

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-621**

**PHARMACOLOGY REVIEW**

## PHARMACOLOGY/TOXICOLOGY REVIEW

**NDA number:** 21-621

**Drug name:** Zyrtec Chewable tablets

**Sponsor (or agent):** Pfizer, Inc.

**Indication:** Seasonal allergic rhinitis for adults and children 2 years of age and older and perennial allergic rhinitis and chronic idiopathic urticaria in adults and children 6 months of age and older.

**Division Name:** Division of Pulmonary and Allergy Drug Products

**Reviewer Name:** Jui R. Shah, Ph.D.

**Regulatory recommendation:** AP

**Date:** February, 2004

**APPEARS THIS WAY  
ON ORIGINAL**

## TABLE OF CONTENTS

EXECUTIVE SUMMARY .....	1
PHARMACOLOGY/TOXICOLOGY REVIEW .....	3
3.1 INTRODUCTION AND DRUG HISTORY .....	3
3.2 PHARMACOLOGY.....	6
3.2.1 Brief summary.....	6
3.2.2 Primary pharmacodynamics.....	6
3.2.3 Secondary pharmacodynamics.....	6
3.2.4 Safety pharmacology.....	6
3.2.5 Pharmacodynamic drug interactions .....	6
3.3 PHARMACOKINETICS/TOXICOKINETICS .....	6
3.3.1 Brief summary.....	6
3.3.3 Absorption.....	7
3.3.4 Distribution.....	7
3.3.5 Metabolism.....	7
3.3.6 Excretion.....	7
3.3.7 Pharmacokinetic drug interactions .....	7
3.3.10 Tables and figures to include comparative TK summary.....	7
3.4 TOXICOLOGY.....	7
3.4.1 Overall toxicology summary.....	7
3.4.2 Single-dose toxicity.....	7
3.4.3 Repeat-dose toxicity .....	7
3.4.4 Genetic toxicology.....	7
3.4.5 Carcinogenicity .....	7
3.4.6 Reproductive and developmental toxicology .....	7
3.4.7 Local tolerance.....	7
3.4.8 Special toxicology studies.....	7
3.6 OVERALL CONCLUSIONS AND RECOMMENDATIONS .....	7
3.7 APPENDIX/ATTACHMENTS.....	11

APPEARS THIS WAY  
ON ORIGINAL

## **EXECUTIVE SUMMARY**

### **1. Recommendations**

#### **1.1 Recommendation on approvability**

This application is recommended for approval from a non-clinical perspective, pending acceptance of minor edits to the "Pregnancy" section of the label.

#### **1.2 Recommendation for nonclinical studies**

No new studies are recommended for this NDA.

#### **1.3 Recommendations on labeling**

The sponsor submitted proposed labeling for the use of cetirizine hydrochloride chewable tablets. The labeling of the carcinogenesis, mutagenesis and impairment of fertility, nursing mothers and overdose sections is identical to that for Zyrtec syrup/tablets and is appropriate (although minor edits are suggested for the "Pregnancy" section of the label to conform to the CFR (see section 3.6 of this review). The pregnancy category is selected as B which is appropriate.

### **2. Summary of nonclinical findings**

#### **2.1 Brief overview of nonclinical findings**

The chronic toxicity studies conducted to support NDA 19-835 include a 6-month rat toxicology study and 1-year toxicology studies in cynomolgus monkeys and beagle dogs. The target organ of toxicity was the liver. In mice (up to 4-week studies) as well as rats (up to 6-month studies) enlarged liver, increased liver weights, hepatocellular hypertrophy and vacuolation were noted. No target organs were identified in dogs (up to 1 year) and cynomolgus monkey (up to 1 year) toxicology studies.

The genetic toxicology battery (which included the Ames test, In vitro chromosomal aberration assay in human peripheral lymphocytes, mouse lymphoma assay and mouse micronucleus test) was conducted and showed no genotoxic potential for cetirizine. Reproductive toxicology studies included segment I (mouse), segment II (mouse, rat and rabbit) and segment III (rat) studies. Zyrtec is labeled a pregnancy category B, which appears appropriate based on preclinical data.

Two year dietary mouse and rat carcinogenicity studies were conducted. Male mice (HD only) in carcinogenicity studies had an increase in benign liver tumors which was not significant. Rats showed thyroid follicular adenomas (HDM) which were judged not to be clinically relevant, pituitary tumors (MD & HD F) were within the historical control range; increased malignant liver tumors were seen in MD males but showed no statistical significance and finally mammary fibroadenomas were increased in all treated females. Thus cetirizine appears to have no relevant carcinogenic potential in man.

