CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 18-658/S-017

Name: Delsym (Dextromethorphan Polistirex) Extended-Release Suspension

Sponsor: Celltech Pharmaceuticals, Inc.

Approval Date: November 10, 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 18-658/S-017

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 18-658/S-017

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-658/S-017

Celltech Pharmaceuticals, Inc.
Attention: Sean Alan F. X. Reade
Vice President, Regulatory Affairs
755 Jefferson Road
P.O. Box 31710
Rochester, NY 14603-1710

Dear Mr. Reade:

Please refer to your supplemental new drug application dated July 9, 2004, received July 12, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Delsym® (dextromethorphan polistirex) Extended-Release Suspension.

We acknowledge receipt of your submissions dated August 11 and September 30, 2004.

This supplemental new drug application provides for the following:

- addition of edetate disodium (EDTA) to the formulation
- change to a different grade of an excipient, high fructose corn syrup
- change to a non-alcoholic orange flavor
- drug product manufacturing process changes – elimination of [redacted]
- additional batch size [redacted] in drug product manufacture
- establishment of a specification limit for the assay testing of the impurity. [redacted] throughout the shelf life of the drug product
- carton and container labeling for the 15 mL, 89 mL, and 148 mL packages.

Your supplemental new drug application also requested a waiver of the in vivo bioequivalence requirement (21 CFR 320.21(c)(1)) for the reformulated drug product.

We have completed our review of this supplemental application, as amended, and it is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling (89 mL immediate container and carton labeling submitted on July 7, 2004 and the 15 mL and 148 mL immediate container and carton labeling submitted on August 11, 2004).

Please submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA.* Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 18-658/S-017." Approval of this submission by FDA is not required before the labeling is used.

We remind you to remove the word "NEW" on the principal display panel (PDP) after 180 days of marketing.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Elaine Abraham, R.Ph., Regulatory Project Manager, at (301) 827-2276.

Sincerely,

{See appended electronic signature page}

Curtis Rosebraugh, M.D., M.P.H.
Deputy Director
Division of Over-the-Counter Drug Products
Office of Drug Evaluation V
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/

Curtis Rosebraugh
11/10/04 02:57:33 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 18-658/S-017

APPROVED LABELING

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

DIRECTIONS: **SHAKE BOTTLE WELL BEFORE USING.**

Dose as follows or as directed by a doctor
Adults and Children 12 years of age and over: 2 teaspoonfuls every 12 hours, not to exceed 4 teaspoonfuls in 24 hours.
Children 6 to under 12 years of age: 1 teaspoonful every 12 hours, not to exceed 2 teaspoonfuls in 24 hours.
Children 2 to under 6 years of age: 1/2 teaspoonful every 12 hours, not to exceed 1 teaspoonful in 24 hours.
Children under 2 years of age: Consult a doctor.

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 teaspoonful (5 mL) contains dextromethorphan polistirex equivalent to 30 mg dextromethorphan hydrobromide

Store at 20°-25°C (68°-77°F).

3 53014 46361 4
Lot:
Exp:
CELLTECH
Celltech Pharmaceuticals, Inc.
Rochester, NY 14623 USA
L525

PMS 172 Orange, PMS 108 Yellow, PMS 2738 Blue
05/26/04

ENLARGED TO 110%
BY FOIA STAFF

TAMPER-EVIDENT FEATURE-DO NOT USE IF

436

Delsym®

12 Hour Cough Relief

Drug Facts

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

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

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**
- dose as follows or as directed by a doctor

adults and children 12 years of age and over	2 teaspoonfuls every 12 hours, not to exceed 4 teaspoonfuls in 24 hours
children 6 to under 12 years of age	1 teaspoonful every 12 hours, not to exceed 2 teaspoonfuls in 24 hours
children 2 to under 6 years of age	1/2 teaspoonful every 12 hours, not to exceed 1 teaspoonful in 24 hours
children under 2 years of age	consult a doctor

436

Delsym®

12 Hour Cough Relief

Drug Facts (continued)

Other information
- **each 5 mL teaspoonful contains:** sodium 6 mg
- store at 20°-25°C (68°-77°F)

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
Toll free, Mon-Fri, 8 am-5 pm, Eastern Time

Instrucciones en español adentro.
Instructions in Spanish inside.

CELLTECH
Celltech Pharmaceuticals, Inc.
Rochester, NY 14623 USA

 www.Delsym.com

Delsym®

12 Hour Cough Relief

dextromethorphan polistirex
Extended-Release Suspension
COUGH SUPPRESSANT

NEW
• Alcohol Free
Instrucciones en español adentro

12 HOUR Cough Relief

3 53014 46361 4

Lot No.:

Exp. Date:

436

PMS 172 Orange, PMS 2738 Blue, and 4 Color Pr
06/28/04

B436

Delsym®

12 Hour Cough Relief

COMPARE COST PER DOSE

DELSYM® DOSING
SHAKE WELL BEFORE USE.

Age (yr)	Dose (1 TSP = 5 mL)
12 years to adult	2 TEASPOONFULS EVERY 12 HOURS
6 to under 12	1 TEASPOONFUL EVERY 12 HOURS
2 to under 6	1/2 TEASPOONFUL EVERY 12 HOURS

COUGH SUPPRESSANT

Contains no fever reducer or pain reliever

Great orange taste

Información sobre el medicamento

Principio activo (en cada cucharadita de 5 mL) ***Propósito***

Dextrometorfano polistirex equivalente a 30 mg de hidrobromuro de dextrometorfano ..... Antitusivo

Uso su uso temporal alivia la tos producida por una irritación leve de la garganta y de los bronquios, como puede suceder durante una gripe común o al inhalar irritantes

Advertencias

No usar si ya está tomando un inhibidor de monoamino oxidasa de venta con receta (monoamine oxidase inhibitor, MAOI) (ciertos medicamentos antidepresivos, para condiciones psiquiátricas o emocionales o enfermedad de Parkinson), ni durante 2 semanas después de haber interrumpido el MAOI. Si usted no sabe si el medicamento de venta con receta contiene un MAOI, consulte a su médico o farmacéutico antes de tomar este producto.

Consulte a su médico antes de usarlo si tiene
- tos crónica persistente como en casos de tabaquismo, asma o enfisema
- tos con mucha flema (mucosidad)

Interrumpa su uso y consulte a su médico si la tos dura más de 7 días, si vuelve, o se produce con fiebre, salpullido cutáneo o dolores de cabeza persistentes. Estos pueden ser signos de una condición grave.

En caso de embarazo o en período de lactancia, consulte a un profesional de la salud antes de usar el medicamento. **Manténgalo fuera del alcance de los niños.** En caso de sobredosis, obtenga asistencia médica o comuníquese inmediatamente con un Centro de Control de Intoxicaciones.

