.73	13913.79	713.3	A	13063.73	13972.05	713.3	1.00000	1.00419	1
8	4	1	2	1	2	12512.60	13049.17	652.2	B	12512.60	13097.63	652.2	1.00000	1.00371	1
9	6	2	1	1	2	31472.21	32044.34	1594.0	B	31472.21	32044.34	1594.0	1.00000	1.00000	1
10	6	2	2	1	1	23326.47	32801.20	1413.0	A	23326.47	24892.44	1413.0	1.00000	0.75889	1
11	7	2	1	1	2	16725.21	17278.04	1150.0	B	16725.21	17265.42	1150.0	1.00000	0.99927	1
12	7	2	2	1	1	12037.10	12530.13	798.7	A	12040.65	12512.91	798.7	1.00029	0.99863	1
13	8	2	1	1	2	105299.93	106299.40	5316.0	B	105328.61	106324.94	5316.0	1.00027	1.00024	1
14	8	2	2	1	1	133239.74	134816.26	8283.0	A	133230.66	134807.18	8283.0	0.99993	0.99993	1
15	9	1	1	1	1	39442.75	40389.14	2417.0	A	39445.48	40358.02	2417.0	1.00007	0.99923	1
16	9	1	2	1	2	34259.23	34554.36	2452.0	B	34259.23	34552.18	2452.0	1.00000	0.99994	1
17	11	1	1	1	1	38075.35	43006.87	2153.0	A	38075.35	42588.05	2153.0	1.00000	0.99026	1
18	11	1	2	1	2	39898.25	40662.37	2879.0	B	40023.75	40753.22	2879.0	1.00315	1.00223	1
19	12	2	1	1	2	50116.06	50415.19	2791.0	B	50134.73	50433.61	2791.0	1.00037	1.00037	1
20	12	2	2	1	1	56318.50	56705.58	4086.0	A	56318.50	56705.58	4086.0	1.00000	1.00000	1
21	13	2	1	1	2	415967.20	439393.41	17990.0	B	415967.20	439393.41	17990.0	1.00000	1.00000	1
22	13	2	2	1	1	345191.35	370664.49	14540.0	A	345191.35	370664.49	14540.0	1.00000	1.00000	1
23	14	2	1	1	2	15473.81	15947.84	1162.0	B	15476.46	15804.58	1162.0	1.00017	0.99102	1

Obs	sub	seq	per	grp	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
24	14	2	2	1	1	15497.08	15740.95	1163.0	A	15505.67	15899.58	1163.0	1.00055	1.01008	1
25	15	1	1	1	1	44477.00	46508.58	2493.0	A	44477.00	46386.20	2493.0	1.00000	0.99737	1
26	15	1	2	1	2	78267.15	81927.61	4077.0	B	78267.15	81927.61	4077.0	1.00000	1.00000	1
27	16	1	1	1	1	32395.68	32552.81	2142.0	A	32395.68	32554.58	2142.0	1.00000	1.00005	1
28	16	1	2	1	2	58263.05	58742.64	3521.0	B	58263.05	58742.64	3521.0	1.00000	1.00000	1
29	17	2	1	1	2	17768.19	18087.16	1692.0	B	17794.36	18106.41	1692.0	1.00147	1.00106	1
30	17	2	2	1	1	26528.29	27065.74	2403.0	A	26534.71	27072.19	2403.0	1.00024	1.00024	1
31	18	1	1	1	1	55962.39	56282.66	3145.0	A	56099.27	56468.46	3145.0	1.00245	1.00330	1
32	18	1	2	1	2	38012.43	38213.26	2828.0	B	38447.14	38615.56	2828.0	1.01144	1.01053	1
33	19	1	1	1	1	17271.69	17442.96	1575.0	A	17271.69	17442.96	1575.0	1.00000	1.00000	1
34	19	1	2	1	2	16777.63	17038.24	1377.0	B	16777.63	16996.54	1377.0	1.00000	0.99755	1
35	20	1	1	1	1	7454.92	7583.95	517.0	A	7399.36	7543.47	517.0	0.99255	0.99466	1
36	20	1	2	1	2	10283.85	12001.72	622.5	B	7925.85	9414.88	622.5	0.77071	0.78446	1
37	21	1	1	1	1	39092.02	39839.98	3277.0	A	39100.01	39903.95	3277.0	1.00020	1.00161	1
38	21	1	2	1	2	42753.54	43261.98	4102.0	B	42753.54	43254.10	4102.0	1.00000	0.99982	1
39	22	2	1	1	2	32639.73	33496.09	2140.0	B	32645.78	33514.07	2140.0	1.00019	1.00054	1
40	22	2	2	1	1	49662.95	49903.82	3151.0	A	49682.68	49925.68	3151.0	1.00040	1.00044	1
41	24	2	1	1	2	14372.61	14690.12	1147.0	B	14372.61	14690.12	1147.0	1.00000	1.00000	1
42	24	2	2	1	1	15270.60	16715.94	897.8	A	11605.80	14496.48	897.8	0.76001	0.86722	1
43	25	2	1	1	2	87512.26	88023.97	5393.0	B	87503.22	87971.60	5393.0	0.99990	0.99941	1
44	25	2	2	1	1	89799.00	89959.13	6066.0	A	89799.00	89973.65	6066.0	1.00000	1.00016	1
45	26	2	1	1	2	12103.18	12263.17	978.8	B	12103.18	12264.40	978.8	1.00000	1.00010	1
46	26	2	2	1	1	4296.19	4499.29	335.3	A	4296.19	4510.78	335.3	1.00000	1.00255	1
47	27	1	1	1	1	47768.19	48604.29	2949.0	A	47781.03	48616.89	2949.0	1.00027	1.00026	1
48	27	1	2	1	2	96689.29	97573.95	6089.0	B	96689.29	97476.11	6089.0	1.00000	0.99900	1

Obs	sub	seq	per	grp	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
49	28	1	1	1	1	19530.09	19784.72	1032.0	A	19534.31	19785.16	1032.0	1.00022	1.00002	1
50	28	1	2	1	2	22598.27	23214.24	1463.0	B	22598.27	23215.80	1463.0	1.00000	1.00007	1
51	29	1	1	1	1	1454090.00	.	31840.0	A	1454132.50	.	31840.0	1.00003	.	1
52	29	1	2	1	2	1834937.75	.	34110.0	B	1834947.65	.	34110.0	1.00001	.	1
53	30	2	1	1	2	48385.75	48733.22	3285.0	B	48435.38	48730.06	3285.0	1.00103	0.99994	1
54	30	2	2	1	1	40593.10	40893.87	2592.0	A	40593.10	40878.41	2592.0	1.00000	0.99962	1
55	31	1	1	1	1	43308.12	44208.74	3287.0	A	43308.12	44208.74	3287.0	1.00000	1.00000	1
56	31	1	2	1	2	60847.46	60971.07	4247.0	B	60847.46	60971.07	4247.0	1.00000	1.00000	1
57	32	2	1	1	2	213715.02	214991.11	12870.0	B	213730.09	215024.13	12870.0	1.00007	1.00015	1
58	32	2	2	1	1	205379.75	212280.61	9747.0	A	205379.75	212280.61	9747.0	1.00000	1.00000	1
59	33	2	1	1	2	38571.28	38754.10	2382.0	B	38587.87	38771.96	2382.0	1.00043	1.00046	1
60	33	2	2	1	1	37369.85	38108.79	1911.0	A	37369.85	38112.94	1911.0	1.00000	1.00011	1
61	35	1	1	1	1	9002.07	9161.31	576.3	A	9002.07	9161.31	576.3	1.00000	1.00000	1
62	35	1	2	1	2	8921.63	9084.92	594.5	B	8921.63	9092.72	594.5	1.00000	1.00086	1
63	37	2	1	1	2	5989.71	6702.71	224.6	B	6001.54	6604.60	224.6	1.00198	0.98536	1
64	37	2	2	1	1	7436.24	7913.19	309.5	A	7436.24	7969.27	309.5	1.00000	1.00709	1
65	38	1	1	1	1	7251.35	.	222.5	A	6205.35	.	222.5	0.85575	.	1
66	38	1	2	1	2	5929.67	.	232.4	B	5501.27	.	232.4	0.92775	.	1
67	39	1	1	1	1	229996.50	233756.70	12440.0	A	230152.73	233912.93	12440.0	1.00068	1.00067	1
68	39	1	2	1	2	202229.45	206026.00	9853.0	B	202298.75	206090.92	9853.0	1.00034	1.00032	1
69	40	2	1	1	2	16009.79	16449.86	983.6	B	15345.19	16125.96	983.6	0.95849	0.98031	1
70	40	2	2	1	1	13571.91	13701.01	1103.0	A	13571.91	13701.01	1103.0	1.00000	1.00000	1
71	41	2	1	1	2	22051.28	22311.93	1336.0	B	22052.07	22312.87	1336.0	1.00004	1.00004	1
72	41	2	2	1	1	33571.58	34142.56	1789.0	A	33571.58	34104.72	1789.0	1.00000	0.99889	1

Obs	sub	seq	per	grp	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
73	42	1	1	1	1	6079.22	6217.29	493.5	A	6079.10	6217.18	493.5	0.99998	0.99998	1
74	42	1	2	1	2	7553.53	7659.97	568.8	B	7561.99	7671.24	568.8	1.00112	1.00147	1

4.6 Additional Attachments

None.

APPEARS THIS WAY ON ORIGINAL

BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 091135

APPLICANT: Tris Pharma, Inc.

DRUG PRODUCT: Dextromethorphan Polistirex Extended Release Oral Suspension, EQ. 30 mg Dextromethorphan Hydrobromide per 5 mL

The Division of Bioequivalence (DBE) has completed its review of your submission acknowledged on the cover sheet. The following deficiencies have been identified:

1. Please acknowledge for future submissions that a more appropriate standard curve (SC) and quality control (QC) concentration range should be validated, which fully encompasses the expected plasma concentration ranges for all subjects. Specifically, the Agency recommends you avoid situations in which many subject samples have to be re-assayed due to initial measurements determined as being 'above the limit of quantitation (ALOQ)', which was the case for the fasting study # S08-0445.

2. It was not fully clear whether the fed study # S08-0446 was carried out using a dose of 60 mg (like the fasted study), or a dose of 30 mg as recommended in the draft individual bioequivalence recommendation guidance for the drug product. In the fed study report (page 2 of 547) it lists the dose as 30 mg; however, in the *in vivo* BE summary table, it lists 60 mg as the dose administered. Please clarify which dose was used for the fed bioequivalence (BE) study.

3. With regard to the repeat analyses, please submit the following additional information:

a. Please submit all appropriate raw data (for fasting and fed BE studies) supporting repeat analysis of samples for high/low internal standard responses (HIS/LIS). These repeats should meet the objective criterion established in the SOP (b) (4), page 8 of 19, which says that results are flagged for repeat when there is a deviation by more than 40% of the mean IS for the entire batch run.

b. Please submit the analytical procedure document defining the reason for the "sample processing error" for subject #41, hour 5.5 sample, per SOP (b) (4) : Sample Reanalysis and Reporting Criteria.

We acknowledge you will conduct dissolution testing for your test product as follows:

The dissolution testing should be conducted in 500 mL of 0.1 N HCl at 37°C + 0.5°C, with addition of 400 mL of Phosphate Buffer, at 37°C + 0.5°C, 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: (b) (4) %
12 hrs: NLT (b) (4) %.

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

4.7 Outcome Page

ANDA: 091135

Reviewer: DeHaven, Wayne

Date Completed:

Verifier:

Date Verified:

Division: Division of Bioequivalence

Description: Dextromethorphan Polistirex Extended Release Oral Suspension, EQ. 30 mg dextromethorphan hydrobromide per 5 mL

Productivity:

ID	Letter Date	Productivity Category	Sub Category	Productivity	Subtotal
12958	1/9/2009	Bioequivalence Study	Fasting Study	1	1
12958	1/9/2009	Bioequivalence Study	Fed Study	1	1
12958	9/25/2009	Other	Study Amendment Without Credit (WC)	0	0
12958	10/9/2009	Other	Study Amendment Without Credit (WC)	0	0
				Bean Total:	2

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

/s/

WAYNE I DEHAVEN
02/14/2011

SHRINIWAS G NERURKAR
02/14/2011

HOAINHON N CARAMENICO on behalf of DALE P CONNER
02/14/2011

DIVISION OF BIOEQUIVALENCE DISSOLUTION AMENDMENT REVIEW

ANDA No.	91-135	
Drug Product Name	Dextromethorphan Polistirex Extended Release Oral Suspension	
Strength (s)	30 mg/5 mL (eq. to 30 mg dextromethorphan hydrobromide per 5 mL)	
Applicant Name	Tris Pharma, Inc.	
Address	2033 Route 130 Monmouth Junction, NJ 08852	
Applicant's Point of Contact	W. Scott Groner, Director RA and Compliance 2033 Route 130 Monmouth Junction, NJ 08852	
Contact's Phone Number	732-940-0358	
Contact's Fax Number	732-940-0374	
Submission Date(s)	January 9, 2009 & August 14, 2009 (Amendment with dissolution data)	
First Generic	Yes	
Reviewer	Anitha Palamakula, Ph.D.	
Study Number (s)	S08-0445	S08-0446
Study Type (s)	Fasting	Fed
Strength(s)	60 mg (10 mL)	60 mg (10 mL)
Clinical Site	Cetero Research	
Clinical Site Address	400 Fountain Lakes Blvd. St. Charles, MO 63301 (314) 419-6592	
Analytical Site	(b) (4)	
Analytical Address		
OUTCOME DECISION	**INCOMPLETE**	

I. EXECUTIVE SUMMARY

This is a review of the dissolution amendment submitted on August 14, 2009.

The firm submitted comparative dissolution testing data for both the firm's proposed method and the FDA-recommended method. The firm conducted dissolution testing using the FDA-recommended method in 500 mL of 0.1 N HCl using Apparatus II (Paddles) at 50 rpm. The sampling times are 30, 60, 90, and 180 minutes. The sampling for the dissolution testing conducted using the FDA-recommended method was not taken to the time point of complete dissolution: At 180 minutes, less than (b) (4)% LC of both the test and RLD products was dissolved.

However, the firm also conducted dissolution with its own proposed method: 500 mL of 0.1 N HCl using USP Apparatus II (Paddles) at 50 rpm followed by addition of 400 mL of Phosphate Buffer after 1 hr sample. The sampling times are 1, 3, 6 and 12 hours. The firm's proposed method can only be compared partially as the sampling times were not the same as used in the FDA method. The firm's method provided faster dissolution at 180 minutes for both the test and RLD product, (b) (4) The variability for the firm's method was slightly better based on the CV% data. In addition, the firm's method is sufficiently discriminating. For this reason, the firm's proposed method is accepted.

However, the firm's proposed specifications for the 3-hour and 12-hour sampling time points are too liberal and not acceptable. The firm should acknowledge the following FDA-recommended specifications with their proposed method.

Specifications: 1 hr: NMT (b) (4)%, 3 hrs: (b) (4)% - (b) (4)%, 6 hrs: (b) (4)% - (b) (4)%, 12 hrs: NLT (b) (4)%.

The firm also submitted acceptable multi-media dissolution testing data using USP Apparatus II at 50 rpm in four dissolution media (pH 1.2, pH 4.5 and pH 6.8 buffers and water).

The Division of Scientific Investigations (DSI) inspection of the analytical sites was completed on (b) (4) and the outcome is reported as (b) (4). The DSI inspection of the clinical site is pending for a related ANDA 90740.

The dissolution testing is acceptable pending the firm's acknowledgement of the firm's proposed method and the FDA recommended data driven specifications.

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

Table 1: SUBMISSION CONTENT CHECKLIST

Information			YES	NO	N/A
Did the firm use the FDA-recommended 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	PK parameters	☐	☐	☒
		Plasma concentrations	☐	☐	☒
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.					

Current FDA recommendations for this product from FDA website for individual product guidance are:

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	0.1 N HCl	500	30, 60, 90 and 180	10/06/2008

II. Dissolution Data

Detailed Summary of *In Vitro* Dissolution Studies - Tris In-house Method:

Dissolution Conditions	**Apparatus:**	USP II (Paddle)
	Speed of Rotation:	50 rpm
	Medium:	0.1 N HCl, for 1 hr and after sampling add 400 mL of Phosphate Buffer
	Volume:	500 mL
	Temperature:	37 °C ± 0.5 °C
Firm's Proposed Specifications	1 hour NMT (b)(4)%. 3 hour (b)(4)% 6 hour (b)(4)%. 12 hour NLT (b)(4)%	
Dissolution Testing Site (Name, Address)	Tris Pharma, Inc. 3022 Route 130, Monmouth Junction, NJ 08852	

Study Ref No.	Testing Date	Product ID \ Batch No.	Dosage Strength & Form	No. of Dosage Units		Collection Times (hours) 1	3	6	12	Study Report Location
N/A	9/17/08	Dextromethorphan Polistirex ER Oral Suspension TB-023A (Date of Mfr: 09/03/08)	Oral Suspension, eq. to 30 mg/5mL	12	Mean	30.9	58.3	73.7	86.4	Notebook: QC0170 Page: 055 and 65
					Range	(b)(4)				
					SD	1.6	2.8	2.8	2.2	
					%CV	5.3	4.7	3.8	2.6	
N/A	8/31/07	Delsym® ER Oral Suspension 39469 (Expiry Date: Dec 08)	Oral Suspension, eq. to 30 mg/5mL	12	Mean	22.8	64.2	77.4	83.6	Notebook: QC0170 Page: 001
					Range	(b)(4)				
					SD	1.0	1.8	1.1	1.0	
					%CV	4.4	2.9	1.4	1.2	

Table 5 Summary of In Vitro Dissolution Studies - FDA Recommended Method

Dissolution Conditions	**Apparatus:**	USP II (Paddle)
	Speed of Rotation:	50 rpm
	Medium:	0.1 N HCl
	Volume:	500 mL
	Temperature:	37 ºC ± 0.5 ºC
Firm's Proposed Specifications	Not applicable	
Dissolution Testing Site (Name, Address)	Tris Pharma, Inc. 3022 Route 130, Monmouth Junction, NJ 08852	

Study Ref No.	Testing Date	Product ID \ Batch No.	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes) 30	60	90	180	Study Report Location
N/A	12/03/08	Dextromethorphan Polistirex ER Oral Suspension TB-023A (Date of Mfr: 09/03/08)	Oral Suspension, eq. to 30 mg/5mL	12	Mean	26.2	30.0	32.7	36.0	Notebook: QC0212
					Range	(b) (4)				
					SD	2.1	2.4	2.4	1.9	Page: 008
					%CV	8.0	7.9	7.4	5.5	
N/A	09/27/07	Delsym® ER Oral Suspension 39469 (Expiry Date: Dec 08)	Oral Suspension, eq. to 30 mg/5mL	12	Mean	21.3	23.3	24.6	27.7	Notebook: QC0151
					Range	(b) (4)				
					SD	1.4	1.8	2.4	3.6	Page: 068
					%CV	6.8	7.9	9.6	12.9	

Table 5 Summary of In Vitro Dissolution Studies - pH 1.2 Buffer

Dissolution Conditions	**Apparatus:**	USP II (Paddle)
	Speed of Rotation:	50 rpm
	Medium:	pH 1.2 Buffer
	Volume:	900 mL
	Temperature:	37 °C ± 0.5 °C
Firm's Proposed Specifications	Not applicable	
Dissolution Testing Site (Name, Address)	Tris Pharma, Inc. 3022 Route 130, Monmouth Junction, NJ 08852	

Study Ref No.	Testing Date	Product ID \ Batch No.	Dosage Strength & Form	No. of Dosage Units		Collection Times (hours) 1	2	4	6	8	10	12	Study Report Location
N/A	12/05/08	Dextromethorphan Polistirex ER Oral Suspension TB-023A (Date of Mfr: 09/03/08)	Oral Suspension, eq. to 30 mg/5mL	12	Mean	56.0	66.5	74.1	77.0	78.3	79.1	78.9	Notebook: QC0212 Page: 013
					Range	[redacted] (b) (4)							
					SD	1.9	1.7	1.5	1.4	1.4	1.4	1.3	
					%CV	3.4	2.6	2.0	1.8	1.8	1.7	1.7	
N/A	10/02/07	Delsym® ER Oral Suspension 39469 (Expiry Date: Dec 08)	Oral Suspension, eq. to 30 mg/5mL	12	Mean	38.2	47.5	55.6	59.0	60.9	62.2	63.2	Notebook: QC0170 Page: 016
					Range	[redacted] (b) (4)							
					SD	0.8	1.3	1.8	2.0	2.0	1.8	1.8	
					%CV	2.0	2.7	3.2	3.4	3.3	3.0	2.8	

Table 5 Summary of In Vitro Dissolution Studies - pH 4.5 Buffer

Dissolution Conditions	**Apparatus:**	USP II (Paddle)
	Speed of Rotation:	50 rpm
	Medium:	pH 4.5 Buffer
	Volume:	900 mL
	Temperature:	37 °C ± 0.5 °C
Firm's Proposed Specifications	Not applicable	
Dissolution Testing Site (Name, Address)	Tris Pharma, Inc. 3022 Route 130, Monmouth Junction, NJ 08852	