The formulation for Zyrtec chewable tablets includes novel excipients Betadex<sup>®</sup> (betacyclodextrin) as well as                      Artificial Grape Flavor                      a mix of 32 different constituents (see Chemistry consult, dated 1/30/04), which are acceptable for use.

## 2.2 Pharmacologic activity

Cetirizine, a human metabolite of hydroxyzine (an anti-anxiety agent), is an antihistamine; its principal effects are mediated via selective inhibition of peripheral H<sub>1</sub> receptors. The antihistaminic activity of cetirizine has been documented in a variety of animal and human models, and cetirizine shows negligible anticholinergic and antiserotonergic activity in *in vivo* and *ex vivo* studies. In clinical studies, however, dry mouth was more common with cetirizine than with placebo. *In vitro* receptor binding studies have shown no measurable affinity for receptors other than H<sub>1</sub> receptors. Autoradiographic studies with radiolabeled cetirizine in the rat have shown negligible penetration into the brain. *Ex vivo* experiments in the mouse have shown that systemically administered cetirizine does not significantly occupy cerebral H<sub>1</sub> receptors.

## 2.3 Nonclinical safety issues relevant to clinical use

In toxicology studies, decreased food intake and body weights were seen in dogs and cynomolgus monkeys, the liver was identified as the target organ of toxicity in rodents.

**APPEARS THIS WAY  
ON ORIGINAL**

## PHARMACOLOGY/TOXICOLOGY REVIEW

### 3.1 INTRODUCTION AND DRUG HISTORY

Cetirizine is currently marketed as a prescription only anti-histamine. Cetirizine HCl is available in tablet and syrup formulations. The current submission contains two pivotal PK and 4 supportive PK studies, demonstrating the bioequivalence of 10 mg chewable cetirizine tablet, taken with or without water with the approved 10 mg immediate release tablet to be swallowed whole with water. The safety profiles of the two formulations appear comparable.

Cetirizine hydrochloride was first approved in December 1995. Cetirizine is approved for the symptomatic treatment of seasonal allergic rhinitis in adults and children 2 years old and above, and for perennial allergic rhinitis and chronic idiopathic urticaria in adults and children aged 6 months and above. The recommended dosage is 5-10 mg once daily for those 6 yr. and older, 2.5-5.0 mg once daily for those 2-5 yrs old and 2.5 mg once daily for those between 6-months to 2 years of age. Cetirizine HCl is available in immediate-release tablet and syrup formulations. This NDA is for a chewable tablet containing cetirizine (5 & 10 mg) for the treatment of seasonal and perennial allergic rhinitis and chronic urticaria. The chewable tablet will deliver cetirizine HCl in an immediate release form and will be administered once daily with or without water.

**NDA number:** 21-621  
**Review number:** 1  
**Sequence number/date/type of submission:** 000/May 16, 2003/Original NDA  
**Information to sponsor:** No  
**Sponsor (or agent):** Pfizer, Inc.  
**Manufacturer for Drug Substance:** UCB S.A., Chemin du Foriest, 1420  
Braine-L'Alleud, Belgium.  
**Reviewer Name:** Jui R. Shah, Ph.D.  
**Division Name:** Division of Pulmonary and Allergy Drug  
Products  
**HFD #:** 570  
**Review Completion Date:** February, 2004

**Drug:**  
**Generic Name:** Cetirizine  
**Trade Name:** Zyrtec  
**Code Name:** Ziptek, Setir, Hitrizin, Cetryn  
**Chemical Name:** Cetirizine: (+/-)- [2-[4-[(4-chlorophenyl)  
phenylmethyl]-1-piperazinyl] ethoxy]  
acetic acid, dihydrochloride.  
**CAS Registry #:** 83881-51-0



Ingredient (mg/tablet)	10 mg Chewable	5 mg Chewable
<b>ACTIVE LAYER</b>		
Cetirizine HCl	10.0	5
_____	T	J
Acesulfame potassium*		
Colloidal silicon dioxide		
Microcrystalline cellulose		
Artificial grape flavor*		
_____ sweet flavor powder*		
Lactose monohydrate		
Carmines _____ Dye*		
FD&C Blue _____ dye*		
Magnesium stearate		
Total	L	J
<b>INACTIVE LAYER</b>		
Mannitol	T	J
Acesulfame potassium*		
Artificial grape flavor*		
_____ sweet flavor powder*		
Carmines _____ Dye <sup>a</sup>		
FD&C Blue _____ dye <sup>b</sup>		
Magnesium stearate		
Total		