Instrucciones
- **antes de usar** el medicamento, **agite bien el frasco**
- se recomienda tomar las dosis indicadas por el médico o bien las siguientes

adultos y niños de 12 años de edad o más	2 cucharaditas cada 12 horas, no tomar más de 4 cucharaditas en 24 horas
niños entre 6 y 12 años de edad	1 cucharadita cada 12 horas, no tomar más de 2 cucharaditas en 24 horas
niños entre 2 y 6 años de edad	1/2 cucharadita cada 12 horas, no tomar más de 1 cucharadita en 24 horas
niños menores de 2 años de edad	consulte a su médico

Información adicional
- **cada cucharadita de 5 mL contiene:** 6 mg de sodio
- almacénelo a una temperatura de 20°-25°C (68°-77°F)

Principio inactivo ácido cítrico, edetato disódico, eilicelulosa, FD&C Amarillo N° 6, saborizante, jarabe de maíz rico en fructosa, metilparabeno, polietilenglicol 3350, polisorbato 80, propileno glicol, propilparabeno, agua purificada, sacarosa, tragacanto, aceite vegetal, goma Xantana

¿Preguntas? 1-866-485-9428
Línea gratuita, de lunes a viernes, de 8 a.m. a 5 p.m., hora del Este

GRAIN

CELL TECH
C030256B

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

DIRECTIONS: **SHAKE BOTTLE WELL BEFORE USING.**

Dose as follows or as directed by a doctor
Adults and Children 12 years of age and over: 2 teaspoonfuls every 12 hours, not to exceed 4 teaspoonfuls in 24 hours.
Children 6 to under 12 years of age: 1 teaspoonful every 12 hours, not to exceed 2 teaspoonfuls in 24 hours.
Children 2 to under 6 years of age: 1/2 teaspoonful every 12 hours, not to exceed 1 teaspoonful in 24 hours.
Children under 2 years of age: Consult a doctor.

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 teaspoonful (5 mL) contains dextromethorphan polistirex equivalent to 30 mg dextromethorphan hydrobromide.

Store at 20°-25°C (68°-77°F).

Delsym®

COUGH SUPPRESSANT

12 Hour Cough Relief

Contains no fever reducer or pain reliever
Great Orange Taste
For Children & Adults

3 53014 46343 0

CELLTECH

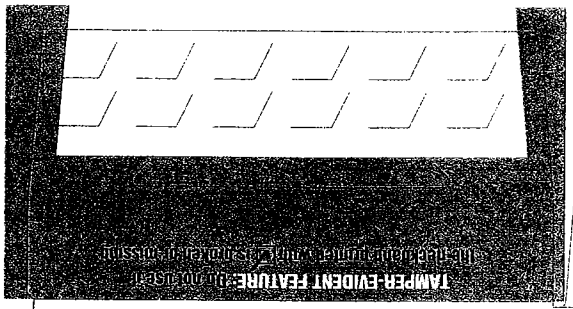
Celltech Pharmaceuticals, Inc.
Rochester, NY 14623 USA

Lot:
Exp.:

L526

PMS 172 Orange, PMS 108 Yellow, PMS 2738 Blue
05/26/04

ENLARGED TO 110%
BY FOIA STAFF



438

Delsym®

12 Hour Cough Relief

Drug Facts

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

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

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**
- dose as follows or as directed by a doctor

adults and children 12 years of age and over	2 teaspoonfuls every 12 hours, not to exceed 4 teaspoonfuls in 24 hours
children 6 to under 12 years of age	1 teaspoonful every 12 hours, not to exceed 2 teaspoonfuls in 24 hours
children 2 to under 6 years of age	1/2 teaspoonful every 12 hours, not to exceed 1 teaspoonful in 24 hours
children under 2 years of age	consult a doctor

Delsym®
12 Hour Cough Relief

Drug Facts (continued)

Other information
- **each 5 mL teaspoonful contains:** sodium 6 mg
- store at 20°-25°C (68°-77°F)

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
Toll free, Mon-Fri, 8 am-5 pm, Eastern Time

Instrucciones en español adentro.
Instructions in Spanish inside.

CELLTECH
Celltech Pharmaceuticals, Inc.
Rochester, NY 14623 USA
® Celltech Manufacturing, Inc. **www.Delsym.com**

438

3 53014 46343 0

Lot No.:

Exp. Date:

PMS 172 Orange, PMS 2738 Blue, and 4 Color
4/C picture of girl is FPO
06/28/04

B438

Delsym®

12 Hour Cough Relief

COMPARE COST PER DOSE

DELSYM® DOSING
SHAKE WELL BEFORE USE.

Age (yr)	Dose (1 TSP = 5 mL)
Under 2	CONSULT DOCTOR
2 to under 6	1/2 TEASPOONFUL EVERY 12 HOURS
6 to under 12	1 TEASPOONFUL EVERY 12 HOURS

COUGH SUPPRESSANT

Contains no fever reducer or pain reliever

Great orange taste

Información sobre el medicamento

Principio activo (en cada cucharadita de 5 mL) ***Propósito***

Dextrometorfano polistirex equivalente a 30 mg de hidrobromuro de dextrometorfano ..... Antitusivo

Uso su uso temporal alivia la tos producida por una irritación leve de la garganta y de los bronquios, como puede suceder durante una gripe común o al inhalar irritantes

Advertencias

No usar si ya está tomando un inhibidor de monoamino oxidasa de venta con receta (monoamine oxidase inhibitor, MAOI) (ciertos medicamentos antidepresivos, para condiciones psiquiátricas o emocionales o enfermedad de Parkinson), ni durante 2 semanas después de haber interrumpido el MAOI. Si usted no sabe si el medicamento de venta con receta contiene un MAOI, consulte a su médico o farmacéutico antes de tomar este producto.

Consulte a su médico antes de usarlo si tiene
- tos crónica persistente como en casos de tabaquismo, asma o enfisema
- tos con mucha flema (mucosidad)

Interrumpa su uso y consulte a su médico si la tos dura más de 7 días, si vuelve, o se produce con fiebre, salpullido cutáneo o dolores de cabeza persistentes. Estos pueden ser signos de una condición grave.

En caso de embarazo o en período de lactancia, consulte a un profesional de la salud antes de usar el medicamento. **Manténgalo fuera del alcance de los niños.** En caso de sobredosis, obtenga asistencia médica o comuníquese inmediatamente con un Centro de Control de Intoxicaciones.

Instrucciones
- **antes de usar el medicamento, agite bien el frasco**
- se recomienda tomar las dosis indicadas por el médico o bien las siguientes

adultos y niños de 12 años de edad o más	2 cucharaditas cada 12 horas, no tomar más de 4 cucharaditas en 24 horas
niños entre 6 y 12 años de edad	1 cucharadita cada 12 horas, no tomar más de 2 cucharaditas en 24 horas
niños entre 2 y 6 años de edad	1/2 cucharadita cada 12 horas, no tomar más de 1 cucharadita en 24 horas
niños menores de 2 años de edad	consulte a su médico

Información adicional
- **cada cucharadita de 5 mL contiene:** 6 mg de sodio
- almacénelo a una temperatura de 20°-25°C (68°-77°F)

Principio inactivo ácido cítrico, edetato disódico, etilcelulosa, FD&C Amarillo N° 6, saborizante, jarabe de maíz rico en fructosa, metilparabeno, polietilenglicol 3350, polisorbato 80, propileno glicol, propilparabeno, agua purificada, sacarosa, tragacanto, aceite vegetal, goma Xantana

¿Preguntas? 1-866-485-9428
Línea gratuita, de lunes a viernes, de 8 a.m. a 5 p.m., hora del Este

ess

← GRAIN →

CELL TECH
C030256B

NDA 18-658/S-017
Delsym® Extended-Release Suspension
Minor Amendment to Pending Supplement
August 11, 2004

15 mL Professional Sample

Immediate Container Label

L307

PMS 172 Orange, PMS 108 Yellow, PMS 2738 Blue
07/23/04

ENLARGED TO 120%
BY FOIA STAFF

NDA 18-658/S-017
Delsym® Extended-Release Suspension
Minor Amendment to Pending Supplement
August 11, 2004