Study Ref No.	Testing Date	Product ID \ Batch No.	Dosage Strength & Form	No. of Dosage Units		Collection Times (hours) 1	2	4	6	8	10	12	Study Report Location
N/A	12/03/08	Dextromethorphan Polistirex ER Oral Suspension TB-023A (Date of Mfr: 09/03/08)	Oral Suspension, eq. to 30 mg/5mL	12	Mean	36.5	45.5	54.1	58.0	60.1	61.2	62.0	Notebook: QC0170 Page: 072
					Range							(b) (4)	
					SD	1.5	1.3	1.0	0.8	0.7	0.6	0.6	
					%CV	4.0	2.9	1.9	1.4	1.2	1.0	1.0	
N/A	10/17/07	Delsym® ER Oral Suspension 39469 (Expiry Date: Dec 08)	Oral Suspension, eq. to 30 mg/5mL	12	Mean	17.8	27.3	38.4	44.6	48.3	50.6	52.2	Notebook: QC0151 Page: 080
					Range							(b) (4)	
					SD	1.5	1.9	1.9	1.4	1.1	0.8	0.7	
					%CV	8.7	6.9	5.0	3.2	2.2	1.7	1.3	

Table 5 Summary of In Vitro Dissolution Studies - Water

Dissolution Conditions	**Apparatus:**	USP II (Paddle)
	Speed of Rotation:	50 rpm
	Medium:	Water
	Volume:	900 mL
	Temperature:	37 °C ± 0.5 °C
Firm's Proposed Specifications	Not applicable	
Dissolution Testing Site (Name, Address)	Tris Pharma, Inc. 3022 Route 130, Monmouth Junction, NJ 08852	

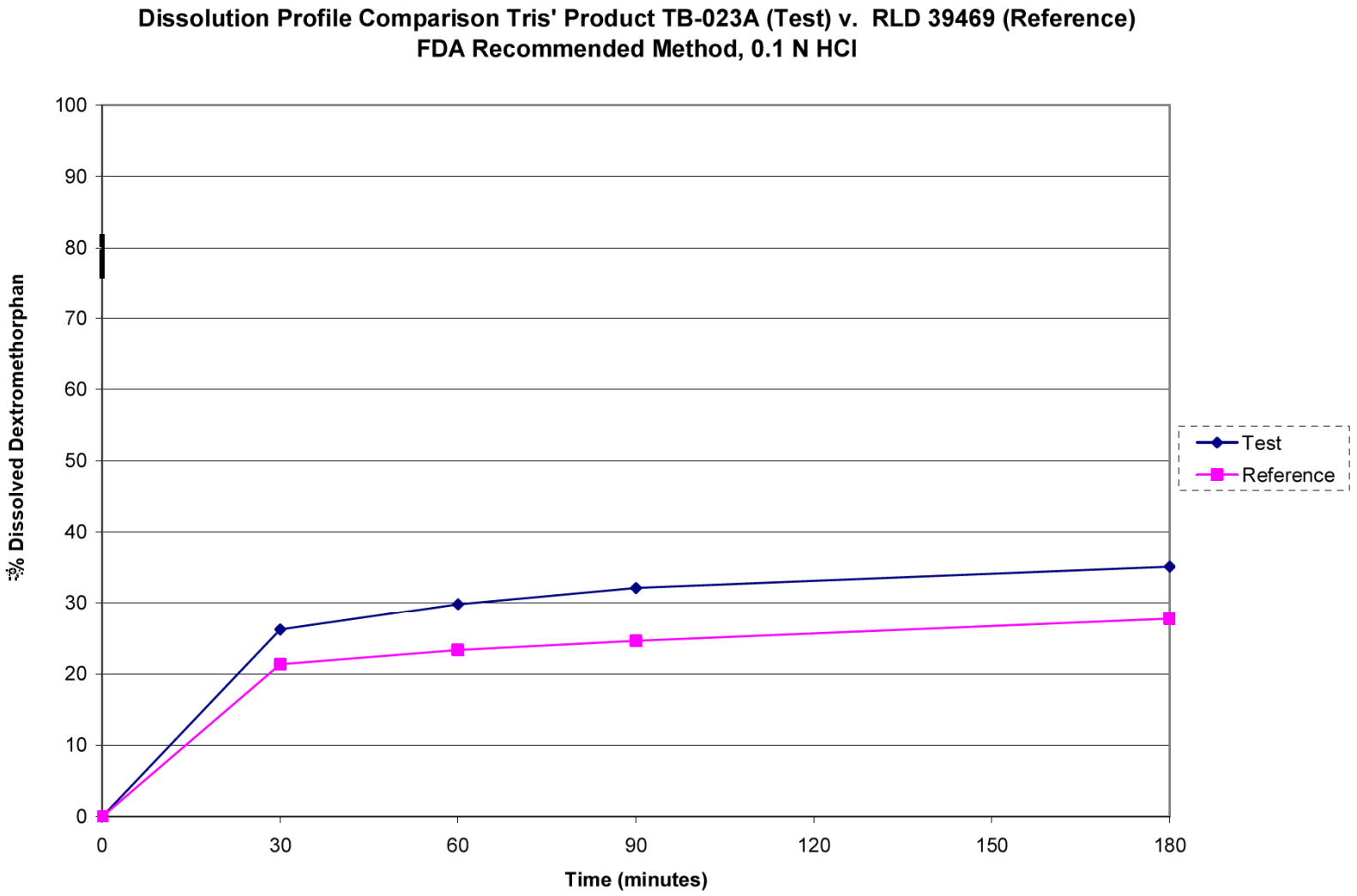
Study Ref No.	Testing Date	Product ID \ Batch No.	Dosage Strength & Form	No. of Dosage Units		Collection Times (hours) 1	2	4	6	8	10	12	Study Report Location
N/A	08/06/09	Dextromethorphan Polistirex ER Oral Suspension TB-023A (Date of Mfr: 09/03/08)	Oral Suspension, eq. to 30 mg/5mL	12	Mean	2.5	2.5	2.5	3.0	2.9	3.1	3.1	Notebook: QC0151 Page: 106
					Range							(b) (4)	
					SD	0.2	0.3	0.3	0.4	0.4	0.6	0.4	
					%CV	7.5	11.4	11.2	12.4	14.1	17.9	13.8	
N/A	08/06/09	Delsym® ER Oral Suspension 49775 (Expiry Date: Feb 11)	Oral Suspension, eq. to 30 mg/5mL	12	Mean	0.6	0.7	0.8	0.8	1.0	0.8	0.8	Notebook: QC0153 Page: 046
					Range							(b) (4)	
					SD	0.1	0.1	0.1	0.1	0.1	0.1	0.1	
					%CV	10.4	15.2	13.8	13.0	14.7	15.4	16.2	

Table 5 Summary of In Vitro Dissolution Studies - pH 6.8 Buffer

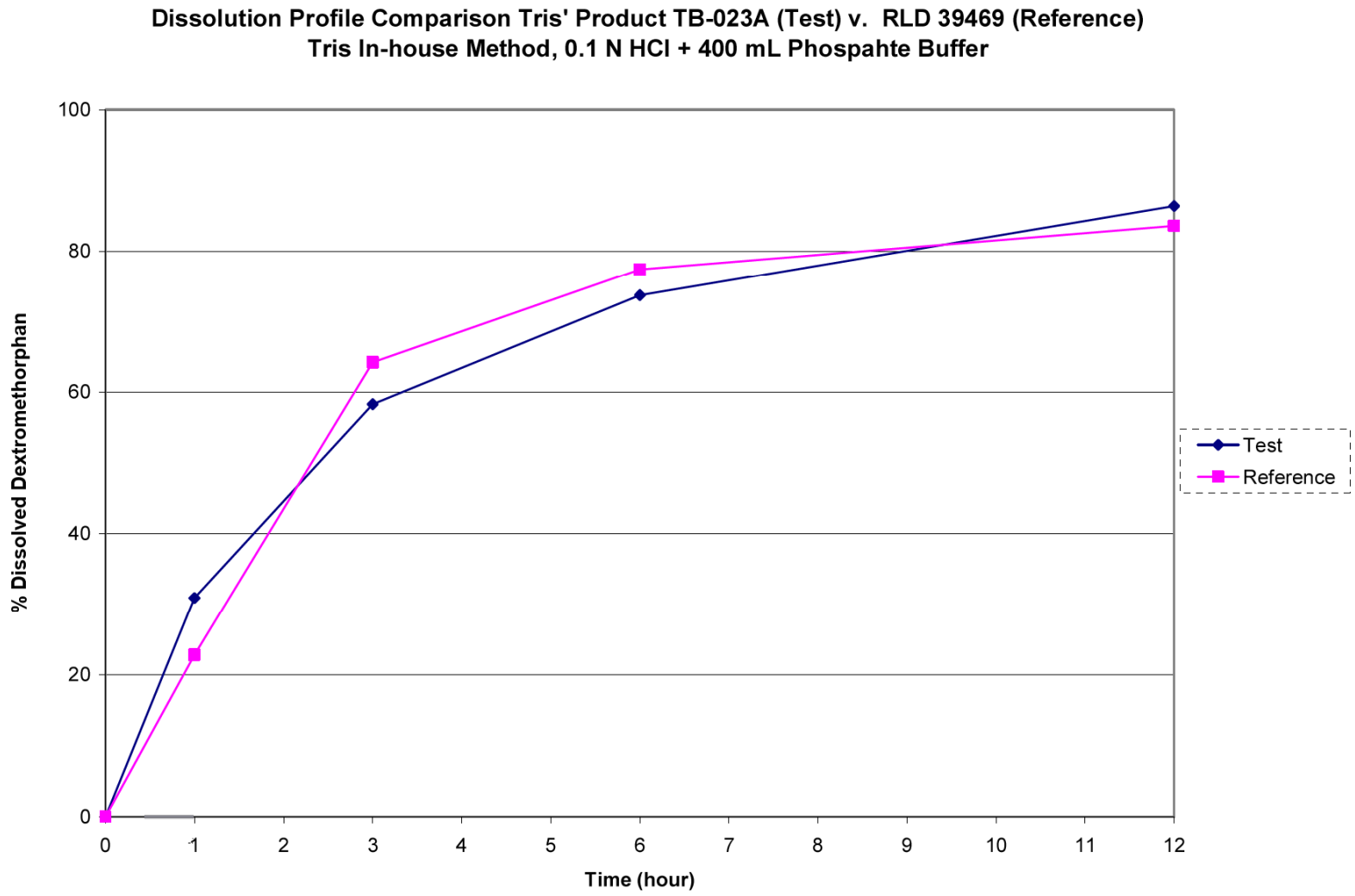
Dissolution Conditions	**Apparatus:**	USP II (Paddle)
	Speed of Rotation:	50 rpm
	Medium:	pH 6.8 Buffer
	Volume:	900 mL
	Temperature:	37 ºC ± 0.5 ºC
Firm's Proposed Specifications	Not applicable	
Dissolution Testing Site (Name, Address)	Tris Pharma, Inc. 3022 Route 130, Monmouth Junction, NJ 08852	

Study Ref No.	Testing Date	Product ID \ Batch No.	Dosage Strength & Form	No. of Dosage Units		Collection Times (hours) 1	2	4	6	8	10	12	Study Report Location
N/A	12/08/08	Dextromethorphan Polistirex ER Oral Suspension TB-023A (Date of Mfr: 09/03/08)	Oral Suspension, eq. to 30 mg/5mL	12	Mean	33.9	43.8	56.4	63.5	68.7	70.9	72.9	Notebook: QC0151 Page: 080
					Range							(b) (4)	
					SD	1.4	2.3	4.9	6.2	7.4	7.1	7.0	
					%CV	1.4	5.3	8.7	9.7	10.8	10.0	9.7	
N/A	11/11/07	Delsym® ER Oral Suspension 39469 (Expiry Date: Dec 08)	Oral Suspension, eq. to 30 mg/5mL	12	Mean	26.5	38.2	52.9	60.6	64.9	67.3	69.0	Notebook: QC0170 Page: 036
					Range							(b) (4)	
					SD	1.8	2.8	3.9	4.4	4.7	4.7	4.4	
					%CV	6.7	7.4	7.4	7.3	7.2	7.0	6.4	

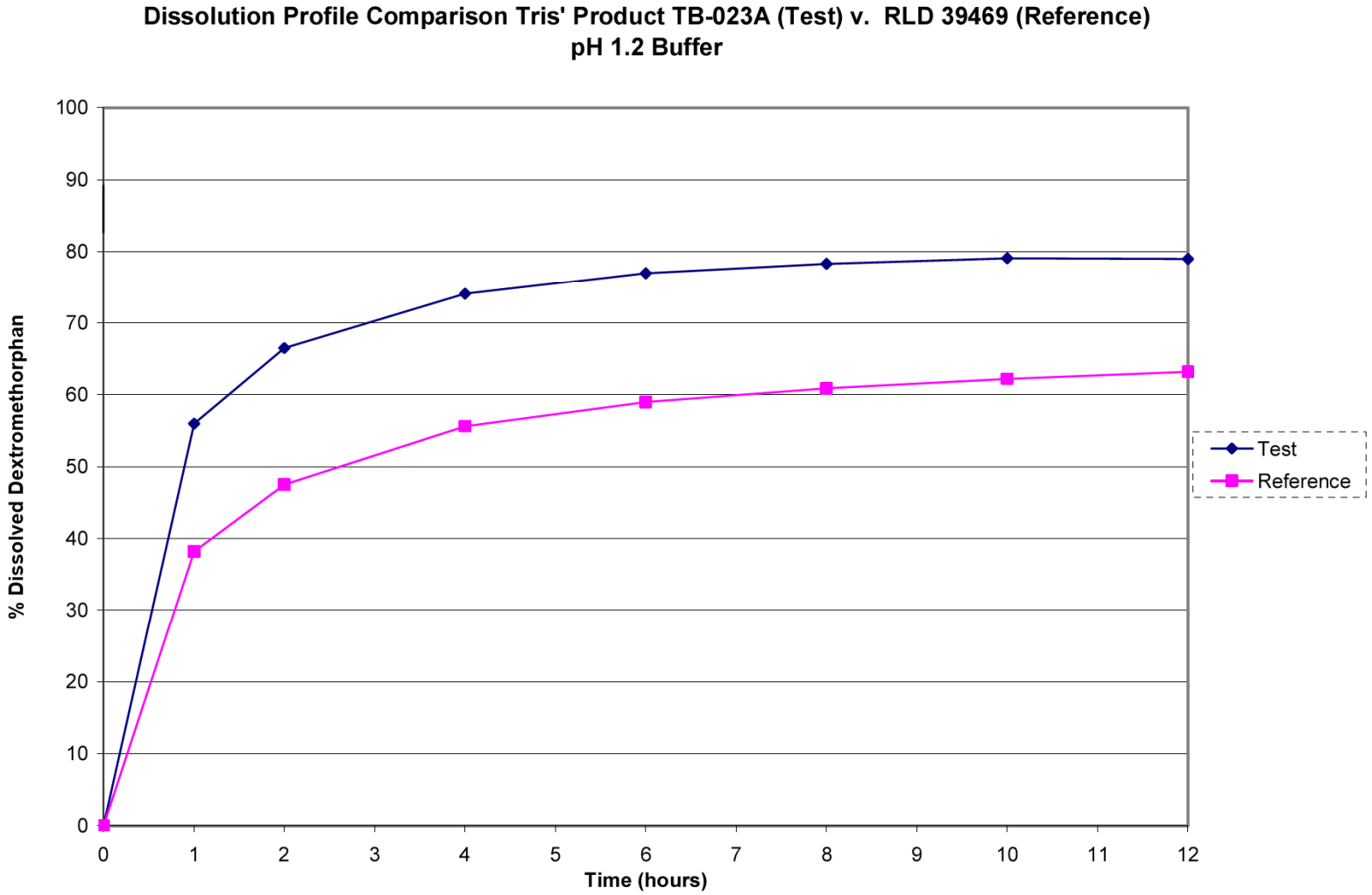
Comparative Chart of *In Vitro* Dissolution Studies - FDA Recommended Method:



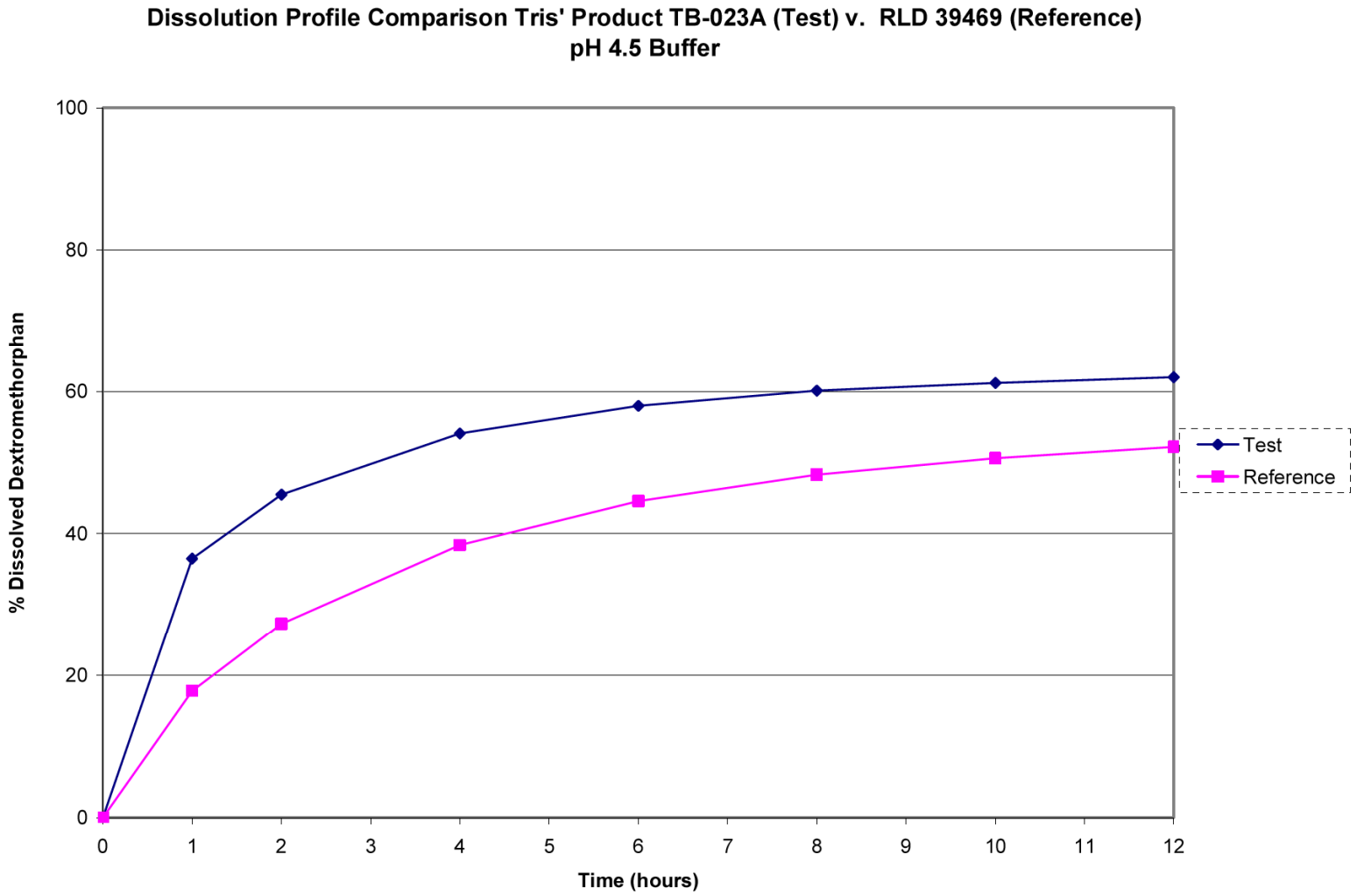
Comparative Chart of *In Vitro* Dissolution Studies - Tris In-house Method:



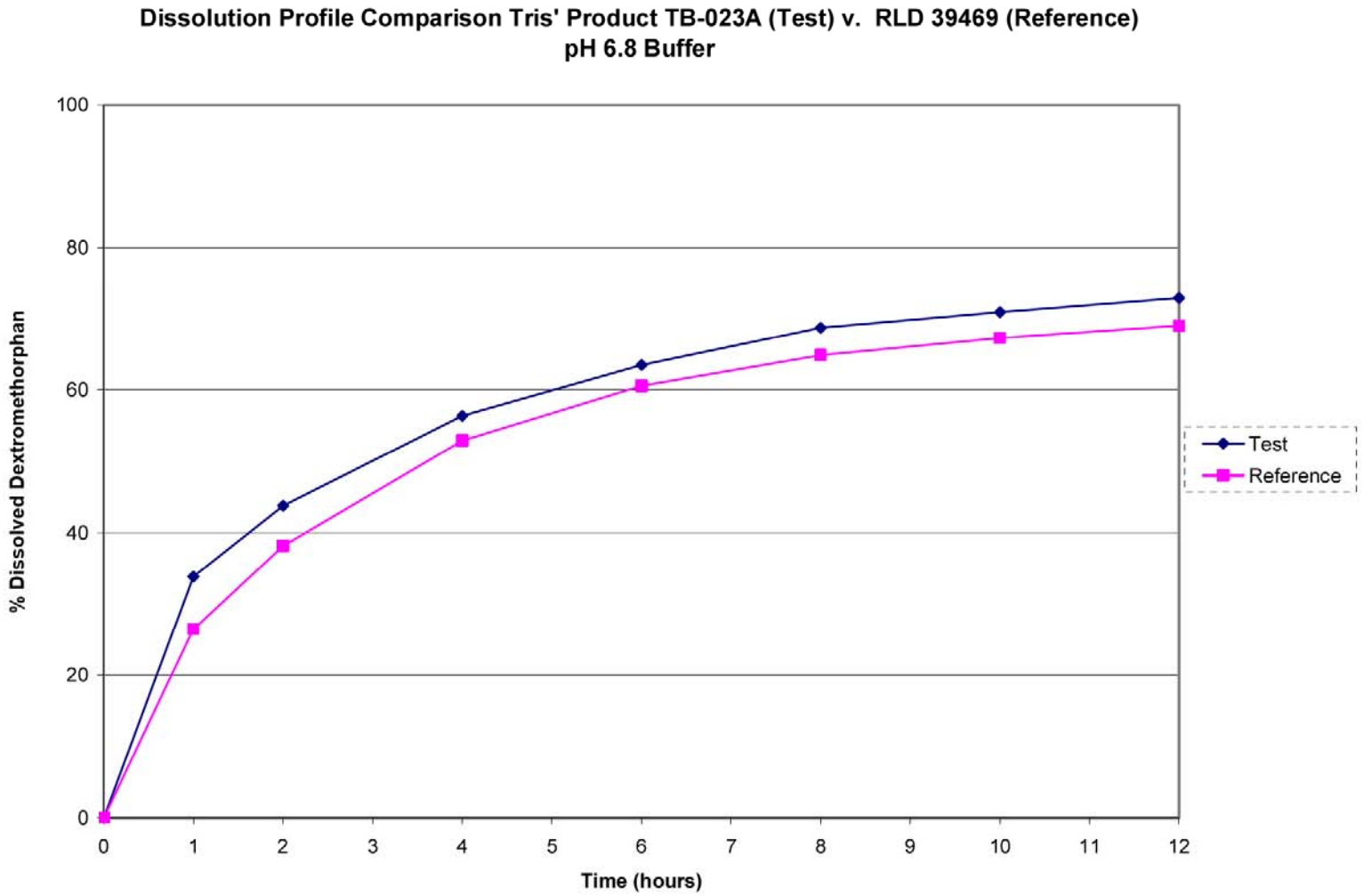
Comparative Chart of *In Vitro* Dissolution Studies - pH 1.2 Buffer:



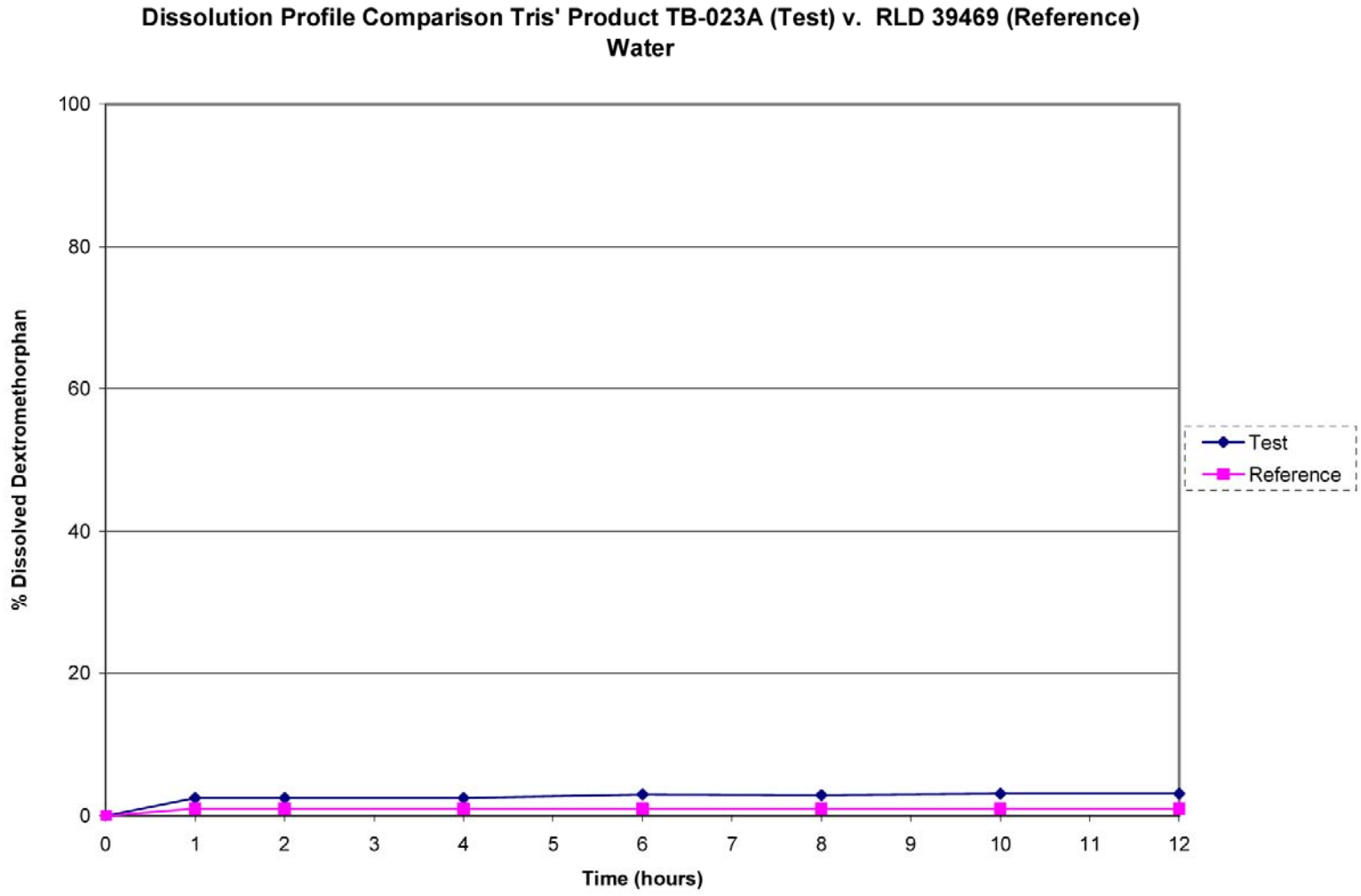
Comparative Chart of *In Vitro* Dissolution Studies - pH 4.5 Buffer:



Comparative Chart of *In Vitro* Dissolution Studies - pH 6.8 Buffer:



Comparative Chart of *In Vitro* Dissolution Studies - Water:



Individual Results of *In Vitro* Dissolution Studies - FDA Recommended Method:

Sample No.	Tris' Dextromethorphan Polistirex Oral Suspension Lot: TB-023A			
	30 min	60 min	90 min	180 min
1	(b) (4)			
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	26.2	30.0	32.7	36
Range	(b) (4)			
SD	2.1	2.4	2.4	1.9
%RSD	8.0	7.9	7.4	5.5

Sample No.	Delsym® Lot: 39469			
	30 min	60 min	90 min	180 min
1	(b) (4)			
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	21.3	23.3	24.6	27.7
Range	(b) (4)			
SD	1.4	1.8	2.4	3.6
%RSD	6.8	7.9	9.6	12.9

Individual Results of *In Vitro* Dissolution Studies - Tris In-house Method:

Sample No.	Tris' Dextromethorphan Polistirex Oral Suspension Lot: TB-023A			
	1 hour	3 hour	6 hour	12 hour
1	(b) (4)			
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	30.9	58.3	73.7	86.4
SD	1.6	2.8	2.8	2.2
Range	(b) (4)			
%RSD	5.3	4.7	3.8	2.6

Sample No.	Delsym® Lot: 39469			
	1 hour	3 hour	6 hour	12 hour
1	(b) (4)			
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	22.8	64.2	77.4	83.6
SD	1.0	1.8	1.1	1.0
Range	(b) (4)			
%RSD	4.4	2.9	1.4	1.2

Individual Results of *In Vitro* Dissolution Studies: pH 1.2 Buffer

Sample No.	Tris' Dextromethorphan Polistirex Oral Suspension Lot: TB-023A						
	1 hour	2 hour	4 hour	6 hour	8 hour	10 hour	12 hour
1	(b) (4)						
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Mean	56.0	66.5	74.1	77.0	78.3	79.1	78.9
Range	(b) (4)						
SD	1.9	1.7	1.5	1.4	1.4	1.4	1.3
%RSD	3.4	2.6	2.0	1.8	1.8	1.7	1.7

Sample No.	Delsym® Oral Suspension Lot: 39469						
	1 hour	2 hour	4 hour	6 hour	8 hour	10 hour	12 hour
1	(b) (4)						
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Mean	38.2	47.5	55.6	59.0	60.9	62.2	63.2
Range	(b) (4)						
SD	0.8	1.3	1.8	2.0	2.0	1.8	1.8
%RSD	2.0	2.7	3.2	3.4	3.3	3.0	2.8

Individual Results of *In Vitro* Dissolution Studies: pH 4.5 Buffer

Sample No.	Tris' Dextromethorphan Polistirex Oral Suspension Lot: TB-023A						
	1 hour	2 hour	4 hour	6 hour	8 hour	10 hour	12 hour
1	(b) (4)						
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Mean	36.5	45.5	54.1	58.0	60.1	61.2	62.0
Range	(b) (4)						
SD	1.5	1.3	1.0	0.8	0.7	0.6	0.6
%RSD	4.0	2.9	1.9	1.4	1.2	1.0	1.0

Sample No.	Delsym® Oral Suspension Lot: 39469						
	1 hour	2 hour	4 hour	6 hour	8 hour	10 hour	12 hour
1	(b) (4)						
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Mean	17.8	27.3	38.4	44.6	48.3	50.6	52.2
Range	(b) (4)						
SD	1.5	1.9	1.9	1.4	1.1	0.8	0.7
%RSD	8.7	6.9	5.0	3.2	2.2	1.7	1.3

Individual Results of *In Vitro* Dissolution Studies: pH 6.8 Buffer

Sample No.	Tris' Dextromethorphan Polistirex Oral Suspension Lot: TB-023A						
	1 hour	2 hour	4 hour	6 hour	8 hour	10 hour	12 hour
1	(b) (4)						
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Mean	33.9	43.8	56.4	63.5	68.7	70.9	72.9
Range	(b) (4)						
SD	1.4	2.3	4.9	6.2	7.4	7.1	7.0
%RSD	1.4	5.3	8.7	9.7	10.8	10.0	9.7

Sample No.	Delsym® Oral Suspension Lot: 39469						
	1 hour	2 hour	4 hour	6 hour	8 hour	10 hour	12 hour
1							(b) (4)
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Mean	26.5	38.2	52.9	60.6	64.9	67.3	69.0
Range							(b) (4)
SD	1.8	2.8	3.9	4.4	4.7	4.7	4.4
%RSD	6.7	7.4	7.4	7.3	7.2	7.0	6.4

Individual Results of *In Vitro* Dissolution Studies - Water:

Sample No.	Tris' Dextromethorphan Polistirex Oral Suspension Lot: TB-023A						
	1 hour	2 hour	4 hour	6 hour	8 hour	10 hour	12 hour
1	(b) (4)						
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Mean	2.5	2.5	2.5	3.0	2.9	3.1	3.1
Range	(b) (4)						
SD	0.2	0.3	0.3	0.4	0.4	0.6	0.4
%RSD	7.5	11.4	11.2	12.4	14.1	17.9	13.8

Sample No.	Delsym® Oral Suspension Lot: 49775						
	1 hour	2 hour	4 hour	6 hour	8 hour	10 hour	12 hour
1	(b) (4)						
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Mean	0.6	0.7	0.8	0.8	1.0	0.8	0.8
Range	(b) (4)						
SD	0.1	0.1	0.1	0.1	0.1	0.1	0.1
%RSD	10.4	15.2	13.8	13.0	14.7	15.4	16.2

III. COMMENTS:

This is a review of firm's response to the dissolution deficiencies:

Deficiency 1:

Please provide the final pH of your dissolution medium after 400 mL of phosphate buffer was added.

Response 1:

The final pH of the Tris in-house dissolution medium after 400 mL of phosphate buffer was added is 6.8 ± 0.2.

Reviewer Comments: The firm's response is acceptable.

Deficiency 2:

Please conduct and submit dissolution testing on the test and reference products (12 dosage units each) using the following FDA-recommended method:

Apparatus:	*USP II (Paddle)*
Speed of Rotation:	*50 rpm*
Medium:	*0.1 N HCl*
Volume:	*500 mL*
Temperature:	*37°C ± 0.5°C*

The recommended sampling times are 30, 60, 90, and 180 minutes or until at least 80% of the labeled amount of the drug is dissolved. Your proposed method will be evaluated in comparison with the FDA-recommended method when the dissolution data from both methods are available.

Response 2:

Dissolution testing for the test and reference products (12 dosage units each) using the FDA recommended method was provided in the ANDA Original Submission, Sequence 0000, in Module 5.3.1.3 "Dissolution Profile Study".

However, for ease of OGD review the summary table has been included in Module 2.7 "Bioequivalence Data Summary Tables" and the full information including a summary table, individual unit results, and a comparative chart have been represented in Module 5.3.1.3 "In-Vitro-In-Vivo Correlation Study Reports".

Dissolution sampling was stopped at 180 minutes as the test and reference products only showed limited amount of dextromethorphan release, i.e. (b) (4)% and (b) (4)% dissolved, respectively. Furthermore, little change in percent dissolved from 30 minutes to 180 minutes is seen for the test and reference products, i.e. (b) (4)% and (b) (4)%, respectively, indicating a plateau is reached. Tris does not believe that 80% dissolution would be attained due to the equilibrium resulting from the binding affinity, as well as the ionic species/strength present in the dissolution medium.

Tris believes that our in-house method is a more discriminating method than the FDA-recommended method. Not only does our in-house method include a change in pH which is similar to in vivo conditions, but it also exhibits the extended release properties of the product; therefore, Tris proposes the in-house method for release and stability testing.

Reviewer Comments:

The firm's proposed method can only be compared partially as the sampling times were not the same as used in the FDA method. The firm's method provided faster dissolution at 180 minutes for both the test and RLD product, i.e., (b) (4)% and (b) (4)%, respectively. The variability for the firm's method was slightly better based on the CV% data. In addition, the firm's method is sufficiently discriminating. For this reason, the firm's proposed method is accepted. However, specifications for 3-hour and 12-hour sampling time points are too liberal and not acceptable. The firm should acknowledge the following FDA-recommended specifications with their proposed method.

Apparatus:	USP II (Paddle)
Speed of Rotation:	50 rpm
Medium:	0.1 N HCl with addition of 400 mL of Phosphate Buffer after 1 hr sample.
Volume:	500 mL
Temperature:	37 ºC ± 0.5 ºC

Specifications: 1 hr: NMT (b) (4)%, 3 hrs: (b) (4)%, 6 hr: (b) (4)%, 12 hr: NLT (b) (4)%.

Deficiency 3:

Please conduct and submit dissolution testing data using USP Apparatus II (Paddles) at 50 rpm in at least three additional dissolution media (pH 4.5 and 6.8 buffers and water). The following sampling times are recommended: 1, 2, and 4 hours and every 2 hours thereafter, until at least 80% of labeled amount of the drug is dissolved.

Response 3:

Dissolution testing for the test and reference products (12 dosage units each) in three additional dissolution media (pH 1.2, 4.5, and 6.8 buffers) was provided in the ANDA Original Submission, Sequence 0000, in Module 5.3.1.3 "Dissolution Profile Study".

However, for ease of OGD review the summary tables have been included in Module 2.7 "Bioequivalence Data Summary Tables" and the full information including summary tables, individual unit results, and comparative charts have been represented in Module 5.3.1.3 "In-Vitro-In-Vivo Correlation Study Reports". Also, dissolution testing in water as suggested by the Agency has been performed and is also provided.

Dissolution sampling was stopped at 12 hours for all of these additional media (pH 1.2, 4.5, and 6.8 buffers and water) as the test and reference products showed little change in percent dissolved after 4 to 6 hours indicating a plateau is reached.

Reviewer Comments: The firm's response is acceptable.

Deficiency 4:

Comparative dissolution profiles of all additional dissolution testing should include individual dosage unit data as well as the mean, range, and standard deviation at each time point for twelve dosage units of each lot tested.

Response 4:

The full information including summary tables, individual unit results, and comparative charts represented in Module 5.3.1.3 "In-Vitro-In-Vivo Correlation Study Reports" show individual dosage unit data as well as the mean, range, and standard deviation at each time point for twelve dosage units of each lot tested as requested by the Agency.

Reviewer Comments: The firm's response is acceptable.

Deficiency 5:

Please provide summary tables for the dissolution testing data in eCTD table format.

Response 5:

Summary tables for the dissolution testing data have been included in the eCTD table format in this submission. Refer to Module 2.7 "Bioequivalence Data Summary Tables".

Other Information

Upon review of the Bioequivalence Data Summary Tables submitted in the ANDA Original Submission, Sequence 0000, it was observed that there were errors in Tables 2 and 3. These Tables have been revised for this submission. Refer to Module 2.7 "Bioequivalence Data Summary Tables" and Module 2.7.1.3 "Comparison and Analyses of Results Across Studies".

Reviewer Comments: The firm's response is acceptable.

IV. DEFICIENCY COMMENT:

The firm is requested to acknowledge the DBE recommended specifications (provided in the recommendations section).

V. RECOMMENDATIONS:

The in vitro dissolution testing conducted by Tris Pharma Inc. on its Dextromethorphan Polistirex Extended Release Oral Suspension, 30 mg/5 mL is acceptable. Based on the submitted dissolution data, the firm is requested to acknowledge the following FDA-specifications for their proposed method:

Apparatus:	USP II (Paddle)
Speed of Rotation:	50 rpm
Medium:	0.1 N HCl with addition of 400 mL of Phosphate Buffer after 1 hr sample.
Volume:	500 mL
Temperature:	37 ºC ± 0.5 ºC

Specifications: 1 hr: NMT (b) (4)%, 3 hrs: (b) (4)%, 6 hrs: (b) (4)%, 12 hrs: NLT (b) (4)%.

The firm should be informed of the above deficiency comment and recommendations.

BIOEQUIVALENCE DEFICIENCY

ANDA: 91-135

APPLICANT: Tris Pharma Inc.

DRUG PRODUCT: Dextromethorphan Polistirex Extended Release Oral 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:

Based on the dissolution testing data you submitted, we agree that your proposed dissolution method is appropriate for your test product. We also agree with your proposed dissolution method and specifications for the sampling times of 1 and 6 hours. However, the specifications for the sampling time points at 3 hours and 12 hours are not acceptable. Based on the data submitted, we recommend more appropriate specifications. Please provide acknowledgement for your acceptance of the following FDA-recommended specifications for your proposed dissolution method:

Apparatus:	USP II (Paddle)
Speed of Rotation:	50 rpm
Medium:	0.1 N HCl with addition of 400 mL of Phosphate Buffer after 1 hr.
Volume:	500 mL
Temperature:	37 °C ± 0.5 °C
Specifications:	1 hr: NMT (b)(4)% 3 hrs: (b)(4)% 6 hrs: (b)(4)% 12 hrs: NLT (b)(4)%.

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: 91-135

VII. *Completed Assignment for 91135 ID: 9032*

Reviewer: Palamakula, Anitha **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Dissolution Review -Dextromethorphan
Description: Polistirex Extended Release Oral Suspension, 30 mg/5 mL

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
9032	8/14/2009	Other	Dissolution Amendment	1	1
				Bean Total:	1

DIVISION OF BIOEQUIVALENCE 2 REVIEW COMPLEXITY POINTS

Study Amendment	
Study Amendment Dissolution data resubmitted	1
Study Amendment 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/

ANITHA PALAMAKULA
09/02/2009

ETHAN M STIER
09/02/2009

HOAINHON N CARAMENICO on behalf of DALE P CONNER
09/03/2009

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	91-135	
Drug Product Name	Dextromethorphan Polistirex Extended Release Oral Suspension	
Strength (s)	30 mg/5 mL (eq. to 30 mg dextromethorphan hydrobromide per 5 mL)	
Applicant Name	Tris Pharma, Inc.	
Address	2033 Route 130 Monmouth Junction, NJ 08852	
Applicant's Point of Contact	W. Scott Groner, Director RA and Compliance 2033 Route 130 Monmouth Junction, NJ 08852	
Contact's Phone Number	732-940-0358	
Contact's Fax Number	732-940-0374	
Submission Date(s)	January 9, 2009	
First Generic	Yes	
Reviewer	Anitha Palamakula, Ph.D.	
Study Number (s)	S08-0445	S08-0446
Study Type (s)	Fasting	Fed
Strength(s)	60 mg (10 mL)	60 mg (10 mL)
Clinical Site	Cetero Research	
Clinical Site Address	400 Fountain Lakes Blvd. St. Charles, MO 63301 (314) 419-6592	
Analytical Site	(b) (4)	
Analytical Address		
OUTCOME DECISION	**INCOMPLETE**	

I. EXECUTIVE SUMMARY

This is a review of the dissolution testing data only.

The dissolution testing conducted by the firm is incomplete. The firm conducted dissolution testing in 500 mL of 0.1 N HCl using Apparatus II (Paddles) at 50 rpm, with addition of 400mL of Phosphate Buffer after 1 hr sample. The sampling times are 1, 3, 6 and 12 hours. The firm should conduct dissolution testing using the following FDA-recommended dissolution method: 500 mL of 0.1 N HCl using USP Apparatus II (Paddles) at 50 rpm. The sampling times are 30, 60, 90, and 180 minutes or until at least 80% of the drug is dissolved. The firm should also submit multi-media dissolution testing data using USP Apparatus II at 50 rpm in at least three dissolution media (pH 4.5 and 6.8 buffers and water). The following sampling times are recommended: 1, 2, and 4 hours and every 2 hours thereafter, until at least 80% of the drug is dissolved. Comparative dissolution profiles should include individual unit data as well as the mean, range, and standard deviation at each time point for twelve dosage units. Specifications will be determined upon review of the data submitted in the application.

The Division of Scientific Investigations (DSI) inspection of the analytical sites was completed in (b) (4) and the outcome is reported as (b) (4). The DSI inspection of the clinical site is pending for a related ANDA 90740.

The dissolution testing is incomplete.