\* not USP/NF grade

<sup>a</sup> grandfathered-exempt from certification testing 21CFR 73.1100

<sup>b</sup> tested and certified by FDA, 21CFR102, 21CFR 1102, 21CFR 82.102

<sup>†</sup> Was declared GRAS on Oct. 25, 2001, Gras notice #: GRN000074

**Route of Administration:**

Oral

**Proposed use:**

Zyrtec is available as 5 mg and 10 mg tablets, 5 mg and 10 mg chewable tablets, and 1 mg/ml syrup. The recommended initial dose of Zyrtec is 5 or 10 mg per day in adults and children 12 years and older. The recommended initial dose of Zyrtec in children aged 6 to 11 years is 5 or 10 mg once daily. The recommended initial dose of Zyrtec syrup in children aged 6 months to 5 years is 2.5 mg (½ teaspoon) once daily. The dosage in this age group can be increased to a maximum dose of 5 mg per day given as 1 teaspoon (5 mg) syrup or one 5 mg chewable tablet once daily, or as ½ teaspoon

**APPEARS THIS WAY  
ON ORIGINAL**

(2.5 mg) given every 12 hours (see table below).

Age	Maximum daily dose (mg)
6 – 12 months	2.5
12-23 months	2.5-5.0
2 – 5 years	5
6-11 years	5-10
Adult	10

**Disclaimer:** Tabular and graphical information are constructed by the reviewer unless cited otherwise.

**Studies reviewed within this submission:**

None submitted.

**Studies not reviewed within this submission:**

None.

### **3.2 PHARMACOLOGY**

#### **3.2.1 Brief summary**

A detailed review of the pharmacology related to Cetirizine can be found in the nonclinical reviews under NDA-19-835 (Reviewer: Dr. Lucy Jean, dated: December 17, 1989). A brief summary is included in section 3.6 of this review.

#### **3.2.2 Primary pharmacodynamics**

#### **3.2.3 Secondary pharmacodynamics**

#### **3.2.4 Safety pharmacology**

#### **3.2.5 Pharmacodynamic drug interactions**

### **3.3 PHARMACOKINETICS/TOXICOKINETICS**

#### **3.3.1 Brief summary**

A detailed review of the pharmacokinetics/toxicokinetics related to Cetirizine can be found in the nonclinical reviews under NDA-19-835 (Reviewer: Dr. Lucy Jean, dated: December 17, 1989). A brief summary is included in section 3.6 of this review.

- 3.3.3 Absorption
- 3.3.4 Distribution
- 3.3.5 Metabolism
- 3.3.6 Excretion
- 3.3.7 Pharmacokinetic drug interactions
- 3.3.10 Tables and figures to include comparative TK summary

### 3.4 TOXICOLOGY

#### 3.4.1 Overall toxicology summary

A detailed review of the toxicology related to Cetirizine can be found in the nonclinical reviews under NDA-19-835 (Reviewer: Dr. Lucy Jean, dated: December 17, 1989). A brief summary is included in section 3.6 of this review.

- 3.4.2 Single-dose toxicity
- 3.4.3 Repeat-dose toxicity
- 3.4.4. Genetic toxicology
- 3.4.5. Carcinogenicity
- 3.4.6. Reproductive and developmental toxicology
- 3.4.7 Local tolerance
- 3.4.8 Special toxicology studies

### 3.6 OVERALL CONCLUSIONS AND RECOMMENDATIONS

#### Conclusions:

Cetirizine, a human metabolite of hydroxyzine (an anti-anxiety agent), is an antihistamine; its principal effects are mediated via selective inhibition of peripheral H<sub>1</sub> receptors. The antihistaminic activity of cetirizine has been documented in a variety of animal and human models, and cetirizine shows negligible anticholinergic and antiserotonergic activity in *in vivo* and *ex vivo* studies. In clinical studies, however, dry mouth was more common with cetirizine than with placebo. *In vitro* receptor binding studies have shown no measurable affinity for receptors other than H<sub>1</sub> receptors. Autoradiographic studies with radiolabeled cetirizine in the rat have shown negligible penetration into the brain. *Ex vivo* experiments in the mouse have shown that systemically administered cetirizine does not significantly occupy cerebral H<sub>1</sub> receptors. It should be noted that the adverse events associated with Zyrtec as well as the effects of overdosing with Zyrtec, appear to have a significant CNS component.