15 mL Professional Sample

Carton #1

B439

PMS 172 Orange, PMS 108 Yellow, PMS 2738 Blue
08/04/04

Drug Facts (continued)

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**
- dose as follows or as directed by a doctor

adults and children 12 years of age and over	2 tsp. every 12 hours, not to exceed 4 tsp. in 24 hours
children 6 to under 12 years of age	1 tsp. every 12 hours, not to exceed 2 tsp. in 24 hours
children 2 to under 6 years of age	1/2 tsp. every 12 hours, not to exceed 1 tsp. in 24 hours
children under 2 years of age	consult a doctor

Drug Facts (continued)

Other information

- **each 5 mL teaspoonful contains:** sodium 6 mg
- store at 20°-25°C (68°-77°F)

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 Mon-Fri, 8 am-5 pm, Eastern Time

Celltech Pharmaceuticals, Inc. Rochester, NY 14623 USA **www.Delsym.com**

439

TAMPER-EVIDENT FEATURE

Delsym

12 Hour Cough Relief

B439

Delsym®

dextromethorphan polistirex
Extended-Release Suspension

COUGH SUPPRESSANT

NEW Alcohol Free

12 HOUR Cough Relief

Contains no fever reducer or pain reliever

Great orange taste

PROFESSIONAL SAMPLE - NOT FOR RESALE

CELLTECH

© Celltech Manufacturing, Inc.

Lot No.:

Exp. Date:

Drug Facts

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

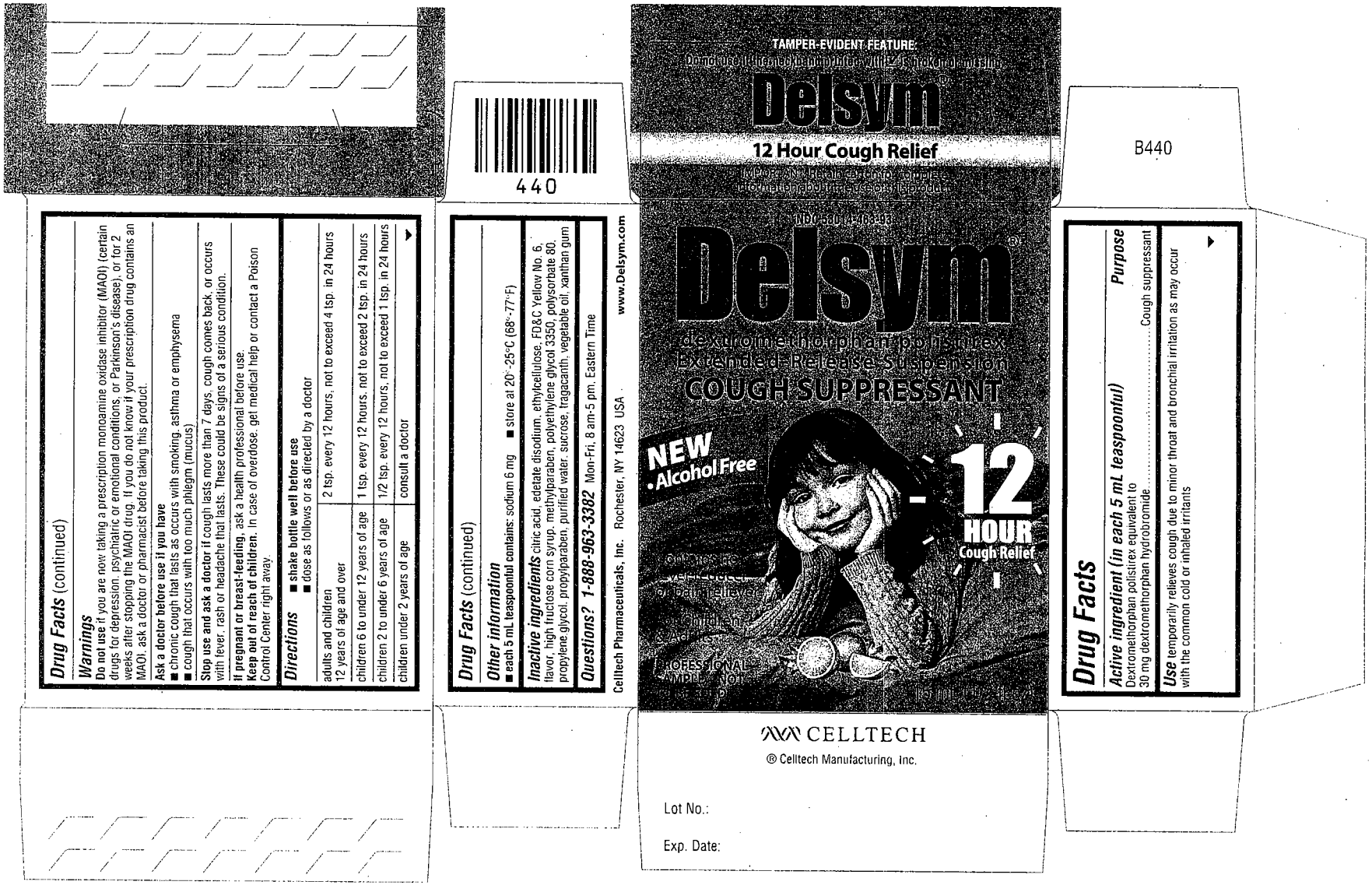
Use temporarily relieves cough due to minor throat and bronchial irritation as may occur with the common cold or inhaled irritants

NDA 18-658/S-017
Delsym® Extended-Release Suspension
Minor Amendment to Pending Supplement
August 11, 2004

15 mL Professional Sample

Carton #2

B440



PMS 172 Orange, PMS 2738 Blue, and 4 Color Process
4/C picture of girl is FPO
08/04/04

NDA 18-658/S-017
Delsym® Extended-Release Suspension
Minor Amendment to Pending Supplement
August 11, 2004

148 mL Retail Package

Immediate Container Label

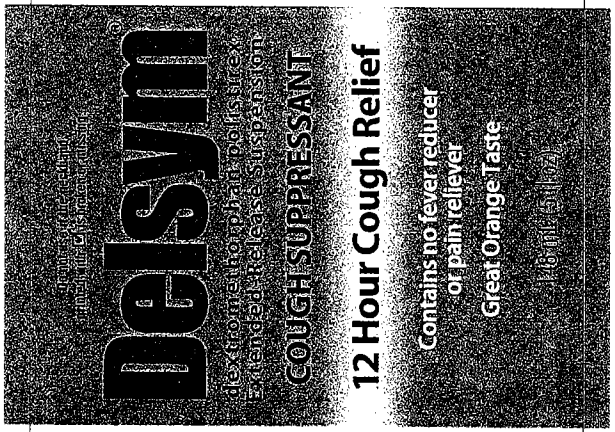
L529

3 53014 46356 0

Lot No.:
Exp. Date:

CELLTECH
Celltech Pharmaceuticals, Inc.
Rochester. NY 14623 USA

L529



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Children 2 to under 6 years of age: 1/2 teaspoonful every 12 hours, not to exceed 1 teaspoonful in 24 hours.
Children under 2 years of age: Consult a doctor.

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.