Table 1: SUBMISSION CONTENT CHECKLIST

Information			YES	NO	N/A
Did the firm use the FDA-recommended 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	PK parameters	☐	☐	☒
		Plasma concentrations	☐	☐	☒
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.					

The firm did not provide summary table for dissolution data using multi media.

The firm conducted dissolution testing the following its own proposed method Medium: 500 mL of 0.1 N HCl **for 1 hr and after sampling add 400mL of Phosphate Buffer,** using USP Apparatus II at 50 rpm.

Current FDA recommendations for this product from FDA website for individual product guidance are:

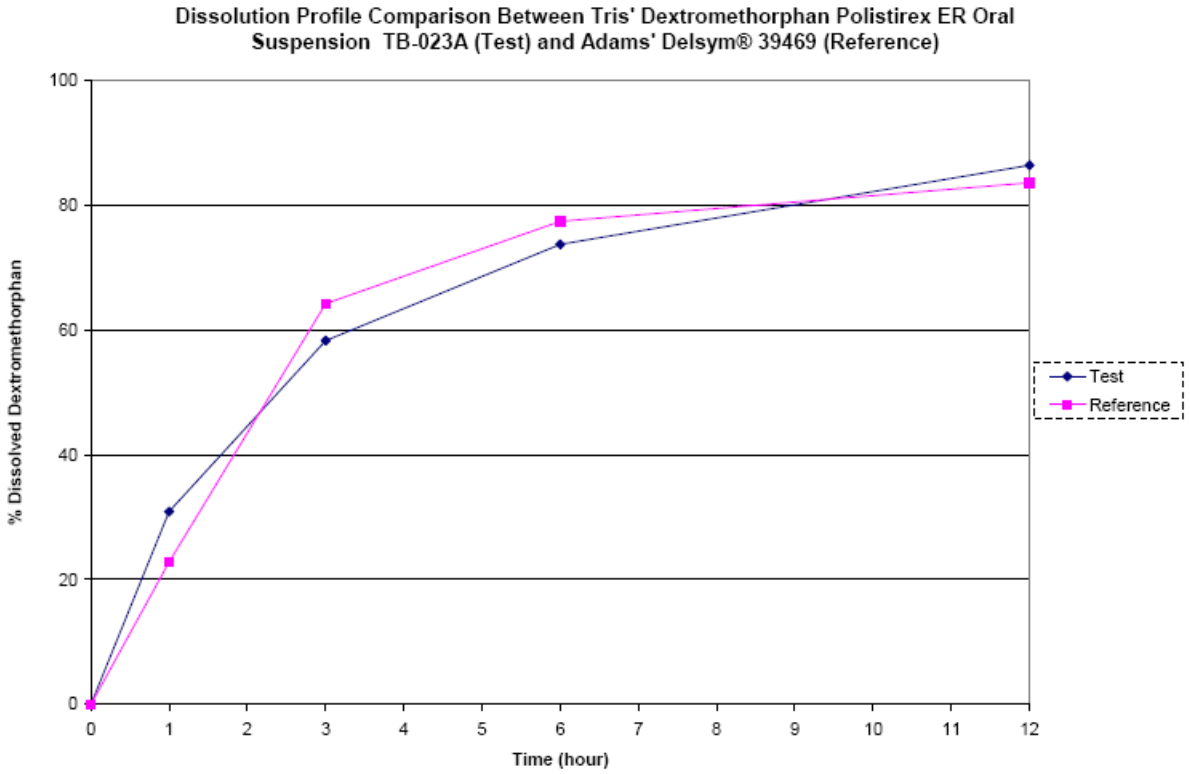
Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)	Date Updated
Dextromethorphan Polistirex	Suspension (Extended Release)	II (Paddle)	50	0.1 N HCl	500	30, 60, 90 and 180	10/06/2008

For modified release products, dissolution profiles 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, water) 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. The following sampling times are recommended: 1, 2, and 4 hours and every 2 hours thereafter, until at least 80% of the drug is dissolved. Comparative dissolution profiles should include individual unit data as well as the mean, range, and standard deviation at each time point for twelve dosage units. Specifications will be determined upon review of the data submitted in the application.

II. Dissolution Data

Dissolution Conditions	**Apparatus:**	USP II (Paddle)
	Speed of Rotation:	50 rpm
	Medium:	0.1 N HCl, **for 1 hr and after sampling add 400mL of Phosphate Buffer**
	Volume:	500 mL
	Temperature:	37 °C ± 0.5 °C
Firm's Proposed Specifications	1 hour NMT (b) (4) %. 3 hour (b) (4) % 6 hour (b) (4) %. 12 hour NLT (b) (4) %	
Dissolution Testing Site (Name, Address)	Tris Pharma, Inc. 3022 Route 130, Monmouth Junction, NJ 08852	

Study Ref No.	**Testing Date**	**Product ID \ Batch No.**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (hours)** 1	3	6	12	**Study Report Location**
N/A	9/17/08	Dextromethorphan Polistirex ER Oral Suspension TB-023A (Date of Mfr: 09/03/08)	Oral Suspension, eq. to 30 mg/5mL	12	Mean	30.9	58.3	73.7	86.4	Notebook: QC0170 Page: 055 and 65
					Range	(b) (4)				
					%CV	5.3	4.7	3.8	2.6	
N/A	8/31/07	Delsym® ER Oral Suspension 39469 (Expiry Date: Dec 08)	Oral Suspension, eq. to 30 mg/5mL	12	Mean	22.8	64.2	77.4	83.6	Notebook: QC0170 Page: 001
					Range	(b) (4)				
					%CV	4.4	2.9	1.4	1.2	



III. COMMENTS:

1. The dissolution testing conducted is incomplete. The firm conducted dissolution testing using Apparatus II (Paddles) at 50 rpm in 500 mL of 0.1 N HCl for 1 hr and after sampling added 400mL of Phosphate Buffer.

2. The firm should conduct dissolution testing using the following FDA-recommended dissolution method: 500 mL of 0.1 N HCl using USP Apparatus II (Paddles) at 50 rpm. The sampling times are 30, 60, 90, and 120 minutes or until at least 80% of the drug is dissolved.

3. The firm should also submit multi-media dissolution testing data using USP Apparatus II at 50 rpm in at least three dissolution media (pH 4.5 and 6.8 buffers and water). The following sampling times are recommended: 1, 2, and 4 hours and every 2 hours thereafter, until at least 80% of the drug is dissolved. Comparative dissolution profiles should include individual dosage unit data as well as the mean, range, and standard deviation at each time point for twelve dosage units. Specifications will be determined upon review of the data submitted in the application.

IV. DEFICIENCY COMMENT:

1. The firm should conduct and submit dissolution testing on the test and reference products (12 dosage units each) using the following FDA-recommended method:

Medium: 500 mL of 0.1 N HCl using USP Apparatus II (Paddles) at 50 rpm. The sampling times are 30, 60, 90, and 180 minutes or until at least 80% of the drug is dissolved.

2. The firm should also submit multi-media dissolution data using USP Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffers) and water. The following sampling times are recommended: 1, 2, and 4 hours and every 2 hours thereafter, until at least 80% of the drug is dissolved. Comparative dissolution profiles should include individual dosage unit data as well as the mean, range, and standard deviation at each time point for twelve dosage units.

3. The firm should provide summary tables for the dissolution testing data in multimedia to test and reference.

V. RECOMMENDATIONS:

The dissolution testing conducted by Tris Pharma Inc. on its Dextromethorphan Polistirex Extended Release Oral Suspension, 30 mg/5 mL is incomplete. The dissolution testing should be conducted in 500 mL of 0.1 N HCl using USP Apparatus II (Paddles) at 50 rpm. The sampling times are 30, 60, 90, and 180 minutes or until at least 80% of the drug is dissolved.

The firm should also submit multi-media dissolution data using USP Apparatus II at 50 rpm in at least three dissolution media (pH 4.5 and 6.8 buffers and water). The following sampling times are recommended: 1, 2, and 4 hours and every 2 hours thereafter, until at least 80% of the drug is dissolved. Comparative dissolution profiles should include individual dosage unit data as well as the mean, range, and standard deviation at each time point for twelve dosage units. The firm should provide summary tables for the dissolution testing data in multimedia to test and reference.

BIOEQUIVALENCE DEFICIENCY

ANDA: 91-135

APPLICANT: Tris Pharma Inc.

DRUG PRODUCT: Dextromethorphan Polistirex Extended Release Oral 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:

Your dissolution testing using your proposed method is incomplete. Please provide the final pH of your dissolution medium after 400 mL of phosphate buffer was added. In addition, please conduct and submit dissolution testing on the test and reference products (12 dosage units each) using the following FDA-recommended method:

Apparatus:	USP II (Paddle)
Speed of Rotation:	50 rpm
Medium:	0.1 N HCl
Volume:	500 mL
Temperature:	37 °C ± 0.5 °C

The recommended sampling times are 30, 60, 90, and 180 minutes or until at least 80% of the labeled amount of the drug is dissolved. Your proposed method will be evaluated in comparison with the FDA-recommended method when the dissolution data from both methods are available.

Please also conduct and submit dissolution testing data using USP Apparatus II (Paddles) at 50 rpm in at least three additional dissolution media (pH 4.5 and 6.8 buffers and water). The following sampling times are recommended: 1, 2, and 4 hours and every 2 hours thereafter, 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 standard deviation 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: 91-135

VII. *Completed Assignment for 91135 ID: 8495*

Reviewer: Palamakula, Anitha **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Dissolution Review -Dextromethorphan
Description: Polistirex Extended Release Oral Suspension, 30 mg/5 mL

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
8495	1/9/2009	Dissolution Data	Dissolution Review	1	1
				Bean 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/

Anitha Palamakula
6/24/2009 04:47:29 PM
BIOPHARMACEUTICS

Ethan Stier
6/25/2009 10:43:58 AM
BIOPHARMACEUTICS

Hoainhon T. Nguyen
6/25/2009 01:19:48 PM
BIOPHARMACEUTICS
For Dale P. Conner, Pharm. D., Director, Division of Bioequivalence I

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 091135Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ROUTING SHEET

☒ **APPROVAL** ☐ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **CGMP**

Division: III	**Team: 31**	**PM: Sarah Nguyen**

Electronic ANDA: Yes ☒ No ☒

ANDA #:91135
Firm Name:Tris Pharma, Inc.
ANDA Name:Dextromethorphan Polistirex Extended-release Oral Suspension, 30 mg/5mL
RLD Name:Delsym Extended-release suspension; Reckitt Benckiser; 18658

Electronic AP Routing Summary Located:

V:\Chemistry Division III\Team 31\Electronic AP Summary\ 91135 AP_ROUT_SUMRY.doc

AP/TA Letter Located:

V:\Chemistry Division III\Team 31\Final Version For DARRTS Folder\APTA letters\ 91135 AP ltr .doc

Project Manager Evaluation: **Date: 12/16/11 Initials:** SN

☒ Previously reviewed and tentatively approved --- Date 04/20/11
☐ Previously reviewed and CGMP Complete Response issued -- Date n/a

Original Rec'd date 1/12/09	Date of Application 1/9/09	Date Acceptable for Filing 1/12/09
Patent Certification (type) IV '882	Date Patent/Excl. expires 4/16/07	Citizens' Petition/Legal Case? Yes☐ No ☒ (If YES, attach email from PM to CP coord)
First Generic Yes ☒ No ☐ **DMF#:** (b) (4) (provide MF Jackets)	Priority Approval (Top 100, PEPFAR, etc.)? Yes ☐ No ☒ Comment: Prepared Draft Press Release sent to Cecelia Parise Yes ☐ No ☒ Date:	
☐ Suitability Petition/Pediatric Waiver	Pediatric Waiver Request: Accepted ☐ Rejected ☐ Pending ☐	

EER Status: ☐ Pending ☐ Acceptable ☐ OAI *EES Date Acceptable:*_____ ☐ Warning Letter Issued; Date:
Has there been an amendment providing for a Major change in formulation since filling? Yes ☐ No ☐ Comment:
Date of Acceptable Quality (Chemistry) 12/16/11 Addendum Needed: Yes ☐ No ☐ Comment:
Date of Acceptable Bio 3/24/11 Bio reviews in DARRTS: Yes ☒ No ☐ (Volume location:)
Date of Acceptable Labeling 11/18/11 Attached labeling to Letter: Yes ☐ No ☐ Comment:
Date of Acceptable Sterility Assurance (Micro) n/a

Methods Val. Samples Pending: Yes ☐ No ☐; Commitment Rcvd. from Firm: Yes ☐ No ☐

Post Marketing Agreement (PMA): Yes ☒ No ☐ (If yes, email PM Coordinator) Comment:

Modified-release dosage form: Yes ☒ No ☐ (If yes, enter dissolution information in Letter)

Routing:

☒ Labeling Endorsement, Date emailed: 12/16/11; 5/22/12 REMS Required: Yes ☐ No ☒ REMS Acceptable: Yes ☐ No ☐

☒ Regulatory Support

☐ Paragraph 4 Review (Dave Read, Susan Levine), Date emailed: 12/22/11

☐ Division

☐ 1st Generic Review

☐ Bob West / Peter Rickman
☐ Keith Webber

☐Filed AP Routing Summary in DARRTs	☐Notified Firm and Faxed Copy of Approval Letter	☐ Sent Email to "CDER-OGDAPPROVALS" distribution list

OGD APPROVAL ROUTING SUMMARY

1. ***Regulatory Support Branch Evaluation***

Martin Shimer **Date: 12/19/2011**
Chief, Reg. Support Branch **Initials:** MHS

Contains GDEA certification: Yes ☒ No ☐	Determ. of Involvement? Yes ☐ No ☒
(required if sub after 6/1/92)	Pediatric Exclusivity System
	RLD =Delsym NDA# 18-658 Date Checked 5/24/12 Nothing Submitted ☒ Written request issued ☐ Study Submitted ☐
Patent/Exclusivity Certification: Yes ☒ No ☐ If Para. IV Certification- did applicant: Notify patent holder/NDA holder Yes ☒ No ☐ Was applicant sued w/in 45 days:Yes ☒ No ☐ Has case been settled: Yes ☐ No ☒ Date settled: Is applicant eligible for 180 day	
Generic Drugs Exclusivity for each strength: Yes ☒ No ☐	
Date of latest Labeling Review/Approval Summary _____	
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒	
Type of Letter: ☒ APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐CGMP ☐ OTHER:	
Comments:ANDA TA'd on 4/20/2011. At the time the TA was issued the reason given for TA was an unexpired 30 month stay of approval. This stay of approval expired on 11/15/2011. This ANDA holds the exclusivity seat for this product and they secured TA within 30 months of their submission date. As the 30 month stay of approval has expired, this ANDA is eligible for immediate Full Approval with an award of 180 day exclusivity. Addendum: Tris has informed the agency that on December 21, 2011, the district court granted Tris Pharma's motion for summary judgment of the asserted patent claims.	

2. ***Labeling Endorsement***

Reviewer, Jeanne Skanchy:
Date12/16/11; 5/22/12
InitialsJS

Labeling Team Leader, John Grace:
Date12/19/11
InitialsJG

REMS required?
☐Yes ☒No

REMS acceptable?
☐Yes ☐No ☒n/a

Comments:

From: Skanchy, Jeanne
Sent: Tuesday, May 22, 2012 9:36 AM
To: Nguyen, Sarah
Subject: RE: ANDA 91135

Hi Sarah,

I checked DARRTS, Orange Book, Drugs@fda.gov, and USP. The labeling concurrence from December 2011 is still valid.

Thanks,

Jeanne

From: Nguyen, Sarah

Sent: Tuesday, May 22, 2012 9:22 AM
To: Skanchy, Jeanne
Subject: ANDA 91135

Hi Jeanne,

This package has been sitting with Bob W since Dec 2011 and now ready for full approval now that EES has come back AC. Can you check to see if labeling is still ok? You signed off with John back in December 2011. Thanks!

Regards,

Sarah

From: Grace, John F
Sent: Monday, December 19, 2011 11:38 AM
To: Skanchy, Jeanne; Nguyen, Sarah
Subject: RE: Labeling sign off for ANDA 91135; Dextromethorphan Polistirex Extended-release Oral Suspension, 30 mg/5 mL

concur.

John F. Grace
Team Leader, Labeling Review Team 1 (HFD-613)
FDA/CDER/OPS/OGD/DLPS/LRB/LRT1
7520 Standish Place, MPN1
Rockville, MD 20855
(240)276-8985
john.grace@fda.hhs.gov

From: Skanchy, Jeanne
Sent: Friday, December 16, 2011 1:30 PM
To: Nguyen, Sarah
Cc: Grace, John F
Subject: RE: Labeling sign off for ANDA 91135; Dextromethorphan Polistirex Extended-release Oral Suspension, 30 mg/5 mL

Hi Sarah,

I have checked the OB, drugs@fda, and DARRTS. Please sign off for me.

Thanks,

Jeanne

From: Nguyen, Sarah
Sent: Friday, December 16, 2011 11:01 AM
To: Skanchy, Jeanne; Grace, John F
Subject: Labeling sign off for ANDA 91135; Dextromethorphan Polistirex Extended-release Oral Suspension, 30 mg/5 mL

Please conduct labeling sign off for ANDA 91135; Dextromethorphan Polistirex Extended-release Oral Suspension, 30 mg/5 mL

<< File: 91135_review_6[1].pdf >> << File: 91135_ap_ltr.doc >>

Thanks,
Sarah

3. ***Paragraph IV Evaluation*** **PIV's Only**
David Read **Date 23Dec2011**
OGD Regulatory Counsel **InitialsDTR**
Pre-MMA Language included ☐
Post-MMA Language Included ☐
Comments:Changes to AP letter saved to V drive.

4. ***Quality Division Director /Deputy Director Evaluation*** **Date 1/4/12**
Chemistry Div. **III (Sayeed)** **InitialsVAS**
Comments:cmc satisfactory.

5. ***First Generic Evaluation*** **First Generics Only**
Frank Holcombe **Date 5/24/12**
Assoc. Dir. For Chemistry **Initials rlw/for**
Comments: (First generic drug review)
N/A. This ANDA was granted tentative approval on April 20, 2011.

OGD Office Management Evaluation

6. Peter Rickman **Date 5/24/12**
Director, DLPS **Initials rlw/for**
Para.IV Patent Cert: Yes☐ No☐
Pending Legal Action: Yes ☐ No ☐
Petition: Yes☐ No☐
Comments: This ANDA was granted tentative approval on April 20, 2011. Final approval was blocked at that time by Tris Pharma's paragraph IV certification to the '882 patent and the subsequent legal action. Refer to the administrative sign-off form created at the time of the tentative approval. At present, the 30-month statutory stay of approval as a result of the ongoing legal action has expired and this ANDA is eligible for final approval.

Bioequivalence addendum - Revised in-vitro dissolution specification (1 hour) revised from NMT % to NMT %. Office-level bio endorsed 7/28/11.

Final-printed labeling found acceptable for approval 11/18/11, as endorsed 5/22/12. No REMS is required.

CMC found acceptable for approval (Chemistry Review #4) 12/16/11. There have been no CMC updates to the ANDA since this date.

AND/OR

7. Robert L. West **Date 5/25/12**
Deputy Director, OGD **Initials RLWest**
Para.IV Patent Cert: Yes☒ No☐
Pending Legal Action: Yes☒ No☐
Petition: Yes☐ No☒
Press Release Acceptable ☐
Date PETS checked for first generic drug _____

Comments: Acceptable EES dated 5/21/12 (Verified 5/24/12). No "OAI" Alerts noted.

Tris Pharma provided a paragraph IV certification to the '882 patent and was sued within the 45-day period. The 30-month

statutory hold associated with the ongoing litigation has expired. In addition, on December 21, 2011, the district court granted Tris Pharma's motion for summary judgment of noninfringement of the asserted patent claims.

This ANDA is recommended for approval.