The sponsor has conducted toxicology studies in mice, rats, beagles and cynomolgus monkeys for cetirizine. The chronic toxicity studies conducted to support NDA 19-835 include a 6-month rat toxicology study and 1-year toxicology

studies in cynomolgus monkeys and beagle dogs. The target organ of toxicity was the liver. In mice (up to 4-week studies) as well as rats (up to 6-month studies) enlarged liver, increased liver weights, hepatocellular hypertrophy and vacuolation were noted. No target organs were identified in dogs (up to 1 year) and cynomolgus monkey (up to 1 year) toxicology studies. In dogs, NOAELs were selected based on clinical signs, body weight decreases, hematologic (Increased RBC, Hgb, aPTT) and cardiovascular (ECG & BP) changes. In the cynomolgus monkey NOAELs were selected based on clinical signs (vomiting, behavior, etc). Thus, the identified target organ of toxicity appears to be the liver as seen in the rodent studies.

The genetic toxicology battery (which included the Ames test, In vitro chromosomal aberration assay in human peripheral lymphocytes, mouse lymphoma assay and mouse micronucleus test) was conducted and showed no genotoxic potential for cetirizine.

Reproductive toxicology studies included segment I (mouse), segment II (mouse, rat and rabbit) and segment III (mouse) studies. In the segment I study, the only notable toxicity was increased liver weight in the HD (64 mg/kg/d) dams; NOAEL for maternal toxicity was 16 mg/kg/d (decreased mating performance/pregnancy rate) and for fetal toxicity was 4 mg/kg/d (based on cleft palate and skeletal variants/anomalies). Although statistically significantly lower pregnancy rates were noted in HD dams (90% vs. 100%), these numbers are within the historical control data for the testing laboratory (87-100%, 95.4%). Therefore the lower pregnancy rate was not considered significant (N19-835, C. J. Sun, January 1995).

In the segment II study, no effects were seen in the mouse at up to 96 mg/kg/d. In the rat segment II study, 8 dams died (5 due to drug toxicity), maternal toxicity was seen at 75 and 225 mg/kg/d (respiratory difficulties, arched back/nervousness); the NOAEL for maternal toxicity was 25 mg/kg/d and for fetal effects (decreased fetal weight, skeletal variants/anomalies) was 25 mg/kg/d. In the rabbit segment II study, maternal toxicity (decreased weight gain, -23%) was seen at the HD of 135 mg/kg/d and skeletal variants and anomalies were seen at 135 mg/kg/d; thus, the NOAEL for maternal toxicity and fetal toxicity is 45 mg/kg/d. Since the fetal effects in both rats and rabbits were seen at maternally toxic doses, cetirizine was not considered teratogenic (N19-835, C. J. Sun, January 1995). In the segment III study in mice, toxicity was seen at 96 mg/kg/d in the dams (body weight decrease & impaired nursing performance) and lower pup weight as well as M/F ratio were noted at birth and weaning at that dose (probably due to impaired lactation); thus, the NOAEL for maternal and fetal effects was 24 mg/g/d. Zyrtec is labeled a pregnancy category B, which appears appropriate based on preclinical data.

Two year dietary mouse and rat carcinogenicity studies were conducted. Male mice (HD only, 16 mg/kg/d) in carcinogenicity studies had centrilobular

hepatocyte hypertrophy (due to enzyme induction) and smooth endoplasmic reticulum proliferation as well as an increase in benign liver tumors which was not considered relevant as explained below. Cetirizine is not genotoxic and did not produce hepatotoxicity in dogs, monkeys or man, and was also not tumorigenic in rats. The increased incidence of hepatocellular adenomas were seen only in male mice and may be caused by secondary mechanisms. Other compounds (eg. Phenobarbital) which cause liver tumors following liver growth/toxicity, have been shown epidemiologically, to not adversely affect the liver in man. Rats showed thyroid follicular adenomas (HDM) which were judged not to be clinically relevant (within historical control range, common tumor and negative trend analysis:  $p=0.039$ ). The pituitary tumors (MD & HD F) which were within the historical control range were also judged not to be clinically relevant. Increased malignant liver tumors were seen in MD males but showed no statistical significance and finally mammary fibroadenomas were increased in all treated females. Thus cetirizine appears to have no relevant carcinogenic potential in man.

No preclinical studies were submitted to this NDA. The reviewer was referred to NDA 19-835 submitted June 30, 1988 starting on vol. 3 page 5-1. A detailed review of the pharmacology related to Cetirizine can be found in the nonclinical reviews under NDA-19-835 (Reviewer: Dr. Lucy Jean, dated: December 17, 1989).