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PMS 172 Orange, PMS 108 Yellow, PMS 2738 Blue
07/23/04

ENLARGED TO 110%
BY FDA STAFF

NDA 18-658/S-017
Delsym® Extended-Release Suspension
Minor Amendment to Pending Supplement
August 11, 2004

148 mL Retail Package

Carton

B441

TAMPER-EVIDENT FEATURE

441

Delsym®

12 Hour Cough Relief

Drug Facts

Active ingredient (in each 5 mL teaspoonful)	Purpose
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adults and children 12 years of age and over	2 teaspoonfuls every 12 hours, not to exceed 4 teaspoonfuls in 24 hours
children 6 to under 12 years of age	1 teaspoonful every 12 hours, not to exceed 2 teaspoonfuls in 24 hours
children 2 to under 6 years of age	1/2 teaspoonful every 12 hours, not to exceed 1 teaspoonful in 24 hours
children under 2 years of age	consult a doctor

Other information
- **each 5 mL teaspoonful contains:** sodium 6 mg
- store at 20°-25°C (68°-77°F)

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
Mon-Fri, 8 am-5 pm, Eastern Time

Instrucciones en español adentro.
Instructions in Spanish inside.

Delsym®
12 Hour Cough Relief

COMPARE COST PER DOSE

12 HOUR Cough Relief

COUGH SUPPRESSANT

Contains no fever reducer or pain reliever

Great orange taste

CELLTECH

Celltech Pharmaceuticals Inc.

Delsym
12 Hour Cough Relief

dextromethorphan polistirex
Extended-Release Suspension

COUGH SUPPRESSANT

NEW
• Alcohol Free
Instrucciones en español adentro

12 HOUR Cough Relief

3 53014 46356 0

Lot No.:

Exp. Date:

CELL TECH
5 OZ DELSYM
2.9375 x 2.094 x 6.438
DWG#: C020280B
PRINT SIDE UP
STOCK: .016 SBS
DRAWN BY: —
3/4/02

B441

Delsym®

12 Hour Cough Relief

COMPARE COST PER DOSE

DELSYM® DOSING

SHAKE WELL BEFORE USE.

Age (yr)	Dose (1 TSP = 5 mL)
12 years to adult	2 TEASPOONFULS EVERY 12 HOURS
6 to under 12	1 TEASPOONFUL EVERY 12 HOURS
2 to under 6	1/2 TEASPOONFUL EVERY 12 HOURS

See back panel for full dosing directions.
Instrucciones en español adentro.
Instructions in Spanish inside.

COUGH SUPPRESSANT

Contains no fever reducer or pain reliever

Great orange taste

Bottle contains 2.91 2 teaspoons

Información sobre el medicamento

Principio activo (en cada cucharadita de 5 mL) **Propósito**
Dextrometorfano polistirex equivalente a 30 mg de hidrobromuro de dextrometorfano.....Antitusivo

Uso su uso temporal alivia la tos producida por una irritación leve de la garganta y de los bronquios, como puede suceder durante una gripe común o al inhalar irritantes

Advertencias

No usar si ya está tomando un inhibidor de monoamino oxidasa de venta con receta (monoamine oxidase inhibitor, MAOI) (ciertos medicamentos antidepresivos, para condiciones psiquiátricas o emocionales o enfermedad de Parkinson), ni durante 2 semanas después de haber interrumpido el MAOI. Si usted no sabe si el medicamento de venta con receta contiene un MAOI, consulte a su médico o farmacéutico antes de tomar este producto.

Consulte a su médico antes de usarlo si tiene
- tos crónica persistente como en casos de tabaquismo, asma o enfisema
- tos con mucha flema (mucosidad)

Interrumpa su uso y consulte a su médico si la tos dura más de 7 días, si vuelve, o se produce con fiebre, salpullido cutáneo o dolores de cabeza persistentes. Estos pueden ser signos de una condición grave.

En caso de embarazo o en período de lactancia, consulte a un profesional de la salud antes de usar el medicamento.
Manténgalo fuera del alcance de los niños. En caso de sobredosis, obtenga asistencia médica o comuníquese inmediatamente con un Centro de Control de Intoxicaciones.

Instrucciones

- **antes de usar el medicamento, agite bien el frasco**
- **se recomienda tomar las dosis indicadas por el médico o bien las siguientes**

adultos y niños de 12 años de edad o más	2 cucharaditas cada 12 horas, no tomar más de 4 cucharaditas en 24 horas
niños entre 6 y 12 años de edad	1 cucharadita cada 12 horas, no tomar más de 2 cucharaditas en 24 horas
niños entre 2 y 6 años de edad	1/2 cucharadita cada 12 horas, no tomar más de 1 cucharadita en 24 horas
niños menores de 2 años de edad	consulte a su médico

Información adicional

- **cada cucharadita de 5 mL contiene:** 6 mg de sodio
- **almacénelo a una temperatura de 20°-25°C (68°-77°F)**

Principio inactivo ácido cítrico, edetato disódico, etilcelulosa, FD&C Amarillo Nº 6, saborizante, jarabe de maíz rico en fructosa, metilparabeno, polietilenglicol 3350, polisorbato 80, propileno glicol, propilparabeno, agua purificada, sacarosa, tragacanto, aceite vegetal, goma Xantana

¿Preguntas? 1-866-485-9428
Línea gratuita, de lunes a viernes, de 8 a.m. a 5 p.m., hora del Este

PMS 172 Orange, PMS 108 Yellow, PMS 2738 Blue
07/23/04

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 18-658/S-017

LABELING REVIEW(S)

OTC Drug Labeling Review

Division of Over-The-Counter Drug Products (HFD-560)

Center for Drug Evaluation and Research • Food and Drug Administration

NDA Supplement Labeling Review

NDA # 18-658; SCF-017

Submission: 7/9/04 and 8/11/04
Review date: 9/02/04

Applicant: Celltech Americas, Inc.

Applicant's Representative: Mary Evelyn Towne
Manager, Regulatory Affairs

Drug: Delsym (dextromethorphan polistirex) Extended-Release Suspension, 30 mg/5 mL

Pharmacologic Category: Antitussive

Submitted Labels:

Sample Pack (15 mL):
- Carton labeling (B439)
- Immediate Container labeling (L307)

- Carton labeling - "Children & Adults" (B440)

Retail Pack (89 mL):
- Carton labeling (B436)
- Immediate Container labeling (L525)

- Carton labeling - "Children & Adults" (B438)
- Immediate Container labeling - "Children & Adults" (L526)

Retail Pack (148 mL) :
- Carton labeling (B441)
- Immediate Container labeling (L529)

Background:

NDA # 18-658 was approved on October 8, 1982. In the submissions of July 9, 2004 and August 11, 2004, Celltech seeks approval to revised the labeling for its OTC Delsym (dextromethorphan polistirex) Extended-Release Suspension) drug product to include the following:

- addition of edetate disodium (EDTA) to the Drug Facts inactive ingredient listing
- a flag on the PDP that states: "New . Alcohol Free" and the Spanish phrase "Instrucciones en espanol adentro"

- deletion of alcohol percentage statement from the immediate container and carton labels
- deletion of alcohol from inactive ingredients listings
- revision of sodium content under "Other information" section
- Spanish translation on the carton interior. (Note: Certification of the Spanish translation included in the submission.)
- additional labeling changes previously requested by the Agency in its February 2, 2004 letter as agreed upon by Celltech in its April 15, 2004 letter.