8. ***OGD Director Evaluation***

Keith Webber
Deputy Director, OPS

Comments: RLWest for Keith Webber, Ph.D.
First Generic Approval ☐
PD or Clinical for BE ☐
Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

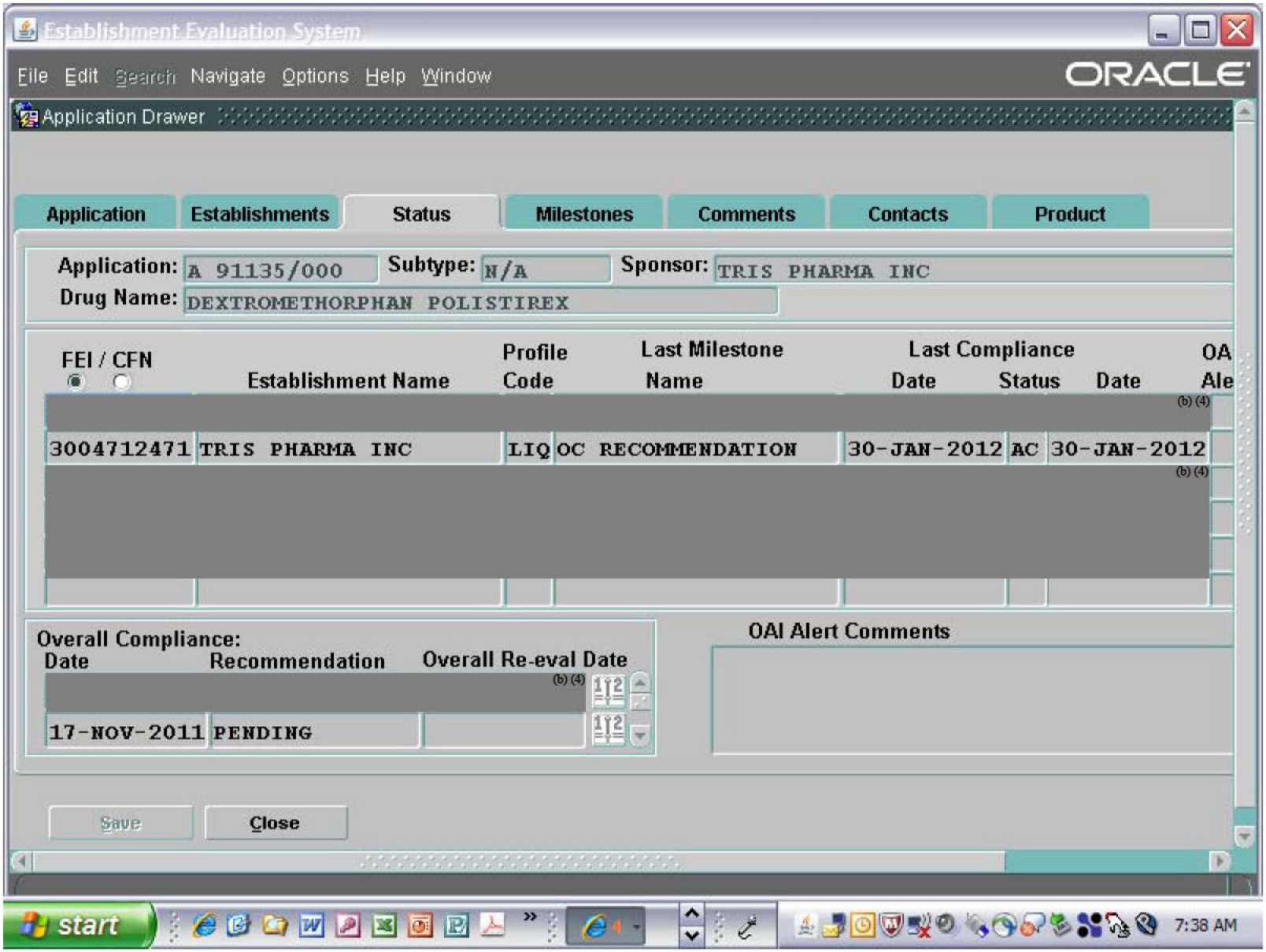
Comments:

9. Project Manager

Date 5/25/12
Initials SN

Check Communication and Routing Summary into DARRTS

EER DATA:



Reference ID: 3136320

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

-
- [1]
- [2]

- FDA Home[3]
- Drug Databases[4]
- Orange Book[5]

-

Patent and Exclusivity Search Results from query on Appl No 018658 Product 001 in the OB_OTC list.

Patent Data

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		

Exclusivity Data

There is no unexpired exclusivity for this product.

Bio: Revised in-vitro dissolution specification (1 hr) revised from [(b) (4)] to NMT [(b) (4)] 1/28/11.

ROUTING SHEET

☒ APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ CGMP

FR OLC – 11/18/11 – No REMS required; 5/20/12 –

Division: III	Team: 31	PM: Sarah Nguyen	Electronic ANDA: Yes ☒ No ☒

CMC OLC Rev. #4 12/16/11.

ANDA #:91135
Firm Name:Tris Pharma, Inc.
ANDA Name:Dextromethorphan Polistirex Extended-release Oral Suspension, 30 mg/5mL
RLD Name:Delsym Extended-release suspension; Reckitt Benckiser; 18658

Electronic AP Routing Summary Located:

V:\Chemistry Division III\Team 31\Electronic AP Summary\ 91135 AP ROUT SUMRY.doc

AP/TA Letter Located:

V:\Chemistry Division III\Team 31\Final Version For DARRTS Folder\APTA letters\ 91135 AP ltr .doc

Project Manager Evaluation:

Date: 12/16/11 Initials: SN

☒ Previously reviewed and tentatively approved --- Date 04/20/11
☐ Previously reviewed and CGMP Complete Response issued -- Date n/a

Original Rec'd date 1/12/09	Date of Application 1/9/09	Date Acceptable for Filing 1/12/09
Patent Certification (type) IV '882	Date Patent/Excl. expires 4/16/07	Citizens' Petition/Legal Case? Yes☐ No ☒ (If YES, attach email from PM to CP coord)
First Generic Yes ☒ No ☐ DMF#: [(b) (4)] (provide MF Jackets)	Priority Approval (Top 100, PEPFAR, etc.)? Yes ☐ No ☒ Comment: Prepared Draft Press Release sent to Cecelia Parise Yes ☐ No ☒ Date:	
☐ Suitability Petition/Pediatric Waiver	Pediatric Waiver Request: Accepted ☐ Rejected ☐ Pending ☐	

EER Status: ☐ Pending ☐ Acceptable ☐ OAI *EES Date Acceptable:*_____ ☐ Warning Letter Issued; Date:
Has there been an amendment providing for a Major change in formulation since filling? Yes ☐ No ☐ Comment:
Date of Acceptable Quality (Chemistry) 12/16/11 Addendum Needed: Yes ☐ No ☐ Comment:
Date of Acceptable Bio 3/24/11 Bio reviews in DARRTS: Yes ☒ No ☐ (Volume location:)
Date of Acceptable Labeling 11/18/11 Attached labeling to Letter: Yes ☐ No ☐ Comment:
Date of Acceptable Sterility Assurance (Micro) n/a

Methods Val. Samples Pending: Yes ☐ No ☐; Commitment Rcvd. from Firm: Yes ☐ No ☐

Post Marketing Agreement (PMA): Yes ☒ No ☐ (If yes, email PM Coordinator) Comment:

Modified-release dosage form: Yes ☒ No ☐ (If yes, enter dissolution information in Letter)

Routing:

☑ Labeling Endorsement, Date emailed: 12/16/11 REMS Required: Yes ☐ No ☒ REMS Acceptable: Yes ☐ No ☐

☑ Regulatory Support MAR 12/19/2011

☑ Paragraph 4 Review (Dave Read, Susan Levine), Date emailed: 12/22/11

☑ Division 1/4/12

☑ 1st Generic Review

☑ Bob West / Peter Rickman

☐ Keith Webber

5/25/2012

☐ Filed AP Routing Summary in DARRTs	☐ Notified Firm and Faxed Copy of Approval Letter	☐ Sent Email to "CDER-OGDAPPROVALS" distribution list

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

/s/

SARAH K NGUYEN
05/25/2012

BIOEQUIVALENCE AMENDMENT

ANDA 091135

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Pl.
Rockville, MD 20855-2810

APPLICANT: Tris Pharma, Inc. TEL: (732) 940-0358

ATTN: W. Scott Groner FAX: (732) 940-0374

FROM: Diana Solana-Sodeinde FDA CONTACT PHONE: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on January 9, 2009, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Dextromethorphan Polistirex Extended Release Oral Suspension, EQ. 30 mg dextromethorphan hydrobromide per 5 mL.

Reference is also made to your amendments dated September 25, 2009; October 9, 2009 and March 4, 2011.

The Division of Bioequivalence has completed its review of the submissions referenced above and has comments and recommendations which are presented on the attached **1** page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You may submit a response to these comments and recommendations in accord with 21 CFR 314.96. **Facsimiles or partial replies will not be considered for review.** If you respond, your cover letter should clearly indicate:

Bioequivalence Information

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: 091135

APPLICANT: Tris Pharma, Inc.

DRUG PRODUCT: Dextromethorphan Polistirex Extended-Release Oral Suspension, EQ. 30 mg Dextromethorphan Hydrobromide per 5 mL

The Division of Bioequivalence (DBE) has completed its review of the "additional information" section from your amendment dated March 4, 2011. In this section, you requested that the Agency change the 1 hour dissolution specification from *NMT* (b)(4)% to *NMT* (b)(4)% dissolved in 1 hour. In support of this request, you submitted stability testing results from the biobatch (#TB-023A) as well as an additional lot (#TB-081A).

Your proposed dissolution specifications based on stability data are not acceptable. Since FDA-recommended dissolution specification is determined based on the data of the freshly manufactured biobatch, which underwent acceptable bioequivalence testing and not on the aged batches, the rationale used for justifying your proposed dissolution specifications are not acceptable.

However, the DBE has re-evaluated the previously recommended 1 hour specification of *NMT* (b)(4)% and considered it too restrictive with respect to the mean and range of the data at this time point. Therefore, the DBE has revised the recommended specification of *NMT* (b)(4)% to *NMT* (b)(4)% in 1 hour. It is important to emphasize that the revised dissolution specification is based on the original dissolution testing results submitted for the freshly manufactured biobatch and not on stability data of aged batches.

The DBE acknowledges that you will continue to conduct dissolution testing in 500 mL of 0.1 N HCl at 37°C + 0.5°C with the addition of 400 mL of Phosphate Buffer, at 37°C + 0.5°C, 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:	(b)(4)%
12 hrs:	NLT (b)(4)%

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
07/28/2011

ROUTING SHEET

☐ APPROVAL ☒ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ CGMP

Division: III	Team: 31	PM: Sarah Nguyen

Electronic ANDA: Yes ☒ No ☐

ANDA #:91135
Firm Name:Tris Pharma, Inc.
ANDA Name:Dextromethorphan Polistirex Extended-release Oral Suspension, 30 mg/5 mL
RLD Name:Delsym Extended-release Suspension; Reckitt Benckiser; 18658

Electronic AP Routing Summary Located:

V:\Chemistry Division III\Team 31\Electronic AP Summary\ 91135 TA_ROUT_SUMRY.doc

AP/TA Letter Located:

V:\Chemistry Division III\Team 31\Final Version For DARRTS Folder\APTA letters\ 91135 TA ltr .doc

Project Manager Evaluation: **Date: 2/2/11 Initials:** SN

☐ Previously reviewed and tentatively approved --- Date n/a
☐ Previously reviewed and CGMP Complete Response issued -- Date n/a

Original Rec'd date 1/12/09	Date of Application 1/9/09	Date Acceptable for Filing 1/12/09
Patent Certification (type) IV	Date Patent/Excl. expires Apr 16, 2017	Citizens' Petition/Legal Case? Yes☐ No ☐ (If YES, attach email from PM to CP coord)
First Generic Yes ☒ No ☐ **DMF#:** (b) (4) (provide MF Jackets)	Priority Approval (Top 100, PEPFAR, etc.)? Yes ☐ No ☐ Comment: Prepared Draft Press Release sent to Cecelia Parise Yes ☐ No ☐ Date:	
☐ Suitability Petition/Pediatric Waiver	Pediatric Waiver Request: Accepted ☐ Rejected ☐ Pending ☐	

EER Status: ☐ Pending ☒ Acceptable ☐ OAI *EES Date Acceptable: 5-14-10* ☐ Warning Letter Issued; Date:
Has there been an amendment providing for a Major change in formulation since filling? Yes ☐ No ☐ Comment:
Date of Acceptable Quality (Chemistry) 2-4-11 Addendum Needed: Yes ☐ No ☐ Comment:
Date of Acceptable Bio 3/24/11 Bio reviews in DARRTS: Yes ☐ No ☐ (Volume location:)
Date of Acceptable Labeling 10-19-10 Attached labeling to Letter: Yes ☐ No ☐ Comment:
Date of Acceptable Sterility Assurance (Micro) n/a

Methods Val. Samples Pending: Yes ☐ No ☐; Commitment Rcvd. from Firm: Yes ☐ No ☐

Post Marketing Agreement (PMA): Yes ☒ No ☐ (If yes, email PM Coordinator) Comment:

Modified-release dosage form: Yes ☒ No ☐ (If yes, enter dissolution information in Letter)

Routing:

☒ Labeling Endorsement, Date emailed: 3/24/11 REMS Required: Yes ☐ No ☒ REMS Acceptable: Yes ☐ No ☐

☒ Regulatory Support

☒ Paragraph 4 Review (Dave Read, Susan Levine), Date emailed: 4/05/2011

☐ Division

☐ 1st Generic Review

☐ Bob West / Peter Rickman
☐ Keith Webber

☐ Filed AP Routing Summary in DARRTs	☐ Notified Firm and Faxed Copy of Approval Letter	☐ Sent Email to "CDER-OGDAPPROVALS" distribution list

OGD APPROVAL ROUTING SUMMARY

1. ***Regulatory Support Branch Evaluation***

Martin Shimer **Date: 28 March 2011**
Chief, Reg. Support Branch **Initials:** MHS

Contains GDEA certification: Yes ☒ No ☐	Determ. of Involvement? Yes ☐ No ☒
(required if sub after 6/1/92)	Pediatric Exclusivity System
Patent/Exclusivity Certification: Yes ☒ No ☐ If Para. IV Certification- did applicant: Notify patent holder/NDA holder Yes ☒ No ☐ Was applicant sued w/in 45 days:Yes ☒ No ☐ Has case been settled: Yes ☐ No ☒ Date settled: Is applicant eligible for 180 day	RLD =Delsym NDA#18-658 Date Checked 4/20/11 Nothing Submitted ☒ Written request issued ☐ Study Submitted ☐
Generic Drugs Exclusivity for each strength: Yes ☐ No ☐	
Date of latest Labeling Review/Approval Summary _____	
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒	
Type of Letter: ☐ APPROVAL ☒ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ CGMP ☐ OTHER:	
Comments:ANDA submitted on 1/12/2009, BOS=Delsym NDA 18-658, PIV to '882. ANDA ack for filing with a PIV on 1/12/2009 (LO dated 5/13/2009). Patent Amendment submitted on 5/19/2009-notice sent via (b) (4) to Celltech in Rochester NY with notice delivered on 5/15/2009, notice sent via Fed Ex to Reckitt Benckiser in Parsippany NJ with notice delivered on 5/15/2009. Patent Amendment submitted on 7/23/2009-CA 09 CV 3125 filed in the D of NJ on 6/26/2009 for infringement of the '882 patent. Patent Amendment rec'd on 8/17/2009-Letter from Fitzpatrick, Cella, Harper and Scinto-counsel for innovator provided a copy of CA 09 CV 3125. Since suit was filed within 45 days the 30 month stay of approval for this ANDA will expire on 11/15/2011. ANDA is eligible for TA only due to unexpired 30 month stay of approval.	

2. ***Labeling Endorsement***

Reviewer, Jeanne Skanchy:
Date4/05/2011
Initials LS for JS

Labeling Team Leader, John Grace:
Date4/05/2011
Initials LS for JG

REMS required? ☐Yes ☒No

REMS acceptable? ☐Yes ☐No ☒n/a

Comments:

From: Grace, John F
Sent: Tuesday, April 05, 2011 11:19 AM
To: Sears, Leigh Ann
Subject: RE: Sign-off for ANDA 091135 (Dextromethorphan Polistirex Extended-release Oral Suspension, 30 mg/5 mL)
concur.

John F. Grace
Team Leader, Labeling Review Team 1 (HFD-613)
FDA/CDER/OPS/OGD/DLPS/LRB/LRT1
7520 Standish Place, MPN1
Rockville, MD 20855
(240)276-8985
john.grace@fda.hhs.gov

It does not bind or otherwise commit the Agency to the views expressed.

From: Skanchy, Jeanne
Sent: Tuesday, April 05, 2011 11:05 AM
To: Sears, Leigh Ann
Cc: Grace, John F
Subject: RE: Sign-off for ANDA 091135 (Dextromethorphan Polistirex Extended-release Oral Suspension, 30 mg/5 mL)
Hi Leigh Ann,

I have checked the OB, USP/PF, DARRTS, and Drugs@fda.gov. Please sign-off for me.

Thanks,

Jeanne

From: Sears, Leigh Ann
Sent: Tuesday, April 05, 2011 10:52 AM
To: Skanchy, Jeanne; Grace, John F
Subject: Sign-off for ANDA 091135 (Dextromethorphan Polistirex Extended-release Oral Suspension, 30 mg/5 mL)
Hello John and Jeanne,

Please perform labeling sign-off for this ANDA. It is ready for tentative approval.

Thanks,
Leigh Ann

3. ***Paragraph IV Evaluation*** **PIV's Only**
David Read **Date 7Apr2011**
OGD Regulatory Counsel **InitialsDTR**
Pre-MMA Language included ☐
Post-MMA Language Included ☐
Comments:Changes to TA letter saved to V drive.

4. ***Quality Division Director /Deputy Director Evaluation*** **Date 4/18/11**
Chemistry Div. **III (Sayeed)** **InitialsVAS**
Comments:cmc satisfactory.

5. ***First Generic Evaluation*** **First Generics Only**
Frank Holcombe **Date 4/20/11**
Assoc. Dir. For Chemistry **Initials rlw/for**
Comments: (First generic drug review)
N/A. By endorsing this tentative approval package, the CMC division director has confirmed that there are no precident setting issues associated with the CMC review of this drug product. Thus, no further CMC review is necessary.

OGD Office Management Evaluation

6. Peter Rickman **Date 4/20/11**
Director, DLPS **Initials rlw/for**
Para.IV Patent Cert: Yes☐ No☐
Pending Legal Action: Yes ☐ No ☐
Petition: Yes☐ No☐
Comments: Bioequivalence studies (fasting and non-fasting) on 60 mg/10 mL dose found acceptable. In-vitro dissolution testing also found acceptable. Bio study sites have acceptable DSI inspection histories. Office-level bio endorsed 2/14/11, 3/24/11.

Labeling found acceptable for tentative approval 4/18/11.

CMC found acceptable for approval (Chermistry Review #3) 2/4/11.

AND/OR

7. Robert L. West **Date 4/20/11**
Deputy Director, OGD **Initials RLWest**
Para.IV Patent Cert: Yes☒ No☐
Pending Legal Action: Yes☒ No☐
Petition: Yes☐ No☒
Press Release Acceptable ☐
Date PETS checked for first generic drug _____

Comments: Acceptable EES dated 5/14/10 (Verified 4/20/11). No "OAI" Alerts noted.

Tris Pharma submitted a paragraph IV certification to the '882 patent and was sued within the 45-day period. Litigation is ongoing. The 30-month statutory hold associated with this ANDA will expire on 11/15/11. There are no additional patents or exclusivity listed in the current "Orange Book" for this drug product.

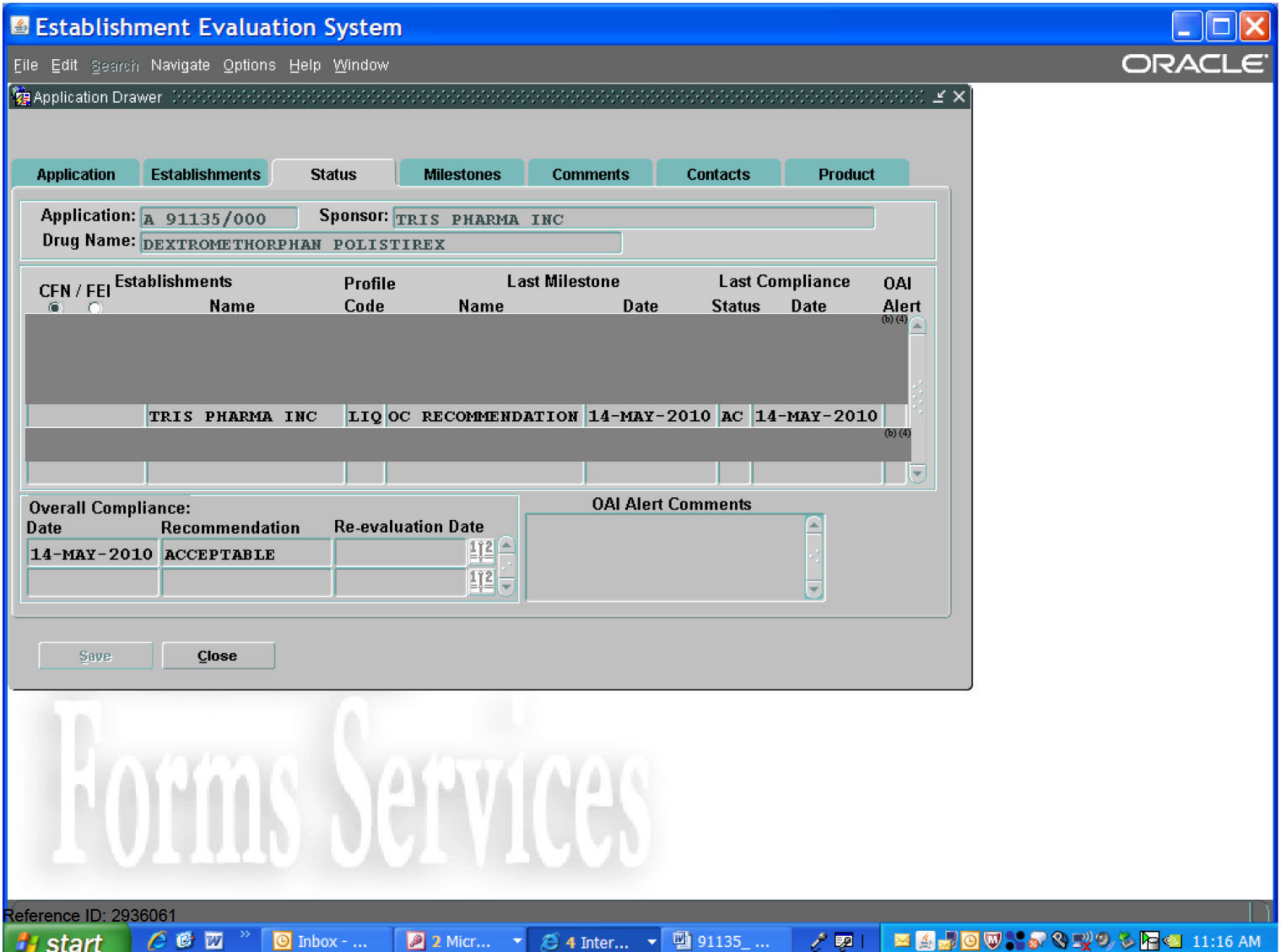
This ANDA is recommended for tentative approval.