Dr. Jao, the CMC reviewer, sent in a consult to assess the safety of Betadex (betacyclodextrin, \_\_\_\_\_ in Zyrtec chewable tablets, 10 mg cetirizine HCl) which would give daily exposures of \_\_\_\_\_ mg in children 2-11 yrs and \_\_\_\_\_ mg in adults and children ages 12 yrs and up. An additional concern was the \_\_\_\_\_ used during the manufacturing of Betadex, which was present at NMT \_\_\_\_\_. The consult also requested evaluation of \_\_\_\_\_ Artificial Grape Flavor which would have a daily dose of \_\_\_\_\_ mg in children 2-11 yrs and \_\_\_\_\_ mg in adults and children ages 12 yrs and up. A review of the consult was concluded on 1/30/04 and determined that, based on available data, the levels of Betadex in Zyrtec chewable tablets appears safe and acceptable from a pharmacology/toxicology perspective. In addition, presence of \_\_\_\_\_ betacyclodextrin at NMT \_\_\_\_\_ is within the acceptable federal EPA drinking water limits with a safety factor of ~12. However, due to its potential to induce carcinogenic effects, levels of \_\_\_\_\_ should be lowered as much as technically feasible. The ingredients in \_\_\_\_\_ grape flavor all have acceptable margins of safety for oral use compared to accepted use in various food products and approved drug products. Thus, there are no safety concerns from the nonclinical perspective for Betadex or \_\_\_\_\_ artificial grape flavor.

Unresolved toxicology issues (if any):

None.

Recommendations:

This product is recommended for approval from a non-clinical perspective, based on the safety of the active ingredient as well as the excipients used in the formulation of Zyrtec chewable tablets.

Suggested labeling:

The proposed labeling submitted with the NDA is appropriate. Minor edits (underlined>) are recommended for the "Pregnancy" section of the label, to conform to the CFR. The final label should read as shown below.

**Mechanism of Actions:** Cetirizine, a human metabolite of hydroxyzine, is an antihistamine; its principal effects are mediated via selective inhibition of peripheral H<sub>1</sub> receptors. The antihistaminic activity of cetirizine has been clearly documented in a variety of animal and human models. *In vivo* and *ex vivo* animal models have shown negligible anticholinergic and antiserotonergic activity. In clinical studies, however, dry mouth was more common with cetirizine than with placebo. *In vitro* receptor binding studies have shown no measurable affinity for other than H<sub>1</sub> receptors. Autoradiographic studies with radiolabeled cetirizine in the rat have shown negligible penetration into the brain. *Ex vivo* experiments in the mouse have shown that systemically administered cetirizine does not significantly occupy cerebral H<sub>1</sub> receptors.

**Carcinogenesis, Mutagenesis and Impairment of Fertility:** In a 2-year carcinogenicity study in rats, cetirizine was not carcinogenic at dietary doses up to 20 mg/kg (approximately 15 times the maximum recommended daily oral dose in adults on a mg/m<sup>2</sup> basis, or approximately 7 times the maximum recommended daily oral dose in infants on a mg/m<sup>2</sup> basis). In a 2-year carcinogenicity study in mice, cetirizine caused an increased incidence of benign liver tumors in males at a dietary dose of 16 mg/kg (approximately 6 times the maximum recommended daily oral dose in adults on a mg/m<sup>2</sup> basis, or approximately 3 times the maximum recommended daily oral dose in infants on a mg/m<sup>2</sup> basis). No increase in the incidence of liver tumors was observed in mice at a dietary dose of 4 mg/kg (approximately 2 times the maximum recommended daily oral dose in adults on a mg/m<sup>2</sup> basis, or approximately equivalent to the maximum recommended daily oral dose in infants on a mg/m<sup>2</sup> basis). The clinical significance of these findings during long-term use of ZYRTEC is not known.

Cetirizine was not mutagenic in the Ames test, and not clastogenic in the human lymphocyte assay, the mouse lymphoma assay, and *in vivo* micronucleus test in rats.

In a fertility and general reproductive performance study in mice, cetirizine did not impair fertility at an oral dose of 64 mg/kg (approximately 25 times the maximum recommended daily oral dose in adults on a mg/m<sup>2</sup> basis).

**Pregnancy Category B:** In mice, rats, and rabbits, cetirizine was not teratogenic at oral doses up to 96, 225, and 135 mg/kg, respectively (approximately 40, 180 and 220 times the maximum recommended daily oral dose in adults on a mg/m<sup>2</sup> basis). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, ZYRTEC should be used — during pregnancy only if clearly needed.

**Nursing Mothers:** In mice, cetirizine caused retarded pup weight gain during lactation at an oral dose in dams of 96 mg/kg (approximately 40 times the maximum recommended daily oral dose in adults on a mg/m<sup>2</sup> basis). Studies in beagle dogs indicated that approximately 3% of the dose was excreted in milk. Cetirizine has been reported to be excreted in human breast milk. Because many drugs are excreted in human milk, use of ZYRTEC in nursing mothers is not recommended.