In addition, the carton PDP label of each of the SKUs (package size without the graphics of a child) contains the following labeling changes:

- the bulleted phrases "Nonnarcotic" and "For Adults and Children" do not appear.
- the phrase "Pleasant Orange Flavor" is revised to "Great orange taste".

Reviewer comments:

1. The draft labeling of the carton and immediate container labels for the 15 mL professional sample, and the 89 and 148 mL SKUs are acceptable. An approval letter can be issued to the sponsor requesting final printed 15, 89, and 148 mL carton and immediate container labels (i.e., with and without the child presentation on the carton PDP and corresponding immediate container labels). The final printed labels must be identical to the 89 mL carton and immediate container labels submitted on July 7, 2004 and the 15 and 148 mL carton and immediate container labels submitted on August 11, 2004.
2. Inform the sponsor that the word "New" must be deleted from the PDP six months after introduction into the market place.

Cazemiro R. Martin
IDS: Reg. Review Scientist

Concur: Marina Chang, R.Ph.
Team Leader

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/s/

Cazemiro Martin
9/2/04 09:10:34 AM
INTERDISCIPLINARY

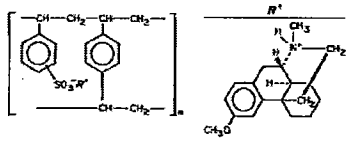
Marina Chang
9/2/04 10:10:49 AM
INTERDISCIPLINARY

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 18-658/S-017

CHEMISTRY REVIEW(S)

Chemistry Review # 1	1. Division HFD-560	2. NDA Number 18-658
3. Name and Address of Applicant Celltech Pharmaceuticals, Inc. Attention: Sean Allen F.X. Read, Vice President, Regulatory Affairs 755 Jefferson Road P.O. Box 31710 Rochester, NY 14603-1710 Phone: 585-475-9000		**4. Supplement:** SCF-017 **Letter Date:** 7/09/04 **Stamp Date:** 7/12/04 **User Fee Due Date:** 11/12/04
5. Name of Drug Delsym® Extended-Release Suspension	**6. Nonproprietary Name** Dextromethorphan polistirex	
7. Supplement Provides for: Formulation changes, process change, additional batch size, and tightening of acceptance criterion for an impurity		**8. Amendment(s)** N/A
9. Pharmacological Category Antitussive	**10. How Dispensed** OTC	**11. Related Documents** N/A
12. Dosage Form Suspension	**13. Potency(ies)** 30 mg /5 mL (dextromethorphan HBr)	
14. Chemical Name and Structure see USAN Sulfonated styrene-divinylbenzene copolymer complex with 3-methoxy-17-methyl-9α,13α,14α-morphinan		

15. Comments **Prior Approval Supplement**

This supplement provides for formulation changes, process change, additional batch size, and tightening of acceptance criterion for an impurity

The submission included:
1) Revised drug product formula,
2) Revised drug product specification,
3) Comparative dissolution profiles with f_2 analysis
3) Executed and master batch records
4) Three months of stability data at 25°C/60%RH and 40°C/75%RH on one production batch packaged in 15 mL, 89 mL, and 148 mL amber glass bottles.

16. Conclusions and Recommendations
This supplement is recommended for approval.
This supplement contains labeling. Action letter will be issued by the HFD-560.

17. Name **Date**
Rao Puttagunta, Ph.D., Reviewer 10/22/04

18. Concurrence
John Smith, Ph.D., Team Leader

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confidential commercial

information from

CHEMISTRY REVIEW

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/s/

Rao Puttagunta
10/25/04 09:11:00 AM
CHEMIST

John Smith
10/25/04 10:51:55 AM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 18-658/S-017

PHARMACOLOGY REVIEW

Office of Clinical Pharmacology and Biopharmaceutics Review

NDA #	18-658 (SCF-017)
Submission Date (s)	July 9th, 2004 and September 30th, 2004
User Fee Date	November 12th, 2004
Brand Name	Delsym ® Extended-Release Suspension
Generic Name	Dextromethorphan Polistirex
Formulation; Strength(s)	Suspension ; 30 mg/5 mL (dextromethorphan HBr)
Reviewer	Abimbola Adebowale Ph.D.
Team Leader	Dennis Bashaw Pharm.D.
OCPB Division	DPE-III
OND division	HFD-560
Sponsor	Celltech Pharmaceuticals, Inc. Rochester, NY 14603
Submission Type; Code	Prior Approval Supplement: Reformulation of Drug Product & Request for a Biowaiver
Pharmaceutical Category	Antitussive

Introduction:

This application is a Prior Approval Supplement to provide for a reformulation of the currently marketed drug product and also request for a waiver of the in vivo bioequivalence requirement (21 CFR 320.21 (c) (1)) for the reformulated drug product. Delsym ® Extended-Release Suspension was approved on October 8th, 1982 for OTC drug marketing.

This supplement provides for formulation changes in flavor to a non-alcoholic orange flavor, changes in the technical grade of high fructose corn syrup and, addition of edetate sodium (EDTA) as a new inactive ingredient. The supplement also provides for process changes (elimination of [redacted], additional batch size of [redacted] and a tightening of the acceptance criterion for an impurity [redacted].

Regulatory History:

The changes proposed in this submission were previously provided in an October 7, 2003 information package and, subsequently discussed during a Type B meeting with the Agency via teleconference on November 20, 2003. A copy of the dissolution test protocol P03128 as the proposed supportive data to allow them to request for a waiver of in vivo bioequivalence data was included in the package. A copy of the sponsor's question for OCPB and the FDA response discussed at the meeting is inserted below:

Sponsor's Question
The supplemental application will contain a request for waiver for the requirement for submission of in vivo bioequivalence data for the drug product in accordance with CFR 21 §320.22(d) (4)... The supplemental application will include...supportive in vitro data...A copy of Celltech Protocol P03128 is provided for your review in Tab 2 of this submission... Does the division confirm that the aforementioned proposed data collection meets the requirements for the granting of a biowaiver?

FDA response:
The dissolution test protocol for the suspension under Tab 2 is acceptable. The submission of *in vitro* test results to the NDA is acceptable. The appropriate data should be included in the supplement and can support a biowaiver.

Review of Data Included in this Submission

Based on the aforementioned discussions, the sponsor has provided a revised composition of the drug product and, comparative dissolution profiles with f2 analysis to support a waiver for the requirement for submission of in vivo bioequivalence data for their reformulated drug product. The sponsor also included data to support the process changes proposed. This has been reviewed by the chemistry reviewer (Dr. R. Puttagunta). This reviewer will only be reviewing the information and data provided to support a waiver.

Information and Data provided to support a biowaiver:

1. The applicant stated that:

- The proposed Delsym Extended-Release Suspension (Reformulation) consists of the same active ingredient, coated and uncoated dextromethrophan polistirex, has the same release mechanism, and is manufactured using the same type of equipment and same process at the same site as the current commercial Delsym Extended-Release Suspension.

Reviewer's Evaluation:

This reviewer is in agreement with the sponsors' statement #1 above. This is based on an evaluation of the comparison of the revised drug product composition with that of the currently approved drug product and, discussions with the chemistry reviewer. A review of the supportive data is discussed below:

The composition of the current approved Delsym suspension and the proposed Delsym suspension are shown in the Table below.