8. ***OGD Director Evaluation***
Keith Webber
Deputy Director, OPS
Comments: RLWest for Keith Webber, Ph.D. 4/20/11.
First Generic Approval ☐
PD or Clinical for BE ☐
Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

Comments:

9. Project Manager
Date 4/20/11
Initials SN

Check Communication and Routing Summary into DARRTS


Establishment Evaluation System
File Edit Search Navigate Options Help Window
ORACLE
Application Drawer
Application
Establishments
Status
Milestones
Comments
Contacts
Product
Application: A 91135/000
Sponsor: TRIS PHARMA INC
Drug Name: DEXTROMETHORPHAN POLISTIREX
CFN / FEI
Establishments Name
Profile Code
Last Milestone Name
Last Milestone Date
Last Compliance Status
Last Compliance Date
OAI Alert
(b) (4)
TRIS PHARMA INC
LIQ
OC RECOMMENDATION
14-MAY-2010
AC
14-MAY-2010
(b) (4)
Overall Compliance:
Date
Recommendation
Re-evaluation Date
14-MAY-2010
ACCEPTABLE
OAI Alert Comments
Save
Close
Forms Services
Reference ID: 2936061
start
Inbox - ...
2 Micr...
4 Inter...
91135_ ...
11:16 AM

Orange Book Report:

-

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

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.**

View a list of all patent use codes
View a list of all exclusivity codes

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - **Monthly**

Reference ID: 2936061

Generic Drug Product Information & Patent Information - **Daily**
Orange Book Data Updated Through March, 2011
Patent and Generic Drug Product Data Last Updated: April 19, 2011

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-
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/s/

SARAH K NGUYEN
04/20/2011

BIOEQUIVALENCE AMENDMENT

ANDA 091135

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Tris Pharma, Inc. TEL: 732-940-0358

ATTN: W. Scott Groner FAX: 732-940-0374

FROM: Teresa Ramson FDA CONTACT PHONE: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on January 9, 2009, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Dextromethorphan Polistirex Extended Release Oral Suspension, EQ. 30 mg dextromethorphan hydrobromide per 5 mL.

Reference is also made to your amendments dated September 25, 2009 and on October 9, 2009.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **2** pages. 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 will be:

Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, Maryland 20855

After the effective date, 01-Aug-2010, ANDAs will only be accepted at the new mailing address listed above. DO NOT submit your ANDA Regulatory documents to this address prior to 01-Aug-2010. 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: 091135

APPLICANT: Tris Pharma, Inc.

DRUG PRODUCT: Dextromethorphan Polistirex Extended Release Oral Suspension, EQ. 30 mg Dextromethorphan Hydrobromide per 5 mL

The Division of Bioequivalence (DBE) has completed its review of your submission acknowledged on the cover sheet. The following deficiencies have been identified:

1. Please acknowledge for future submissions that a more appropriate standard curve (SC) and quality control (QC) concentration range should be validated, which fully encompasses the expected plasma concentration ranges for all subjects. Specifically, the Agency recommends you avoid situations in which many subject samples have to be re-assayed due to initial measurements determined as being 'above the limit of quantitation (ALOQ)', which was the case for the fasting study # S08-0445.

2. It was not fully clear whether the fed study # S08-0446 was carried out using a dose of 60 mg (like the fasted study), or a dose of 30 mg as recommended in the draft individual bioequivalence recommendation guidance for the drug product. In the fed study report (page 2 of 547) it lists the dose as 30 mg; however, in the *in vivo* BE summary table, it lists 60 mg as the dose administered. Please clarify which dose was used for the fed bioequivalence (BE) study.

3. With regard to the repeat analyses, please submit the following additional information:

a. Please submit all appropriate raw data (for fasting and fed BE studies) supporting repeat analysis of samples for high/low internal standard responses (HIS/LIS). These repeats should meet the objective criterion established in the SOP (b) (4), page 8 of 19, which says that results are flagged for repeat when there is a deviation by more than 40% of the mean IS for the entire batch run.

b. Please submit the analytical procedure document defining the reason for the "sample processing error" for subject #41, hour 5.5 sample, per SOP (b) (4): Sample Reanalysis and Reporting Criteria.

We acknowledge you will conduct dissolution testing for your test product as follows:

The dissolution testing should be conducted in 500 mL of 0.1 N HCl at 37°C + 0.5°C, with addition of 400 mL of Phosphate Buffer, at 37°C + 0.5°C, 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: (b) (4) %
12 hrs: NLT (b) (4) %.

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
02/16/2011

Please send an email to the labeling reviewer (Jeanne.skanchy@fda.hhs.gov) to confirm that you received the labeling comments*

Labeling Comments

ANDA 091135

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773 (240-276-8997)

TO: Tris Pharma, Inc.

TEL: 732-940-0358

ATTN: W. Scott Groner

FAX: 732-940-0374

FROM: Jeanne Skanchy

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Dextromethorphan Polistirex Extended-release Oral Suspension, 30 mg per 5 mL.

Pages (including cover and signature page): 3

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents has become:*

Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, Maryland 20855

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/

REVIEW OF PROFESSIONAL LABELING #2
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 091135

Date of Submission: August 26, 2010

Applicant's Name: Tris Pharma, Inc.

Established Name: Dextromethorphan Polistirex Extended-release Oral Suspension, 30 mg per 5 mL

Propriety Name: None

Labeling Deficiencies:

A. CONTAINER & CARTON LABELS:

Please revise established name to read, “DEXTROMETHORPHAN POLISTIREX EXTENDED-RELEASE ORAL SUSPENSION”.

B. DOSAGE CUP:

Please provide the final printed labeling (FPL) for the dosage cup.

Please submit labels and labeling in electronic format.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. 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.

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with the last approved labeling of the Reference Listed Drug with all differences annotated and explained.

{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/

JOHN F GRACE
09/20/2010
for Wm Peter Rickman

QUALITY DEFICIENCY - MINOR

ANDA 091135

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: Tris Pharma, Inc. TEL: (732) 940-0358

ATTN: W. Scott Groner FAX: (732) 940-0374

FROM: Sarah Nguyen FDA CONTACT PHONE: (240) 276-8467

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated January 9, 2009, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Dextromethorphan Polistirex Extended-release Oral Suspension, eq. to dextromethorphan hydrobromide 30 mg/5 mL.

Reference is also made to your amendment dated February 18, 2010.

The Division of Chemistry has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **3** pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Your amendment should respond to all of the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Your cover letter should clearly indicate that the response is a ***QUALITY MINOR AMENDMENT / RESPONSE TO INFORMATION REQUEST*** and should appear prominently in your cover letter.

We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:*

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

All ANDA documents 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/

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA#: 091135
APPLICANT: Tris Pharma, Inc.
DRUG PRODUCT: Dextromethorphan Polistirex Extended-release Oral Suspension, 30 mg/5 mL (eq. to 30 mg Dextromethorphan Hydrobromide per 5 mL)

The deficiencies presented below represent MINOR deficiencies.

1. (b) (4)
2.
3.
4.
5.
6.
7.
8.

Sincerely yours,

(See appended electronic signature page)

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91135	ORIG-1	TRIS PHARMA INC	DEXTROMETHORPHAN POLISTIREX

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

/s/

SHING HOU H LIU
09/14/2010
For Vilayat A. Sayeed, Ph.D.

Please send an email to the labeling reviewer (Jeanne.skanchy@fda.hhs.gov) to confirm that you received the labeling comments*

Labeling Comments

ANDA 091135

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773 (240-276-8997)

TO: Tris Pharma, Inc.

TEL: 732-940-0358

ATTN: W. Scott Groner

FAX: 732-940-0374

FROM: Jeanne Skanchy

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Dextromethorphan Polistirex Extended-release Oral Suspension, 30 mg per 5 mL.

Pages (including cover and signature page): 3

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents has become:*

Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, Maryland 20855

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/

REVIEW OF PROFESSIONAL LABELING #1
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 091135

Date of Submissions: January 9, 2009 and October 29, 2009

Applicant's Name: Tris Pharma, Inc.

Established Name: Dextromethorphan Polistirex Extended-release Oral Suspension, 30 mg per 5 mL

Propriety Name: None

Labeling Deficiencies:

A. CARTON LABELS:

1. We note that the (b) (4) Please revise so that the strength and the established name are prominent in the principal display panel.

2. In the "*Directions*" section, please add "Do not use dosing cup with other products."

3. In the "*DOSING*" section, please add "Measure only with dosing cup provided. Do not use dosing cup with other products." after "SHAKE WELL BEFORE USE."

B. CONTAINER LABELS:

In the "WARNINGS" section, please revise to read "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."

Please note that RLD's labeling is attached since labeling is not available at Drugs@FDA website.

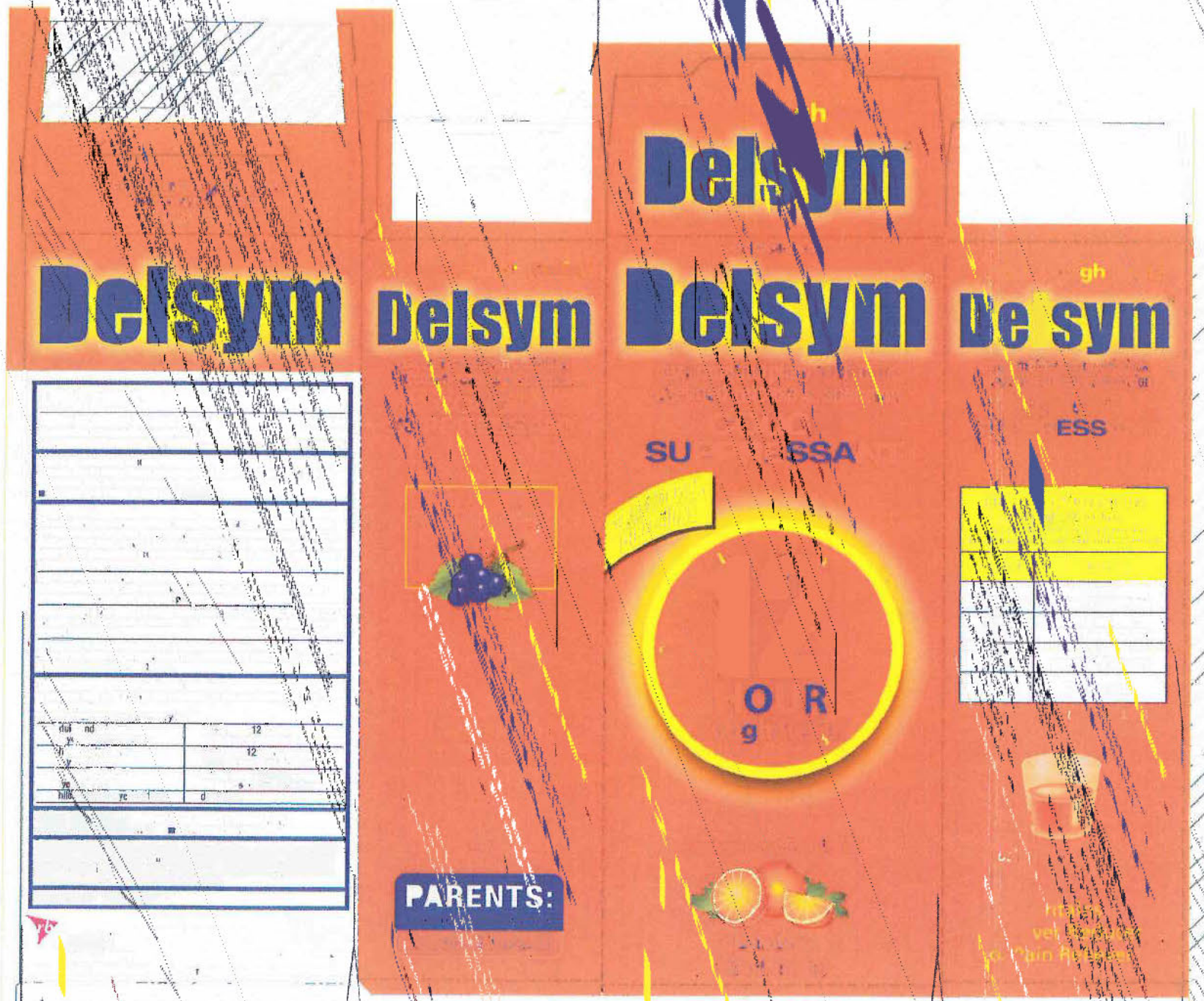
Please submit labels and labeling in electronic format.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. 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.

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with the last approved labeling of the Reference Listed Drug with all differences annotated and explained.

{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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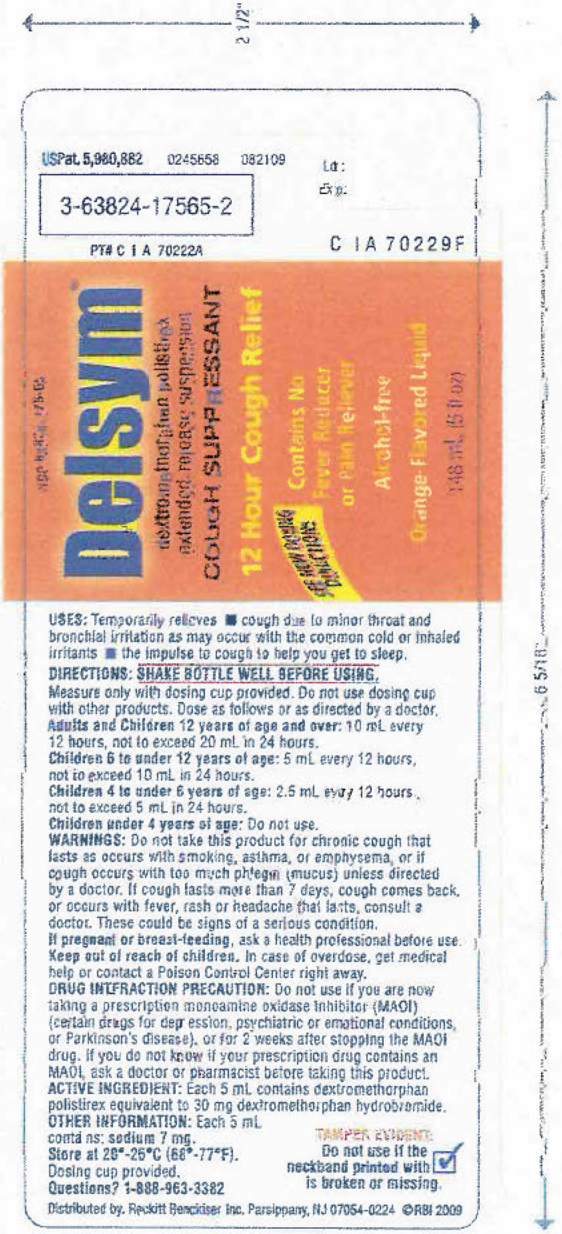
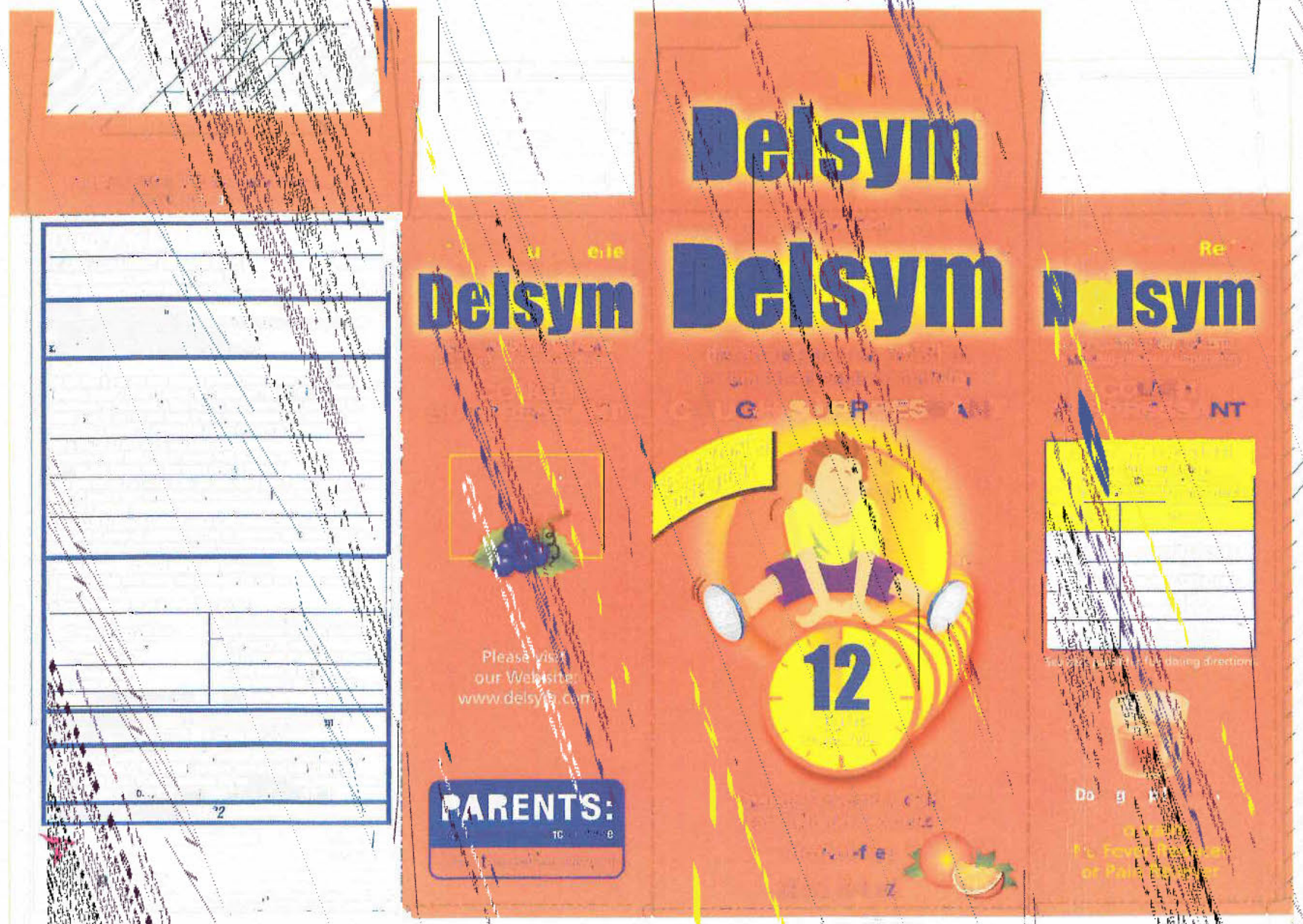
PARENTS:

(b) (4)


2 1/2"
6 5/16"
USPat. 5,980,882 0245658 082109
Lot:
Exp:
3-63824-17565-2
PT# C I A 70222A
C I A 70229F
Delsym
dextromethorphan polistirex
extended-release suspension
COUGH SUPPRESSANT
12 Hour Cough Relief
Contains No Fever Reducer or Pain Reliever
Alcohol-free
Orange-Flavored Liquid
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).
Dosing cup provided.
Questions? 1-888-963-3382
TAMPER EVIDENT:
Do not use if the neckband printed with is broken or missing.
Distributed by: Reckitt Benckiser Inc. Parsippany, NJ 07054-0224 ©RBI 2009

(b) (4)



(b) (4)

2 1/8"

US Pat. 5,980,882 0245654 082109 Lot:

Exp.:

3-63824-27663-2

PT# C I A 70221A

C I A 70226E

Delsym®

COUGH SUPPRESSANT

12 Hour Cough Relief

Contains No Fever Reducer or Pain Reliever

Alcohol free

Orange Flavored Liquid

89 mL (3 fl oz)

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).
Dosing cup provided.
Questions? 1-888-963-3382

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

Distributed by: Reckitt Benckiser Inc. Parsippany, NJ 07054-0224 ©RBI 2009

5 5/8"

(b) (4)

[redacted]


De sym
Boxing Cup
Included
Delsym
Delsym
12
Contains
No Fever Reducer
or Pain Reliever
PARENTS:
Learn about teen medicine abuse
(b) (4)

Cover

PHYSICIAN SAMPLE – NOT TO BE SOLD

Delsym®

dextromethorphan polistirex
Extended-Release Oral Suspension

COUGH SUPPRESSANT

15 mL (1/2 fl oz)

DOSING CUP INCLUDED

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

Active Ingredient (in each 5 mL) Dextromethorphan polistirex equivalent to 30 mg dextromethorphan hydrobromide

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 urge 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 ▶

Lift Here

Back of Cover

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. Use 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. ▶

Base

PHYSICIAN SAMPLE – NOT TO BE SOLD

Delsym®

dextromethorphan polistirex
Extended-Release Oral Suspension

COUGH SUPPRESSANT

15 mL (1/2 fl oz)

Other Information: Each 5 mL contains: sodium 7 mg. Store at 20°-25°C (68°-77°F). Dosing cup provided.

Inactive Ingredients: citric acid, edetate disodium, ethylcellulose, FD&C Yellow No. 6, flavor, high fructose corn syrup, methylparaben, polyethylene glycol 3350, polysorbate 80, propylene glycol, propylparaben, purified water, sucrose, tragacanth, vegetable oil, xanthan gum

Questions? 1-800-9053382

US Pat. 5,980,862

Distributed by:
Reckitt Benckiser Inc.
Parsippany, NJ 07054-0224
©RBI 2009 0245649

080909 PT# C I A 60057

C I A 702800

Lot:

Exp.:

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91135	ORIG-1	TRIS PHARMA INC	DEXTROMETHORPHAN POLISTIREX

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

/s/

JOHN F GRACE
08/17/2010
for Wm Peter Rickman

QUALITY DEFICIENCY - MINOR

ANDA 091135

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Tris Pharma, Inc. TEL: (732) 940-0358

ATTN: W. Scott Groner FAX: (732) 940-0374

FROM: Sarah Nguyen FDA CONTACT PHONE: (240)-276-8467

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated January 9, 2009, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Dextromethorphan Polistirex Extended Release Oral Suspension, 30 mg/5 mL.