#### OVERDOSAGE

Overdosage has been reported with ZYRTEC. In one adult patient who took 150 mg of ZYRTEC, the patient was somnolent but did not display any other clinical signs or abnormal blood chemistry or hematology results. In an 18 month old pediatric patient who took an overdose of ZYRTEC (approximately 180 mg), restlessness and irritability were observed initially; this was followed by drowsiness. Should overdose occur, treatment should be symptomatic or supportive, taking into account any concomitantly ingested medications. There is no known specific antidote to ZYRTEC. ZYRTEC is not effectively removed by dialysis, and dialysis will be ineffective unless a dialyzable agent has been concomitantly ingested. The acute minimal lethal oral doses were 237 mg/kg in mice (approximately 95 times the maximum recommended daily oral dose in adults on a mg/m<sup>2</sup> basis, or approximately 40 times the maximum recommended daily oral dose in infants on a mg/m<sup>2</sup> basis) and 562 mg/kg in rats (approximately 460 times the maximum recommended daily oral dose in adults on a mg/m<sup>2</sup> basis, or approximately 190 times the maximum recommended daily oral dose in infants on a mg/m<sup>2</sup> basis). In rodents, the target of acute toxicity was the central nervous system, and the target of multiple-dose toxicity was the liver.

Signatures (optional):

Reviewer Signature: Jui Shah, Ph.D.

Supervisor Signature: Tim McGovern, Ph.D.

Concurrence:

**APPEARS THIS WAY  
ON ORIGINAL**

### 3.7 Appendix/attachments

Not Applicable

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

/s/  
-----

Jui Shah  
2/10/04 08:59:56 AM  
PHARMACOLOGIST

Timothy McGovern  
2/10/04 09:14:35 AM  
PHARMACOLOGIST  
I concur.

**APPEARS THIS WAY  
ON ORIGINAL**

NDA 21,621  
01/30/04

**REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA  
Chemistry Consult**

**Reviewer:** Jui R. Shah, Ph.D.

**HFD #:** 570

**Review Completion Date:** January 30, 2004

**Review Number:** Original

**IND/NDA Number:** NDA 21-621

**Sponsor (or agent):** Pfizer, Inc.

**Drug:**

Generic Name: Cetirizine

Trade Name: Zyrtec Chewable Tablets 5 & 10 mg

**Relevant INDs/NDAs/DMFs:** IND — also NDA 19-835, NDA 20-346,  
NDA 21-150.

**Drug Class:** Antihistamine (H<sub>1</sub> histamine receptor  
antagonist)

**Indication:** Seasonal and perennial allergic rhinitis with  
nasal congestion.

**Clinical Formulation:** Chewable tablets tablets, 5 and 10 mg. Tablets  
are round, purple grape flavored, bilayer  
tablets (composition tabulated below).

**APPEARS THIS WAY  
ON ORIGINAL**

Ingredient (mg/tablet)	10 mg Chewable	5 mg Chewable		
<b>ACTIVE LAYER</b>				
Cetirizine HCl	10.0	5		
β-Cyclodextrin <sup>†</sup>	[ ]	[ ]		
Acesulfame potassium*				
Colloidal silicon dioxide				
Microcrystalline cellulose				
Artificial grape flavor*				
_____				
Lactose monohydrate				
Carmines _____ Dye*				
FD&C Blue #2 _____ dye*				
Magnesium stearate				
Total	L	J		
<b>INACTIVE LAYER</b>				
Mannitol	[ ]	[ ]		
Acesulfame potassium*				
Artificial grape flavor*				
_____				
Carmines _____ Dye <sup>a</sup>				
FD&C Blue #2 _____ dye <sup>b</sup>				
Magnesium stearate				
Total			L	J

\* not USP/NF grade

<sup>a</sup> grandfathered-exempt from certification testing 21CFR 73.1100

<sup>b</sup> tested and certified by FDA, 21CFR102, 21CFR 1102, 21CFR 82.102

<sup>†</sup> Was declared GRAS on Oct. 25, 2001, Gras notice #: GRN000074

**Route of Administration:** Oral

**Description of Consult:**

Dr. Jao sent in a consult to assess the safety of betadex (betacyclodextrin, a \_\_\_\_\_ excipient in Zyrtec chewable tablets, 10 mg cetirizine HCl) which would give daily exposures of \_\_\_\_\_ mg in children 2-11 yrs and \_\_\_\_\_ mg in adults and children ages 12 yrs and up.