Current Approved Delsym Suspension			Proposed Delsym Suspension		
INGREDIENTS	Spec No	mg/5 ml	mg/5ml	Spec No	INGREDIENTS
Dye FD&C Yellow #6 Certified	0170			0170	Dye FD&C Yellow #6 Certified
Citric Acid,	0036			0036	Citric Acid,
				0078	EDTA
	1098			1098	
High Fructose Corn Syrup	0137			0161	High Fructose Corn Syrup
Propylene Glycol	0484			0484	Propylene Glycol
Methylparaben	0983			0983	Methylparaben
Propylparaben	0891			0891	Propylparaben
Xanthan Gum*	0151			0151	Xanthan Gum*
Gum Tragacanth*	0082			0082	Gum Tragacanth*
Polysorbate 80	1123			1123	Polysorbate 80
Dextromethorphan Polistirex**	0101			0101	Dextromethorphan Polistirex**
Coated Dextromethorphan Polistirex**	0209B			0209B	Coated Dextromethorphan Polistirex**
Flavor Orange	0094			1358	Flavor Orange
Water, Purified	1044			1044	Water, Purified

*Actual quantity is based on moisture content. **Actual quantity is based on assay of Dextromethorphan.

Active ingredient: An examination of the table above shows that the reformulated product consists of the same amount of coated and uncoated dextromethorphan polistirex as the currently approved Delsym® E-R Suspension.

Inactive Ingredient:
Change in flavor to a non-alcoholic orange flavor:
Sponsor stated that the currently used Orange flavor contains alcohol, which results in alcohol concentration in the finished product. The sponsor is proposing to change to a non-alcoholic orange flavor due to the use of the product in the pediatric population. The amount of flavoring will due to the absence of alcohol.

Change to a higher grade of high fructose corn syrup (HFCS):
The HFCS in the current formulation contains . The proposed higher technical grade of HFCS will contain The sponsor stated that the proposed formulation will contain an equal amount of high fructose corn syrup, i.e. — %, as compared to the current formulation.

Addition of edetate disodium (EDTA):
EDTA is a new inactive ingredient, proposed for addition to the reformulated drug product. The currently approved formulation does not contain EDTA. The sponsor stated that addition of edetate disodium significantly impedes the oxidative degradation of dextromethorphan thus enhancing its chemical stability. The chemistry reviewer

concurs with this statement based on the evaluation of the comparative stability data provided by the sponsor.

EDTA has been used as a stabilizer (range 0.005 % -0.1%) and antimicrobial preservative synergist (range 0.01 % to 0.1 % w/v) in pharmaceutical formulations (Handbook of Pharmaceutical Excipients, Third Edition, 2000). The concentration of EDTA in the reformulated product is — % w/v, which is within the usual concentration range for its use as an antioxidant and preservative.

In addition the maximum potency of edetate disodium for oral suspensions in the FDA inactive ingredient database is 0.25 % w/v. The concentration being proposed to be added to the reformulated product is —% of the approved maximum potency therefore safety is not a concern in this case.

Process Changes:
Based on the aforementioned and following discussions with the chemistry reviewer it was agreed that the reformulated product has the same release mechanism in that none of the proposed changes will affect the release mechanism of the reformulated product. In addition the proposed reformulated product is to be manufactured using the same type of equipment and same process at the same site as the current commercial Delsym ® Extended-Release formulation.

2. The applicant stated that

- The proposed Delsym Extended-Release Suspension (Reformulation) and commercial Delsym Extended-Release Suspension have been shown to have similar in vitro dissolution profiles. Comparative dissolution data can be found in section 4.A.3.7, *Specifications and Analytical Methods* (pages 4-301 – 4-326) within Report R03128.1, entitled "Dissolution Profile Comparison of Reformulated and Commercial Delsym Extended-Release Suspension. All similarity factors (f_2) values ranged from 70.5 to 97.3, well within the range of 50 – 100 suggested by the FDA guidance demonstrating that the reformulated and commercial product dissolution profiles are equivalent for each media and condition examined.

Reviewer's Evaluation
This reviewer is in agreement with the sponsor's statement # 2 above. This is based on an evaluation of the comparative dissolution profiles with f2 analysis submitted by the sponsor. A detailed review of the dissolution report (No. R03128.1) is included in the Appendix. The important findings are discussed below:

Dissolution Method
Comparative dissolution profiles of the reformulated and currently marketed Delsym® extended-release suspension using different experimental conditions were submitted. These dissolution profiles were generated using four different media and two different paddle speeds as shown in the table below:

The dissolution profile will be determined at 37 ± 0.5°C in twelve vessels for each experiment.

	Current Dissolution Parameters	Comparative Dissolution Parameters
Media	0.1 N HCl	0.1 N HCl, 0.4 N KCl, 1.0 N KCl, 0.5 N Ammonium Acetate (NH_4OAc)
Media Volume	900 mL	900 mL
Apparatus	USP Apparatus II	USP Apparatus II
Speed	50 RPM	50 & 100 RPM
Timepoints (hr)	0.5, 1, 3	0.5, 1, 2, 3, 5, 7 and 24 hr
Specifications	% of label at 0.5 hr % of label at 1 hr % of label at 3 hr	NA

Applicant's Acceptance Criteria: Dextromethorphan release characteristics for the reformulated suspension will be considered equivalent to those of the current commercial product if:

1) **the average dissolution for the reformulated product, evaluated in 0.1N HCl meets the specifications as stated in the current dissolution procedure**
2) **the comparative dissolution profiles from each media are determined to be similar using the Similarity Factor (f2) test**

Dissolution Results of the Reformulated Drug Product:

The data in the table below shows that the average dissolution for the reformulated product, evaluated in 0.1N HCl using a paddle speed of 50 RPM, meets the specifications as stated in the current dissolution procedure.

Table 1: Dissolution Results for DM in Delsym® ERS Using 0.1 N HCl Media: Average (n = 12) % Released and Range Values

Dissolution Parameter (RPM)	Product Type (Lot #)	Lot #	Time Point (hr.) 0.5	1	2	3	5	7	24	Notebook Reference
50	Commercial (30839)	30839	23	29	41	48	54	56	59	2073-063
50	Reformulated (CL-03142)	CL-03142	23	30	43	50	55	57	60	2073-072
100	Commercial (30839)	30839	42	50	55	56	57	57	59	2073-065
100	Reformulated (CL-03142)	CL-03142	42	50	54	56	57	58	59	2073-072, 2124-001

F2 Analyses: The f2 analysis values are shown in the table below

Table 5: Summary of Similarity Factor (f_2) Results for Reformulated Versus Commercial Delsym® ERS

Media	Paddle Speed (RPM)	f_2 Value
0.1 N HCl	50	89.2
	100	97.3
0.4 N KCl	50	73.7
	100	92.5
1.0 N KCl	50	81.6
	100	81.1
0.5 N NH_4OAC	50	70.5
	100	72.2

The data in the table above shows that the f2 values are between 50 and 100 for the four different media and two different paddle speeds indicating sufficiently similar dissolution profiles of the reformulated and commercial drug product such that further in vivo studies are not needed.

Recommendations(s)

The information provided was adequate to show that the proposed reformulated product is identical, except for a different color, flavor, or preservative that could not affect the bioavailability of the reformulated drug product, to their currently marketed drug product. The following two conditions have also been met:

1) The bioavailability of the currently approved Delsym ® Extended Release Suspension has already been demonstrated; and
2) Both the proposed reformulated drug product and the currently approved drug products meet an appropriate in vitro test approved by the FDA (OCPB review dated October 14th, 1992).