Reference is also made to your amendment dated May 6, May 18, June 12, and July 23, 2009.

The Division of Chemistry has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **__4__** pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Your amendment should respond to all of the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Your cover letter should clearly indicate that the response is a ***QUALITY MINOR AMENDMENT / RESPONSE TO INFORMATION REQUEST*** and should appear prominently in your cover letter.

We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format.
This will improve document availability to review staff.

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA#: 091135
APPLICANT: Tris Pharma, Inc.
DRUG PRODUCT: Dextromethorphan Polistirex Extended Release Oral Suspension, 30 mg/5 mL (eq. to 30 mg Dextromethorphan Hydrobromide per 5 mL)

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. (b) (4)

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(b) (4)

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B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please update your room temperature stability data and provide all available data in your next amendment.

2. The review of the labeling and bioequivalence portions of your application are pending. After the reviews are complete, any deficiencies found will be communicated to you under separate covers.

3. The firms referenced in the application relative to the manufacture and testing of the product must be in compliance with cGMPs at the time of approval.

4. Please be advised that the use of in-house or modified compendial analytical methods for testing the drug substance does not relieve you from meeting the compendial standards. In the event of a dispute, the official USP methods will prevail.

Sincerely yours,

(See appended electronic signature page)

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91135	ORIG-1	TRIS PHARMA INC	DEXTROMETHORPHAN POLISTIREX

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/s/

SHING HOU H LIU
01/12/2010
For Vilayat A. Sayeed, Ph.D.

From: Shimer, Martin
To: "Weiss, Charles";
cc: Shimer, Martin;
Subject: RE: ANDA 91-135: request for permission to use (b) (4) for service of notice letter
Date: Thursday, May 14, 2009 3:05:57 PM

Mr. Weiss,

It is permissible to use (b) (4) in lieu of the US Postal service for the purpose of providing notice to the NDA holder and any patent assignees associated with PIV certifications contained within ANDA 91-135.

Regards,

Martin Shimer

From: Weiss, Charles [mailto:CWeiss@kenyon.com]
Sent: Thursday, May 14, 2009 2:41 PM
To: Shimer, Martin
Subject: ANDA 91-135: request for permission to use (b) (4) for service of notice letter

Dear Mr. Shimer:

I am outside counsel to Tris Pharma, Inc., which has received an accepted for filing letter for its ANDA 91-135 (Dextromethorphan Polistirex Extended Release Suspension). By this e-mail, I request permission to send the notice letter and detailed statement by (b) (4) overnight courier to the NDA holder and patent owner, instead of sending them by Certified or Registered Mail.

If this is acceptable, please let me know by return e-mail.

Thank you in advance for your time and consideration.

Very truly yours,
Charles A. Weiss
for Tris Pharma, Inc.

Charles A. Weiss
Kenyon & Kenyon LLP
One Broadway | New York, NY 10004-1007

212.908.6287 Phone | 212.425.5288 Fax
cweiss@kenyon.com | www.kenyon.com

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91135	ORIG-1	TRIS PHARMA INC	DEXTROMETHORPHAN POLISTIREX

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
12/31/2009

BIOEQUIVALENCE AMENDMENT

ANDA 91-135

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Tris Pharma, Inc. TEL: (732) 940-0358

ATTN: W. Scott Groner FAX: (732) 940-0374

FROM: Teresa Vu FDA CONTACT PHONE: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on August 14, 2009, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Dextromethorphan 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 __1__ page. 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 **Bioequivalence Dissolution Acknowledgement**

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:

Please submit your response in electronic format. This will improve document availability to review staff.

BIOEQUIVALENCE DEFICIENCY

ANDA: 91-135

APPLICANT: Tris Pharma Inc.

DRUG PRODUCT: Dextromethorphan Polistirex Extended Release Oral 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:

Based on the dissolution testing data you submitted, we agree that your proposed dissolution method is appropriate for your test product. We also agree with your proposed dissolution method and specifications for the sampling times of 1 and 6 hours. However, the specifications for the sampling time points at 3 hours and 12 hours are not acceptable. Based on the data submitted, we recommend more appropriate specifications. Please provide acknowledgement for your acceptance of the following FDA-recommended specifications for your proposed dissolution method:

Apparatus:	USP II (Paddle)
Speed of Rotation:	50 rpm
Medium:	0.1 N HCl with addition of 400 mL of Phosphate Buffer after 1 hr.
Volume:	500 mL
Temperature:	37 °C ± 0.5 °C
Specifications:	1 hr: NMT (b) (4) %
	3 hrs: (b) (4) %
	6 hrs: (b) (4) %
	12 hrs: NLT (b) (4) %.

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91135	ORIG-1	TRIS PHARMA INC	DEXTROMETHORPHAN POLISTIREX
ANDA-91135	ORIG-1	TRIS PHARMA INC	DEXTROMETHORPHAN POLISTIREX

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
09/23/2009

BIOEQUIVALENCE AMENDMENT

ANDA 91-135

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Tris Pharma, Inc. TEL: (732) 940-0358

ATTN: W. Scott Groner FAX: (732) 940-0374

FROM: Steven Mazzella FDA CONTACT PHONE: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on January 9, 2009, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Dextromethorphan Extended Release Oral 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 **1** page. 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**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalence Amendment" and 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 both an archival (blue) and 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:

Please submit your response in electronic format.
This will improve document availability to review staff.

ANDA: 91-135

APPLICANT: Tris Pharma Inc.

DRUG PRODUCT: Dextromethorphan Polistirex Extended Release Oral 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:

Your dissolution testing using your proposed method is incomplete. Please provide the final pH of your dissolution medium after 400 mL of phosphate buffer was added. In addition, please conduct and submit dissolution testing on the test and reference products (12 dosage units each) using the following FDA-recommended method:

Apparatus:	USP II (Paddle)
Speed of Rotation:	50 rpm
Medium:	0.1 N HCl
Volume:	500 mL
Temperature:	37 °C ± 0.5 °C

The recommended sampling times are 30, 60, 90, and 180 minutes or until at least 80% of the labeled amount of the drug is dissolved. Your proposed method will be evaluated in comparison with the FDA-recommended method when the dissolution data from both methods are available.

Please also conduct and submit dissolution testing data using USP Apparatus II (Paddles) at 50 rpm in at least three additional dissolution media (pH 4.5 and 6.8 buffers and water). The following sampling times are recommended: 1, 2, and 4 hours and every 2 hours thereafter, 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 standard deviation 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 Conner

7/20/2009 05:24:37 PM

Shimer, Martin

From: Shimer, Martin
Sent: Thursday, May 14, 2009 3:06 PM
To: 'Weiss, Charles'
Cc: Shimer, Martin
Subject: RE: ANDA 91-135: request for permission to use (b) (4) for service of notice letter

Mr. Weiss,

It is permissible to use (b) (4) in lieu of the US Postal service for the purpose of providing notice to the NDA holder and any patent assignees associated with PIV certifications contained within ANDA 91-135.

Regards,

Martin Shimer

From: Weiss, Charles [mailto:CWeiss@kenyon.com]
Sent: Thursday, May 14, 2009 2:41 PM
To: Shimer, Martin
Subject: ANDA 91-135: request for permission to use (b) (4) for service of notice letter

Dear Mr. Shimer:

I am outside counsel to Tris Pharma, Inc., which has received an accepted for filing letter for its ANDA 91-135 (Dextromethorphan Polistirex Extended Release Suspension). By this e-mail, I request permission to send the notice letter and detailed statement by (b) (4) overnight courier to the NDA holder and patent owner, instead of sending them by Certified or Registered Mail.

If this is acceptable, please let me know by return e-mail.

Thank you in advance for your time and consideration.

Very truly yours,
Charles A. Weiss
for Tris Pharma, Inc.

Charles A. Weiss
Kenyon & Kenyon LLP
One Broadway | New York, NY 10004-1007
212.908.6287 Phone | 212.425.5288 Fax
cweiss@kenyon.com | www kenyon.com

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

/s/

Martin Shimer
6/26/2009 10:07:49 AM
CSO

ANDA CHECKLIST FOR CTD or eCTD FORMAT
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION FOR FILING

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/ *****

ANDA #: 91-135 **FIRM NAME**: TRIS PHARMA

PIV: YES **Electronic or Paper Submission:** ELECTRONIC (ECTD FORMAT)

RELATED APPLICATION(S): NA

First Generic Product Received? YES

DRUG NAME: DEXTROMETHORPHAN POLISTIREX (ORANGE FLAVORED)

DOSAGE FORM: EXTENDED-RELEASE ORAL SUSPENSION, 30 MG/PER 5 ML(HYDROBROMIDE)

Bio Assignments:		
☒ **BPH**	☐ **BCE**	☐ **Micro Review (No)**
☐ **BST**	☐ **BDI**	

Random Queue: 4

Chem Team Leader: Liu, Shing Hou Chem PM: Leign Ann Matheny Labeling Reviewer: Postelle Birch
Bio PM: Steven Mazzella

Letter Date: JANUARY 9, 2009 **Received Date**: JANUARY 12, 2009

Comments: EC - 1 YES **On Cards:** YES
Therapeutic Code: 6010400 ANTITUSSIVE

Archival copy: ELECTRONIC (ECTD FORMAT) **Sections** I
Review copy: NA E-Media Disposition: YES SEND TO EDR
Not applicable to electronic sections

PART 3 Combination Product Category N Not a Part3 Combo Product
(Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm

Reviewing CSO/CST Peter Chen	**Recommendation:**
Date 5/6/2009	☒ **FILE** ☐ **REFUSE to RECEIVE**
Supervisory Concurrence/Date: _____	**Date:** _____

ADDITIONAL COMMENTS REGARDING THE ANDA:

(b) (4)

From DBE first generic review:
The Division of Bioequivalence has requested the Test Article Inventory. Please submit this information.
Adequate for filing per 5/6/2009 correspondence; sponsor stated the inventory report was provided in Module 5.3.1.2. Review issue.

Notes:
1. Bio First Generic Review adequate dated 4/28/2009
2. Consult submitted for inactives Sodium polystyrene sulfonate and (b) (4)
3. Dissolution, Clinical and Analytical sites entered into database.

MODULE 1
ADMINISTRATIVE

		ACCEPTABLE
1.1	**1.1.2 Signed and Completed Application Form (356h) (original signature)** (Check Rx/OTC Status) OTC YES *1. Please revise your application form 356h and "Basis of Submission" section 1.12.11 to reflect the holder of the ANDA as reflected in the electronic "Orange Book"* *Adequate for filing per 5/6/2009 correspondence*	☒
1.2	**Cover Letter** Dated: JANUARY 9, 2009	☒
1.2.1	**Form FDA 3674 (PDF) YES 9.b.**	☒
*	**Table of Contents (paper submission only)** YES	☒
1.3.2	**Field Copy Certification (original signature)** NA **(N/A for E-Submissions)**	☒
1.3.3	**Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other:** 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 3454 Disclosure Statement (Form FDA 3455, submit copy to Regulatory Branch Chief) NA	☒
1.3.5	**1.3.5.1 Patent Information** Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations **1.3.5.2 Patent Certification** 1. Patent number(s) 5980882 Apr 16, 2017 PIV 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? b. Expiration of Pediatric Exclusivity? 4. Exclusivity Statement: YES	☒
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 submitted DMF (b) (4) b. Type III DMF authorization letter(s) for container closure submitted 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h])	☐

1.12.11	**Basis for Submission** NDA# : 18-658 Ref Listed Drug: DELSYM Firm: RECKITT BENCKISER ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route or active ingredient) see section 1.9.1 *1. Please revise your application form 356h and "Basis of Submission" section 1.12.11 to reflect the holder of the ANDA as reflected in the electronic "Orange Book"* *Adequate for filing per 5/6/2009 correspondence*	☒

MODULE 1 (Continued)
ADMINISTRATIVE

ACCEPTABLE

1.12.12	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use Same as RLD 2. Active ingredients Same as RLD 3. Inactive ingredients submitted 4. Route of administration Same as RLD 5. Dosage Form Same as RLD 6. Strength Same as RLD	☒
1.12.14	**Environmental Impact Analysis Statement** YES	☒
1.12.15	**Request for Waiver** Request for Waiver of In-Vivo BA/BE Study(ies): NA	☒
1.14.1	**Draft Labeling** **(Mult Copies N/A for E-Submissions)** **1.14.1.1** 4 copies of draft (each strength and container) submitted **1.14.1.2** 1 side by side labeling comparison of containers and carton with all differences annotated and explained submitted **1.14.1.3** 1 package insert (content of labeling) submitted electronically OTC ***Was a proprietary name request submitted? no (If yes, send email to Labeling Reviewer indicating such.)	☒
1.14.3	**Listed Drug Labeling** **1.14.3.1** 1 side by side labeling (package and patient insert) comparison with all differences annotated and explained submitted **1.14.3.3** 1 RLD label and 1 RLD container label submitted	☒

MODULE 2
SUMMARIES ACCEPTABLE

2.3	**Quality Overall Summary (QOS)** **E-Submission: PDF** submitted **Word Processed e.g., MS Word** submitted 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)** **2.3.S** **Drug Substance (Active Pharmaceutical Ingredient)** **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** **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 Bioequivalence Data Summary Tables** **E-Submission: PDF** **Word Processed e.g., MS Word** **2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods** **2.7.1.1 Background and Overview** Table 1. Submission Summary Table 4. Bioanalytical Method Validation Table 6. Formulation Data **2.7.1.2 Summary of Results of Individual Studies** Table 5. Summary of In Vitro Dissolution **2.7.1.3 Comparison and Analyses of Results Across Studies** Table 2. Summary of Bioavailability (BA) Studies Table 3. Statistical Summary of the Comparative BA Data **2.7.1.4 Appendix** **2.7.4.1.3 Demographic and Other Characteristics of Study Population** Table 7. Demographic Profile of Subjects Completing the Bioequivalence Study **2.7.4.2.1.1 Common Adverse Events** Table 8. Incidence of Adverse Events in Individual Studies	☐

MODULE 3

3.2.S DRUG SUBSTANCE ACCEPTABLE

3.2.S.1	**General Information** **3.2.S.1.1 Nomenclature** **3.2.S.1.2 Structure** **3.2.S.1.3 General Properties**	☒
3.2.S.2	**Manufacturer** **3.2.S.2.1** **Manufacturer(s) (This section includes contract manufacturers and testing labs)** **Drug Substance (Active Pharmaceutical Ingredient)** 1. Name and Full Address(es)of the Facility(ies) submitted 2. Function or Responsibility Same as RLD 3. Type II DMF number for API Same as RLD 4. CFN or FEI numbers Same as RLD	☒
3.2.S.3	**Characterization**	☒
3.2.S.4	**Control of Drug Substance (Active Pharmaceutical Ingredient)** **3.2.S.4.1 Specification** Testing specifications and data from drug substance manufacturer(s) submitted **3.2.S.4.2 Analytical Procedures** submitted **3.2.S.4.3 Validation of Analytical Procedures** 1. Spectra and chromatograms for reference standards and test samples submitted 2. Samples-Statement of Availability and Identification of: a. Drug Substance submitted b. Same lot number(s) yes **3.2.S.4.4 Batch Analysis** 1. COA(s) specifications and test results from drug substance mfgr(s) submitted (b) (4) 2. Applicant certificate of analysis submitted (b) (4) **3.2.S.4.5 Justification of Specification**	☒
3.2.S.5	**Reference Standards or Materials submitted**	☒
3.2.S.6	**Container Closure Systems Reference to DMF**	☒
3.2.S.7	**Stability Reference to DMF**	☒

MODULE 3

3.2.P DRUG PRODUCT ACCEPTABLE

3.2.P.1	**Description and Composition of the Drug Product** 1. Unit composition (b) (4) [redacted] 2. Inactive ingredients and amounts are appropriate per IIG yes -Pharm/tox report submitted for sodium polystyrene sulfonate -Pharm/tox report submitted for (b) (4) [redacted]	☒
3.2.P.2	**Pharmaceutical Development** Pharmaceutical Development Report submitted	☒
3.2.P.3	**Manufacture** **3.2.P.3.1 Manufacture(s)** (Finished Dosage Manufacturer and Outside Contract Testing Laboratories) 1. Name and Full Address(es)of the Facility(ies) submitted 2. CGMP Certification: YES 3. Function or Responsibility submitted 4. CFN or FEI numbers **3.2.P.3.2 Batch Formula submitted** **Test Batch** **Production Batch** (b) (4) [redacted] **3.2.P.3.3 Description of Manufacturing Process and Process Controls** 1. Description of the Manufacturing Process submitted 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified submitted 3. If sterile product: Aseptic fill / Terminal sterilization na 4. Reprocessing Statement submitted **3.2.P.3.4 Controls of Critical Steps and Intermediates submitted** **3.2.P.3.5 Process Validation and/or Evaluation** 1. Microbiological sterilization validation na 2. Filter validation (if aseptic fill) na	☒

3.2.P.4	**Controls of Excipients (Inactive Ingredients)** Source of inactive ingredients identified submitted section 3.2.R. **3.2.P.4.1 Specifications** 1. Testing specifications (including identification and characterization) submitted 2. Suppliers' COA (specifications and test results) submitted **3.2.P.4.2 Analytical Procedures submitted** **3.2.P.4.3 Validation of Analytical Procedures submitted** **3.2.P.4.4 Justification of Specifications** Applicant COA submitted (b) (4)	☒

MODULE 3

3.2.P DRUG PRODUCT

ACCEPTABLE

3.2.P.5	**Controls of Drug Product** **3.2.P.5.1 Specification(s)** submitted **3.2.P.5.2 Analytical Procedures** submitted **3.2.P.5.3 Validation of Analytical Procedures** Samples - Statement of Availability and Identification of: 1. Finished Dosage Form submitted section 3.2.S.4.3 2. Same lot numbers TB-023 **3.2.P.5.4 Batch Analysis** Certificate of Analysis for Finished Dosage Form submitted Batch # TB-023A **3.2.P.5.5 Characterization of Impurities submitted** **3.2.P.5.6 Justification of Specifications submitted**	☒
3.2.P.7	**Container Closure System** 1. Summary of Container/Closure System (if new resin, provide data) submitted 2. Components Specification and Test Data submitted 3. Packaging Configuration and Sizes submitted 4. Container/Closure Testing submitted 5. Source of supply and suppliers address submitted section 3.2.R.	☒
3.2.P.8	**3.2.P.8.1 Stability (Finished Dosage Form)** 1. Stability Protocol submitted submitted 2. Expiration Dating Period 24 months **3.2.P.8.2 Post-approval Stability and Conclusion** Post Approval Stability Protocol and Commitments submitted **3.2.P.8.3 Stability Data** 1. 3 month accelerated stability data submitted 2. Batch numbers on stability records the same as the test batch **YES**	☒

MODULE 3

3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Substance)	**3.2.R.1.S Executed Batch Records for drug substance (if available)** **3.2.R.2.S Comparability Protocols** **3.2.R.3.S Methods Validation Package NO** Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☐

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 Theoretical Yield (b) (4) Actual Yield (b) (4) Packaged Yield (b) (4) **3.2.R.1.P.2 Information on Components** **3.2.R.2.P Comparability Protocols** **3.2.R.3.P Methods Validation Package** NO Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

MODULE 5

CLINICAL STUDY REPORTS

ACCEPTABLE

5.2	**Tabular Listing of Clinical Studies**	☐
5.3.1 (complete study data)	**Bioavailability/Bioequivalence** **1. Formulation data same?** a. Comparison of all Strengths (check proportionality of multiple strengths) b. Parenterals, Ophthalmics, Otics and Topicals per 21 CFR 314.94 (a)(9)(iii)-(v) **2. Lot Numbers of Products used in BE Study(ies):** **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) 2. Summary Bioequivalence tables: Table 10. Study Information Table 12. Dropout Information Table 13. Protocol Deviations **5.3.1.3** **In Vitro-In-Vivo Correlation Study Reports** 1. Summary Bioequivalence tables: Table 11. Product Information Table 16. Composition of Meal Used in Fed Bioequivalence Study **5.3.1.4** **Reports of Bioanalytical and Analytical Methods for Human Studies** 1. Summary Bioequivalence table: Table 9. Reanalysis of Study Samples Table 14. Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses Table 15. SOPs Dealing with Bioanalytical Repeats of Study Samples **5.3.7** **Case Report Forms and Individual Patient Listing**	☐
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) 2. EDR Email: Data Files Submitted: YES SENT TO EDR 3. In-Vitro Dissolution: YES	☒
Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO 1. Properly defined BE endpoints (eval. by Clinical Team) 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). 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted	☐
Study Type	**IN-VITRO BE STUDY(IES)** (i.e., in vitro binding assays) NO 1. Study(ies) meets BE criteria (90% CI of 80-125) 2. EDR Email: Data Files Submitted: 3. In-Vitro Dissolution:	☐

Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** 1. Solutions (Q1/Q2 sameness): a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming) 2. Suspensions (Q1/Q2 sameness): a. In-Vivo PK Study 1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted b. In-Vivo BE Study with Clinical End Points 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria (90% CI within +/- 20% of 80-125) 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted c. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming)	☐
Study Type	**IN-VIVO BE STUDY(IES) with PD ENDPOINTS** (e.g., topical corticosteroid vasoconstrictor studies) 1. Pilot Study (determination of ED50) 2. Pivotal Study (study meets BE criteria 90%CI of 80-125)	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** 1. In-Vivo PK Study 1. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted 2. Adhesion Study 3. Skin Irritation/Sensitization Study	☐

Updated 8/11/2008

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:	018658
Product Number:	001
Approval Date:	Oct 8, 1982
Reference Listed Drug	Yes
RX/OTC/DISCN:	OTC
Patent and Exclusivity Info for this product:	View

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - **Monthly**
Generic Drug Product Information & Patent Information - **Daily**
Orange Book Data Updated Through February, 2009
Patent and Generic Drug Product Data Last Updated: April 08, 2009

Patent and Exclusivity Search Results from query on Appl No 018658 Product 001 in the OB_OTC list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
018658	001	5980882	Apr 16, 2017		Y		

Exclusivity Data

There is no unexpired exclusivity for this product.