The consult also requests evaluation of the safety concerns for \_\_\_\_\_ Artificial Grape Flavor which would give daily exposures of \_\_\_\_\_ mg in children 2-11 yrs and \_\_\_\_\_ mg in adults and children ages 12 yrs and up.

## Evaluation:

### **Betadex ( $\beta$ -cyclodextrin) CAS #: 7585-39-9**

In October of 2001, FDA/CFSAN in GRAS notice number GRN 000074 (FDA response attached at the end of this document); stated that it had no questions about the assumption that betacyclodextrin is safe as a food additive. The notice states that JECFA considered 1.25 % betacyclodextrin a NOAEL in the 1-year dog study and allocated an acceptable daily intake (ADI) of 0-5 mg/kg (after applying a 100 fold safety factor) or up to 250 mg/d for a 50 kg person.

In carcinogenicity studies conducted in F344 rats and CD-1 mice, doses up to 675 mg/kg for 122 weeks (rats, Waner T, et al. Investigation of potential oncogenetic effects of betacyclodextrin in the rat and mouse; Arch. Toxicol. 69(9):631-639, 1995) and 93 weeks (mice, Toyoda K, et al. Carcinogenicity study of Betacyclodextrin in F344 rats; Food Chem. Toxicol. 35(3/4):331-336, 1997) were found to be non-carcinogenic.

Based on these data, the levels of betadex in Zyrtec chewable tablets appears safe and acceptable from a pharmacology/toxicology perspective.

CFSAN/OFSA proposed new regulation in 1997 to change the process for having substances declared GRAS. The reviewer had a telephone conversation Dr George Pauli (CFSAN/OFAS/Director of ADSP at 202-418-3090) about the GRAS notification process in which Dr. Pauli explained that the proposed process (which is being implemented although it has not yet been finalized) is essentially an exemption from premarket approval, where the company (based on adequate data and expert scientific advice) claims an exemption and makes the decision to go to market without FDA approval. The FDA does not review the data in depth but instead reviews the plausibility of the submitter's claim for an exemption. The FDA does have the power to notify the company if they do not agree with the claim and to stop use of the substance. There were adequate data for betacyclodextrin and it has been granted exemption (The FDA letter is attached at the end of this review) according to the GRAS exemption claim process which is already being implemented. The old (GRAS petition process) and new (GRAS exemption claim) processes are summarized below.

#### **The Current GRAS Petition Process**

The rulemaking process whereby manufacturers may petition FDA to affirm that a substance is GRAS was designed as a voluntary administrative process to provide a mechanism for official recognition of lawfully made GRAS determinations. However, the GRAS affirmation involves resource-intensive rulemaking process, including: (1) Publishing a filing notice in the Federal Register; (2) requesting comment on the petitioned request; (3) conducting a comprehensive review of the petition's data and information and comments received to the filing notice to determine whether the evidence establishes that the petitioned use of the substance is GRAS; (4) drafting a detailed explanation of why the use is GRAS (as opposed to simply being safe; and (5) publishing that explanation in the Federal Register. FDA believes that, in practice, this resource-intensive process deters many persons from petitioning the agency to affirm their independent GRAS determinations.

### Scope of the Proposed Regulations

FDA is proposing to clarify when use of a substance is exempt from the act's premarket approval requirements because such use is GRAS. In proposing these changes, FDA is: (1) Emphasizing that a GRAS substance is distinguished from a food additive by the common knowledge about the safety of the substance for its intended use; (2) identifying the types of technical evidence that form the basis of a GRAS determination; and (3) clarifying the role of publication in satisfying the general recognition standard. FDA is also proposing to amend the definition of "scientific procedures."

In addition, FDA is proposing to replace the current GRAS affirmation petition process with a notification procedure whereby any person may notify FDA of a determination that a particular use of a substance is GRAS. The submitted notice would include a "GRAS exemption claim" that would provide specific information about a GRAS determination in a consistent format. This GRAS exemption claim would include a succinct description of the "notified substance", the applicable conditions of use, and the basis for the GRAS determination (i.e., scientific procedures or experience based on common use in food) and would be dated and signed by the notifier. The GRAS exemption claim also would include a statement that the information supporting the GRAS determination was available for FDA review and copying or would be sent to FDA upon request. In addition the notice would include detailed information about the identity and properties of the notified substance and a detailed discussion of the basis for the notifier's GRAS determination.

Under the proposed notification procedure, the agency intends to evaluate whether the notice provides a sufficient basis for a GRAS determination and whether information in the notice or otherwise available to FDA raises issues that lead the agency to question whether use of the substance is GRAS. The FDA does not intend to conduct its own detailed evaluation of the data that the notifier relies on to support a determination that a use of a substance is GRAS or to affirm that a substance is GRAS for its intended use.