Therefore the data and information provided fulfill the requirement of 21 CFR 320 (d) (4) for a waiver. Based on the aforementioned, the Office of Clinical Pharmacology and Biopharmaceutics (OCPB), recommends a waiver of the requirement to submit data demonstrating in vivo bioequivalence of the reformulated product to the currently marketed drug product.

Abimbola Adebowale, Ph.D.
Clinical Pharmacology Reviewer
Division of Pharmaceutical Evaluation III
Office of Clinical Pharmacology and Biopharmaceutics

Dennis Bashaw, Pharm.D.
Team Leader
Division of Pharmaceutical Evaluation III
Office of Clinical Pharmacology and Biopharmaceutics

Appendix

Dissolution Data Report No. R03128.1

Title: Dissolution Profile Comparison of Reformulated and Commercial Delsym® Extended–Release Suspension

Methodology: Dissolution profiles were generated in four different media (0.1 N hydrochloric acid (HCl), 0.4 N Potasium Chloride (KCl), 1.0 N Potassium Chloride (KCl), and 0.5 N Ammonium Acetate (NH4OAc) at two different paddle speeds (50 and 100 rpm) comparing reformulated Delsym® Extended-Release suspension (ERS) to currently marketed Delsym® ERS both manufactured at Celltech manufacturing Inc., Rochester, New York. The profiles were determined for twelve units at 7 time points over 24 hours for each test condition. The results from dissolution profiles of DM over24 hours were used to determine similarity factors (f_2 values) for comparison of the reformulated product and commercial product.

Reviewer's Comments: the dissolution profile for the reformulated drug product is similar to that of the currently marketed Delsym E-R suspension using the currently approved dissolution method and also in three different media at different paddle speeds. This similarity is shown in the tables and graphs below.

Dissolution data in the other three mediums (the profile in HCL is included in the review):

Table 2: Dissolution Results for DM in Delsym® ERS Using 0.4 N KCl Media: Average (n = 12) % Released and Range Values

Dissolution Parameter (RPM)	Product Type (Lot #)	Lot #	Time Point (hr.)							Notebook Reference
			0.5	1	2	3	5	7	24	
50	Commercial (30839)	30839	35	41	54	62	73	78	89	2076-029, -033
50	Reformulated (CL-03142)	CL-03142	36	42	57	67	77	82	91	2076-029, -033
100	Commercial (30839)	30839	54	64	74	78	83	85	90	2067-061, -069
100	Reformulated (CL-03142)	CL-03142	55	65	75	79	84	86	91	2067-061, -069

Table 3: Dissolution Results for DM in Delsym® ERS Using 1.0 N KCl Media: Average (n = 12) % Released and Range Values

Dissolution Parameter (RPM)	Product Type (Lot #)	Lot #	Time Point (hr.)							Notebook Reference
			0.5	1	2	3	5	7	24	
50	Commercial (30839)	30839	37	44	55	63	72	78	91	2124-012
50	Reformulated (CL-03142)	CL-03142	38	44	57	65	75	81	93	2073-094
100	Commercial (30839)	30839	51	62	72	78	84	87	93	2124-016
100	Reformulated (CL-03142)	CL-03142	53	65	74	80	86	89	96	2127-001

Table 4: **Dissolution Results for DM in Delsym® ERS Using 0.5 N NH_4OAc Media: Average (n = 12) % Released and Range Values**

Dissolution Parameter (RPM)	Product Type (Lot #)	Lot #	Time Point (hr.) 0.5	1	2	3	5	7	24	Notebook Reference
50	Commercial (30839)	30839	41	49	65	74	81	84	89	2124-001
50	Reformulated (CL-03142)	CL-03142	44	51	70	79	85	88	91	2073-085
100	Commercial (30839)	30839	60	70	78	81	83	85	88	2073-081
100	Reformulated (CL-03142)	CL-03142	63	74	81	85	87	88	91	2073-089

Figure 2: **Comparison of Dissolution Profiles for DM in Reformulated and Commercial Delsym® ERS Using 0.4 N KCl Media**

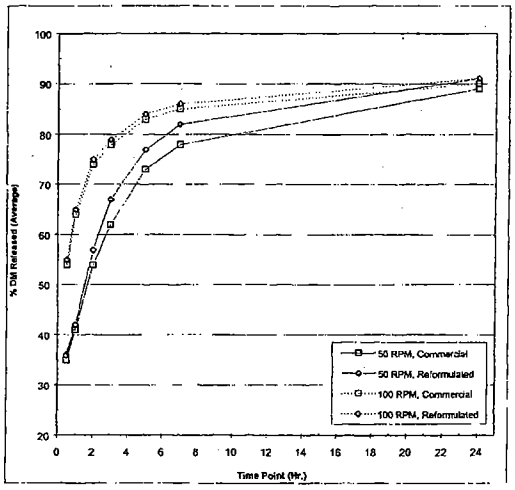


Figure 1: **Comparison of Dissolution Profiles for DM in Reformulated and Commercial Delsym® ERS Using 0.1 N HCl Media**

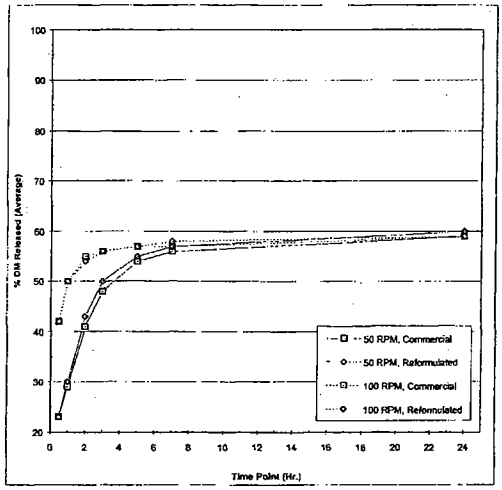


Figure 3: **Comparison of Dissolution Profiles for DM in Reformulated and Commercial Delsym® ERS Using 1.0 N KCl Media**

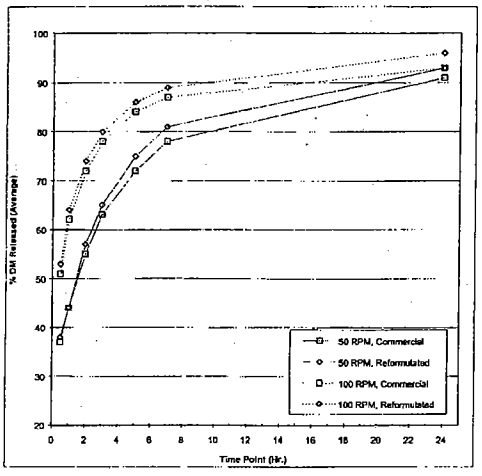
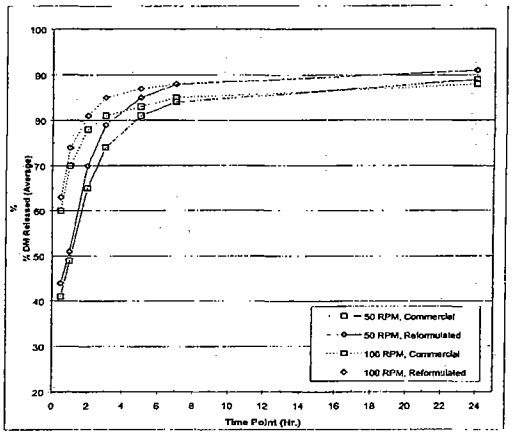