Contains Nonbinding Recommendations

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:

---

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

2.7.1.3 Comparison and Analyses of Results Across Studies (continue)

Statistical Summary of the Comparative Bioavailability Data - Dextromethorphan

Dextromethorphan Polistirex 30 mg / 5 mL (1 x 30 mg / 5 mL) Geometric Means[1], Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data				
Fasted Bioequivalence Study (S08-0445) N=53[2]				
Parameter	**Test**	**Reference**	**% Ratio**	**90% C.I.**
AUC_{0-t}	61350.92	59169.10	103.69	(97.77, 109.96)
AUC_{0-inf}	45007.64	42798.30	105.16	(98.82, 111.91)
C_{max}	3685.37	3714.87	99.21	(93.42, 105.35)
Fed Bioequivalence Study (S08-0446) N=37[2]				
Parameter	**Test**	**Reference**	**% Ratio**	**90% C.I.**
AUC_{0-t}	3804.4 (151.69)	5.50 (2.00 - 12.02)	91031.93 (264.58)	56317.97 (134.41)
AUC_{0-inf}	4219.79 (148.43)	6.00 (4.00 – 12.00)	106974.22 (282.67)	61904.16 (135.32)
C_{max}	3804.4 (151.69)	5.50 (2.00 - 12.02)	91031.93 (264.58)	56317.97 (134.41)

[1]Geometric means are based on least squares means of ln-transformed values
[2]Subjects used in final statistical report

Tris Pharma Inc
Dextromethorphan Polistirex ER Oral Suspension

2.7.1.3 Comparison and Analyses of Results Across Studies (continue)

Statistical Summary of the Comparative Bioavailability Data - Dextrorphan

Dextromethorphan Polistirex 30 mg / 5 mL (1 x 30 mg / 5 mL) Geometric Means[1], Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data				
Fasted Bioequivalence Study (S08-0445) N=53[2]				
Parameter	**Test**	**Reference**	**% Ratio**	**90% C.I.**
AUC_{0-t}	36431.34	35431.87	102.82	(98.15, 107.71)
AUC_{0-inf}	40033.71	38898.86	102.92	(98.24, 107.82)
C_{max}	3008.40	3132.54	96.04	(90.84, 101.54)
Fed Bioequivalence Study (S08-0446) N=37[2]				
Parameter	**Test**	**Reference**	**% Ratio**	**90% C.I.**
AUC_{0-t}	40523.45	44712.97	90.63	(86.27, 95.21)
AUC_{0-inf}	42867.29	47203.98	90.81	(86.52, 95.32)
C_{max}	3596.29	3903.02	92.14	(85.29, 99.55)

[1]Geometric means are based on least squares means of ln-transformed values
[2]Subjects used in final statistical report

BIOEQUIVALENCE CHECKLIST for First Generic ANDA
FOR APPLICATION COMPLETENESS

ANDA# 91-135 **FIRM NAME** Tris Pharma, Inc.

DRUG NAME Dextromethorphan Polistirex Extended Release Oral Suspension, 30 mg/5 m

DOSAGE FORM Oral Suspension

SUBJ: Request for examination of: Bioequivalence study.

Requested by: _____ Date: _____
Chief, Regulatory Support Team, (HFD-615)

	Summary of Findings by Division of Bioequivalence
☒	**Study meets statutory requirements**
☐	**Study does NOT meet statutory requirements**
	Reason:
☐	**Waiver meets statutory requirements**
☐	**Waiver does NOT meet statutory requirements**
	Reason:

RECOMMENDATION: ☒ **COMPLETE** ☐ **INCOMPLETE**

Reviewed by:

_____ Date: _____
Kelly M. Kitchens, Ph.D.
Reviewer

_____ Date: _____
Shriniwas Nerurkar, Ph.D.
Team Leader

********** -COMM. JOURNAL- ********** DATE APR-29-2009 ***** TIME 13:00 *********

MODE = MEMORY TRANSMISSION START=APR-29 12:59 END=APR-29 13:00

FILE NO.-765

STN NO.	COMM.	ABBR NO.	STATION NAME/TEL NO.	PAGES	DURATION
001	OK	8	917329400374	001/001	00:00:38

-FDA CDER OGD LPS -

********** - ***** - **********

FDA FAX

ANDA 91-135

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: Tris Pharma, Inc. TEL: 732-940-0358

ATTN: W. Scott Groner FAX: 732-940-0374

FROM: Peter Chen PC 4/29/09 TEL: (240) 276-8436

Dear Sir:

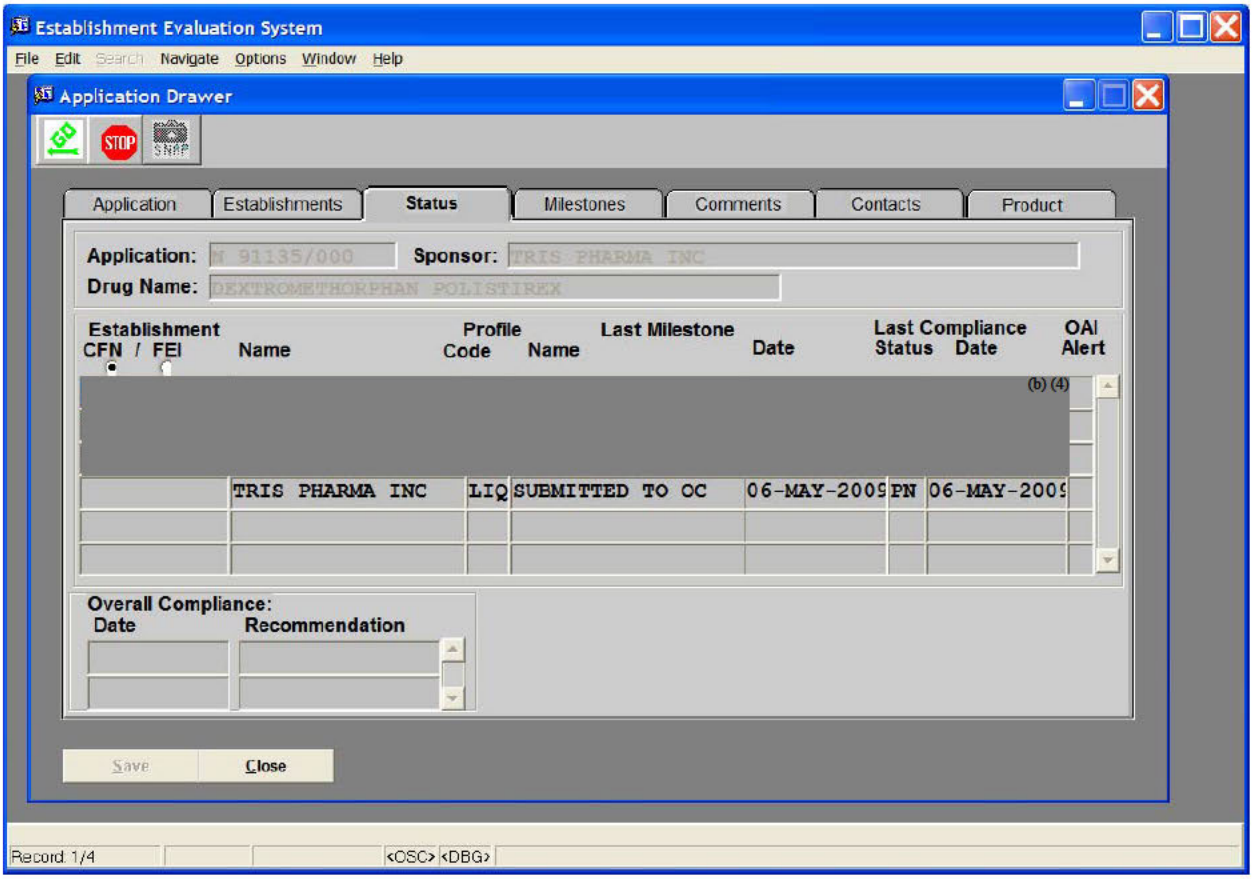
This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Dextromethorphan Polistirex Extended-release Oral Suspension, 30 mg/5 mL.

Total Pages (1)

SPECIAL INSTRUCTIONS: Please respond to the items identified below as a new correspondence to the ANDA within 10 business days. You can fax (240) 276-8440 or email (peter.chen@fda.hhs.gov) the intial response followed by a hardcopy to the ANDA.

(b) (4)

[redacted]


Establishment Evaluation System
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Application Drawer
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Application
Establishments
Status
Milestones
Comments
Contacts
Product
Application: N 91135/000
Sponsor: TRIS PHARMA INC
Drug Name: DEXTROMETHORPHAN POLISTIREX
Establishment CFN / FEI
Name
Profile Code
Name
Last Milestone
Date
Last Compliance Status
Date
OAI Alert
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TRIS PHARMA INC
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DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			**REQUEST FOR CONSULTATION** **Consult No: 2009-0329**	
TO *(Division/Office)* DNCE - HFD-560 Thru: Leah Christl, ONP HFD-560			**FROM:** Peter Chen OGD/DLPS	
DATE: 5/6/2009	**IND NO.**	**ANDA NO.** 091135	**TYPE OF DOCUMENT** Original	**DATE OF DOCUMENT** 1/9/2009,
NAME OF DRUG Dextromethorphan Polistirex Extended-relase Oral Suspension		**PRIORITY CONSIDERATION** 60 days	**CLASSIFICATION OF DRUG** Antitussive	**DESIRED COMPLETION DATE** 7/5/2009
NAME OF FIRM Tris Pharma				

REASON FOR REQUEST

I. GENERAL

- ✆ NEW PROTOCOL
- ✆ PROGRESS REPORT
- ✆ NEW CORRESPONDENCE
- ✆ DRUG ADVERTISING
- ✆ ADVERSE REACTION REPORT
- ✆ MANUFACTURING CHANGE/ADDITION
- ✆ MEETING PLANNED BY _____
- ✆ PRE NDA MEETING
- ✆ END OF PHASE II MEETING
- ✆ RESUBMISSION
- ✆ SAFETY/EFFICACY
- ✆ PAPER NDA
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- ✆ RESPONSE TO DEFICPENCY LETTER
- ✆ FINAL PRINTED LABELING
- ✆ LABELING REVISION
- ✆ ORIGINAL NEW CORRESPONDENCE
- ✆ FORMULATIVE REVIEW
- X *OTHER ('specify below)*

II.BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
✆ TYPE A OR B NDA REVIEW ✆ END QF PHASE II MEETING ✆ CONTROLLED STUDI ES ✆ PROTOCOL REVIEW ✆ OTHER	✆ CHEMISTRY ✆ PHARMACOLOGY ✆ BIOPHARMACEUTICS ✆ OTHER

III.BIOPHARMACEUTICS

- DISSOLUTION
- PROTOCOL-- BIOPHARMACEUTICS
- IN--VIVO WAIVER REQUEST
- DEFICIENCY LETTER RESPONSE
- BIOAVAILABILITY STUDIES
- PHASE IV STUDIES

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- POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

CLINICAL **PRECLINICAL**

COMMENTS

OGD is requesting a pharmacology/toxicology consult for the following 2 inactives: Sodium polystyrene sulfonate and (b) (4). The data for the former is located in EDR under section 4.2.3. The data for the latter is located in DMF (b) (4). Also note the for (b) (4) previous pharm/tox consult was submitted under ANDA (b) (4) and DMF (b) (4).

Please provide your analysis and recommendation if the levels proposed for SPS (b) (4) and (b) (4) is justified for use in this drug product at a maximum daily dose of 20 mL.

Please cc Theresa Liu, HFD-617 (Theresa.Liu@fda.hhs.gov) on the review when it is being checked into DFS. Thank you.

SIGNATURE OF REQUESTER	METHOD OF DE LIVERY *(Check one)* MAIL HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Martin Shimer

5/13/2009 08:41:10 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 91-135

Tris Pharma, Inc.
Attention: W. Scott Groner
2033 Route 130
Monmouth Junction, NJ 08852

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 made to our facsimile dated April 29, 2009 and your correspondence dated May 5, 2009.

NAME OF DRUG: Dextromethorphan Polistirex Extended-release Suspension, 30 mg/5 mL

DATE OF APPLICATION: January 9, 2009

DATE (RECEIVED) ACCEPTABLE FOR FILING: January 12, 2009

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) 276-8419.

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:

Leigh Ann Bradford
Project Manager
(240) 276-8453

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

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/s/

Martin Shimer
5/13/2009 08:40:15 AM
Signing for Wm Peter Rickman

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			**REQUEST FOR CONSULTATION** **Consult No: 2009-0329**	
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NAME OF FIRM Tris Pharma

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Please provide your analysis and recommendation if the levels proposed for SPS (b) (4) and (b) (4) is justified for use in this drug product at a maximum daily dose of 20 mL.

Please cc Theresa Liu, HFD-617 (Theresa.Liu@fda.hhs.gov) on the review when it is being checked into DFS. Thank you.

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

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/s/

Theresa Liu

5/6/2009 03:07:38 PM

BIOEQUIVALENCE CHECKLIST for First Generic ANDA
FOR APPLICATION COMPLETENESS

ANDA# 91-135 **FIRM NAME** Tris Pharma, Inc.

DRUG NAME Dextromethorphan Polistirex Extended Release Oral Suspension, 30 mg/5 mL

DOSAGE FORM Oral Suspension

SUBJ: Request for examination of: Bioequivalence study.

Requested by: _____ Date: _____
Chief, Regulatory Support Team, (HFD-615)

	Summary of Findings by Division of Bioequivalence
☒	**Study meets statutory requirements**
☐	**Study does NOT meet statutory requirements**
	Reason:
☐	**Waiver meets statutory requirements**
☐	**Waiver does NOT meet statutory requirements**
	Reason:

RECOMMENDATION: ☒ **COMPLETE** ☐ **INCOMPLETE**

Reviewed by:

_____ Date: _____
Kelly M. Kitchens, Ph.D.
Reviewer

_____ Date: _____
Shriniwas Nerurkar, Ph.D.
Team Leader

Item Verified:	YES	NO	Required Amount	Amount Sent	Comments
Protocol	☒	☐			Section 16.1.1 of Legacy Study Reports for fasted (S08-0445) and fed (S08-0446) studies in Module 5.3.1.2.1
Assay Methodology	☒	☐			Module 3.2.P.5.2 Analytical Procedures
Procedure SOP	☒	☐			Module 3.2.P.5.2 Analytical Procedures
Methods Validation	☒	☐			Module 3.2.P.5.3 Validation of Analytical Procedures
Study Results Ln/Lin	☒	☐			Module 2.7.1.3 Comparison and Analysis of Results Across Studies
Adverse Events	☒	☐			Section 12.2 of Legacy Study Reports for fasted and fed studies in Module 5.3.1.2.1
IRB Approval	☒	☐			Section 16.1.3 of Legacy Study Reports for fasted and fed studies in Module 5.3.1.2.1
Dissolution Data	☒	☐			Dissolution data (Module 5.3.1.3 In vitro – In vivo Correlation Study Reports) with the FDA method and in 3 other media (pH 1.2, 4.5 and 6.8).
Pre-screening of Patients	☒	☐			Section 9.3.1 of Legacy Study Reports for fasted and fed studies in Module 5.3.1.2.1
Chromatograms	☒	☐			Assay Report/HPLC Chromatograms (Module 3.2.P.5.3 Validation of Analytical Procedures)
Consent Forms	☒	☐			Section 16.1.3 of Legacy Study Reports for fasted and fed studies in Module 5.3.1.2.1
Composition	☒	☐			Module 3.2.P.1 Description and Composition of Drug Product
Summary of Study	☒	☐			Module 2.3 Quality overall Summary; Module 2.7 Clinical Summary
Individual Data & Graphs, Linear & Ln	☒	☐			Module 5.3.1.2 Comparative BA and BE Study Reports
PK/PD Data Disk (Submitted)	☒	☐			Module 5 datasets. SAS files

Randomization Schedule	☒	☐			Section 16.1.7 of Legacy Study Reports for fasted and fed studies in Module 5.3.1.2.1
Protocol Deviations	☒	☐			Section 10.2 of Legacy Study Reports in Module 5.3.1.2.1
Clinical Site	☒	☐			Cetero Research, 400 Fountain Lakes Blvd., St. Charles, MO 63301 (Module 2.7.1.1 Background and Overview)
Analytical Site	☒	☐			(b) (4) (Module 2.7.1.1 Background and Overview)
Study Investigators	☒	☐			Section 16.1.4 of Legacy Study Reports for fasted and fed studies in Module 5.3.1.2.1
Medical Records	☒	☐			Module 5.3.1.4.1 – Fasted study Module 5.3.7 – Fed study
Clinical Raw Data	☒	☐			Section 16.2.7 of Legacy Study Reports for fasted and fed studies in Module 5.3.1.2.1
Test Article Inventory	☐	☒			**Test article inventory not provided by the firm**
BIO Batch Size	☒	☐			Batch Formula (Module 3.2.P.3.2 Components and Composition Statement)
Assay of Active Content Drug	☒	☐			Module 3.2.P.5.2 Analytical Procedures
Content Uniformity	☒	☐			Certificate of Analysis (Module 3.2.P.5.4 Batch Analyses)
Date of Manufacture	☒	☐			September 3, 2008 (Module 5.3.1.3 In-Vitro-In-Vivo Correlation Study Reports)
Exp. Date of RLD	☒	☐			December 2008 (Module 5.3.1.3 In-Vitro-In-Vivo Correlation Study Reports)
BioStudy Lot Numbers	☒	☐			Test lot #: TB-023A RLD lot #: 39469 (Module 5.3.1.3 In-Vitro-In-Vivo Correlation Study Reports)
Statistics	☒	☐			Section 16.1.9 of Legacy Study Reports for fasted and fed studies in Module 5.3.1.2.1

Summary results provided by the firm indicate studies pass BE criteria	☒	☐			Module 2.7.1.3 Comparison and Analysis of Results Across Studies
Waiver requests for other strengths / supporting data	☐	☒			N/A

Additional Comments regarding the ANDA:

1. Tris Pharma, Inc. submitted an electronic application for Dextromethorphan Polistirex Extended Release Oral Suspension, eq. to dextromethorphan hydrobromide 30 mg/5 mL. The reference listed drug (RLD) is DELSYM® Extended Release Suspension (NDA #18-658, approval date October 8, 1982) manufactured by Reckitt Benckiser. DELSYM® temporarily relieves cough due to minor throat and bronchial irritation as may occur with the common cold or inhaled irritants.

2. Based on the **Guidance for Industry: Individual Product Bioequivalence Recommendations**, the recommendations for Dextromethorphan Polistirex (finalized May 2008) are:

Contains Nonbinding Recommendations
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:

---

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.

3. Tris Pharma, Inc. submitted fasting and fed studies for Dextromethorphan Polistirex ER Oral Suspension. Results for plasma concentrations of Dextromethorphan and its metabolite, Dextrorphan, are reported.

4. The 90% C.I. values for fasting and fed bioequivalence studies of Dextromethorphan and Dextrorphan meet the 80%-125% BE criteria.

5. The firm also provided multimedia dissolution testing.

Note to the Reviewer:

- The Module 2.7.1.3 Statistical Summary of the Comparative Bioavailability Data for Dextromethorphan is inaccurately reported for fed BE study results. The Module 5.3.1.2.1 Legacy Study Report accurately reports the AUC and Cmax values for Dextromethorphan in fed BE studies.

Note to the Regulatory Group:

- Please request the Test Article Inventory from the firm.

Productivity:

Completed Assignment for 91135 ID: 8110

Reviewer: Kitchens, Kelly **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description:

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
8110	1/9/2009	Paragraph 4	Paragraph 4 Checklist	1	1
				Bean Total:	1

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/s/

Shriniwas G. Nerurkar

4/28/2009 07:21:38 AM

M E M O R A N D U M

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

DATE : March 9, 2009

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615)

SUBJECT: Examination of the bioequivalence study submitted with an ANDA 91-135 for Dextromethorphan Polistirex Extended-Release Oral Suspension, 30 mg/5 mL to determine if the application is substantially complete for filing and/or granting exclusivity pursuant to 21 USC 355(j)(5)(B)(iv).

Tris Pharma has submitted ANDA 91-135 for Dextromethorphan Polistirex Extended-Release Oral Suspension, 30 mg/5 mL. The ANDA contains a certification pursuant to 21 USC 355(j)(5)(B)(iv) stating that patent(s) for the reference listed drug will not be infringed by the manufacturing or sale of the proposed product. Also it is a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence study is complete, and could establish that the product is bioequivalent.

Please evaluate whether the request for study submitted by Tris Pharma on January 9, 2009 for its Dextromethorphan Polistirex product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

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/s/

Eda Howard
3/11/2009 08:02:58 AM
APPLICATIONS EXA