Figure 4: **Comparison of Dissolution Profiles for DM in Reformulated and Commercial Delsym® ERS Using 0.5 N NH_4OAc Media**



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

/s/

Abi Adebowale
11/8/04 02:14:28 PM
BIOPHARMACEUTICS

Dennis Bashaw
11/8/04 02:31:09 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 18-658/S-017

CORRESPONDENCE

CELLTECH

NDA NO. 18-658 REF NO. 017
NDA SUPPL FOR SCF

July 9, 2004

Division of Over the Counter Drug Products, HFD-560
Office of Drug Evaluation V, Room S205/CRP2
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RECEIVED
JUL 12 2004
MEGA/CDER

Re: NDA 18-658
Delsym® (dextromethorphan polistirex) Extended-Release Suspension

Prior Approval Supplement: Reformulation of Drug Product & Request for a Biowaiver

Dear Sir/Madam:

Please refer to the new drug application cited above, which was approved October 8, 1982. Reference is also made to the following:

- Request for a type B meeting submitted to the OTC Division on October 7, 2003 that outlined a proposal for changes to the formulation, container/closure system and manufacturing process and a request for waiver of *in vivo* bioequivalence data. The correspondence outlined the data to be generated and submitted in a prior approval supplemental application and requested FDA feedback.
- Teleconference on November 20, 2003 at which time the Division informed Celltech that the proposed data collection and the request to waive *in vivo* bioequivalence data was acceptable to the Biopharmaceutics reviewer.

Celltech Pharmaceuticals, Inc., hereby submits in duplicate, a Prior Approval Supplement to provide for the following changes:

1. Addition of edetate disodium (EDTA) to the formulation.
2. Change to a different grade of an excipient, high fructose corn syrup.
3. Change to a non-alcoholic orange flavor.
4. Drug product manufacturing process changes - Elimination of ———
5. Additional batch size ——— in drug product manufacture utilizing equipment of the same operating principle & same design as currently utilized.
6. Establishment of a specification limit for the assay testing of the impurity, —— throughout the shelf life of the drug product.

ORIGINAL

Celltech Pharmaceuticals, Inc. Regulatory Affairs
755 Jefferson Road Rochester, NY 14623
P.O. Box 31710 Rochester, NY 14603-1710
Tel: 585-274-5840 Fax: 585-272-3952 E-Mail: mary.towne@celltechgroup.com

Please note that a Pharmacokinetic Section binder with Items 1, 3, and 6, as well as a desk copy of the entire supplement is included with this submission.

The drug product reformulation and associated changes are being submitted as a Prior Approval Supplement as per section XII of the April 2004 Guidance for Industry, "Changes to an Approved NDA or ANDA."

Per CFR 314.71(b), Celltech is providing under separate cover a certified copy of the supplemental application to the Buffalo NY, FDA office.

Enclosed please find signed Forms 356h and 3397. Should you have any questions regarding this submission, please contact the undersigned at (585) 274-5840, or Sean Alan F.X. Reade, Vice President Regulatory Affairs at (585) 274-5351.

Sincerely,

Mary Evelyn Towne

Mary Evelyn Towne
Manager, Regulatory Affairs

Enclosure

CC: 1 Desk Copy (cover letter only) to Elaine Abraham, Project Manager

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-658/S-017

PRIOR APPROVAL SUPPLEMENT

Celltech Pharmaceuticals, Inc.
Attention: Sean Alan F. X. Reade
Vice President, Regulatory Affairs
755 Jefferson Road
P.O. Box 31710
Rochester, NY 14603-1710

Dear Mr. Reade:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Delsym® (dextromethorphan polistirex) Extended-Release Suspension

NDA Number: 18-658

Supplement Number: S-017

Date of Supplement: July 9, 2004

Date of Receipt: July 12, 2004

This supplemental application proposes the following changes:

- addition of edetate disodium (EDTA) to the formulation
- change to a different grade of an excipient, high fructose corn syrup
- change to a non-alcoholic orange flavor
- drug product manufacturing process changes – elimination of [redacted]
- additional batch size [redacted] in drug product manufacture
- establishment of a specification limit for the assay testing of the impurity, [redacted] throughout the shelf life of the drug product.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on September 10, 2004, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be November 12, 2004.

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Over-the-Counter Drug Products, HFD-560
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Over-the-Counter Drug Products, HFD-560
Attention: Division Document Room
9201 Corporate Blvd.
Rockville, Maryland 20850-3202

If you have any questions, call me at (301) 827-2276.

Sincerely,

{See appended electronic signature page}

Elaine Abraham
Regulatory Project Manager
Division of Over-the-Counter Drug Products
Office of Drug Evaluation V
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/

Elaine Abraham
8/5/04 10:59:31 AM

CELLTECH

ORIGINAL

August 11, 2004

Division of Over the Counter Drug Products, HFD-560
Office of Drug Evaluation V, Room S205/CRP2
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RECEIVED
AUG 12 2004
MEGA/CDER

SCF 017(BL)
NDA SUPPL AMENDMENT

Re: NDA 18-658/S-017
Delsym® (dex tromethorphan polistirex) Extended-Release Suspension

Minor Amendment: Additional Draft Labeling

Dear Sir/Madam:

Please refer to the new drug application cited above approved October 8, 1982, and to Celltech's July 9, 2004 prior approval supplement providing for reformulation of Delsym. The purpose of this submission is to submit additional draft labeling as requested by Elaine Abraham on July 21, 2004.

Our July 9 supplement included a representative copy of draft labeling for the 89 mL package size. This amendment includes draft labeling for the 15 mL and 148 mL packaging presentations as noted in Section 2.

If you have any questions regarding this submission please contact Mary Evelyn Towne at (585) 274-5840 or the undersigned at (585) 274-5346.

Sincerely,

Cheryl A. Rini

Cheryl A. Rini
Senior Manager, Regulatory Affairs

Cc: Elaine Abraham, Project Manager (HFD-560)

Celltech Pharmaceuticals, Inc. Regulatory Affairs
755 Jefferson Road Rochester, NY 14623
P.O. Box 31710 Rochester, NY 14603-1710
Tel: 585-274-5840 Fax: 585-272-3952 E-Mail: mary.towne@celltechgroup.com

CELLTECH

September 30, 2004

Division of Over the Counter Drug Products, HFD-560
Office of Drug Evaluation V, Room S205/CRP2
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 18-658/S-017
Delsym® (dex tromethorphan polistirex) Extended-Release Suspension

Response to Request for Information

Dear Sir/Madam:

Please refer to the new drug application cited above approved October 8, 1982, and to Celltech's July 9, 2004 prior approval supplement providing for reformulation of Delsym. The purpose of this submission is to submit additional information as requested by Elaine Abraham on September 24, 2004.

Attached is a table showing a comparison of the quantitative composition of the currently approved Delsym formulation compared with the proposed reformulation.

If you have any questions regarding this submission please contact Mary Evelyn Towne at (585) 274-5840 or the Sean Alan Reade at (585) 274-5351.

Sincerely,

Cheryl Rini for
Mary Evelyn Towne
Manager, Regulatory Affairs

Cc: Elaine Abraham, Project Manager (HFD-560) *(facsimile copy)*

Celltech Pharmaceuticals, Inc. Regulatory Affairs
755 Jefferson Road Rochester, NY 14623
P.O. Box 31710 Rochester, NY 14603-1710
Tel: 585-274-5840 Fax: 585-272-3952 E-Mail: mary.towne@celltechgroup.com