The proposed notification procedure streamlines the current resource-intensive petition process and would allow FDA to redirect its resources to questions that are a priority with respect to public health protection. In light of its experience in reviewing GRAS petitions, FDA believes that the substitution of the proposed notification procedure for the current GRAS petition process would not adversely affect the public health because the agency would be replacing one voluntary administrative process with a different voluntary administrative procedure. Under both the current and the proposed procedures, a manufacturer may market a substance that the manufacturer determines is GRAS without informing the agency or, if the agency is so informed, while the agency is reviewing that information. Thus, from a legal and regulatory perspective, this substitution is neutral.

\_\_\_\_\_ an organic solvent, is used during the \_\_\_\_\_ step for the manufacture of Betadex. According to GRAS notice 000074, the monograph for beta-cyclodextrin in the Food Chemical Codex lists both \_\_\_\_\_ as solvents that can be used. However, due to its known carcinogenicity the Agency recommends that \_\_\_\_\_ not be used (GRAS 000074). The applicant (DMF \_\_\_\_\_) set the acceptance criterion for \_\_\_\_\_ at not more than (NMT) \_\_\_\_\_ Based on \_\_\_\_\_ of Betadex per chewable tablet (10 mg cetirizine hydrochloride) per day the maximum daily exposure of \_\_\_\_\_ will be \_\_\_\_\_

The federal EPA limit for \_\_\_\_\_ in drinking water is 5 mcg/l. Assuming that ~2 liters of water are consumed per day, we get a maximum allowable exposure of 10 mcg/day.

The expected maximum exposure through use of Zyrtec \_\_\_\_\_, is about 12-fold lower than the acceptable daily intake through drinking water. In addition, \_\_\_\_\_ is allowed by the FDA at up to 25 ppm in decaffeinated coffee and up to 30 ppm in spice oleoresins as per 21 CFR 173.290. However, due to its potential to induce carcinogenic effects, levels of \_\_\_\_\_ should be lowered as much as technically feasible.

**Artificial Grape Flavor**

This flavoring agent is a mix of 32 different ingredients. Although the flavoring agent has not been used in any approved products, the components are commonly used in various food and drug products. The composition, percentage present, CAS & FEMA numbers as well as safety information are listed below. The daily exposures to \_\_\_\_\_ flavor would be \_\_\_\_\_ mg for children 2-11 yrs and \_\_\_\_\_ mg for adults and children ages 12 yrs and up. Please note that the calculations in the table are based on the following daily consumptions (based on serving sizes and estimated daily consumption): chewing gum: 9 g, candy: 9 g, Baked goods: 60 g, ice cream: 100g, gelatins & puddings: 100 g. The data for the use of various flavouring agents in food were obtained from FEMA (Flavor and extract manufacturers association) publications.

Ingredient	Amount/day	CAS # FEMA	Safety Information	Safety ratio
Acetic acid	<1% or <13.5 µg	64-19-7 2006	Used at 10 mg/d (N020346, Zyrtec® oral solution). Exposure from Zyrtec chewable tablets is <0.0135 mg/d. Therefore acceptable.	740
Acetophenone		98-86-2 2009	Used in amounts of 0.01 mg in oral capsules (N012911, Metopirone® or metyrapone a diagnostic agent for testing pituitary-ACTH function). Exposure from Zyrtec chewable tablets is <0.0135 mg. Therefore acceptable.	6 At a minimum of 8 caps/daily adult dose = .08 mg acetophenone
Butyric acid		107-92-6 2221	Present in chewing gum at 270 ppm or 270 µg/g or ~2.43 mg/day. Exposure from Zyrtec chewable tablets is <0.0135 mg. Therefore acceptable.	180

Caprylic acid		124-07-2 2799	Used at concentrations of 0.012% in intravenous injections 0.006-0.1044 mg (N020899). Present in baked goods at 18 ppm or 18 µg/g or 1.08 mg/d. Exposure from Zyrtec chewable tablets is <0.0135 mg. Therefore acceptable.	80 based on baked goods.
Dimethylantranilate		85-91-6 2718	Present in candy at 18 ppm or 18 µg/g or 162 µg/d. Exposure from Zyrtec chewable tablets is <0.0135 mg. Therefore acceptable.	12000
Dimethyl benzyl carbonyl acetate		151-05-3 2392	Present in candy at 22 ppm or 22 µg/g or 198 µg/d. Maximum possible exposure from Zyrtec chewable tablets is <0.0135 mg. Therefore acceptable.	14667
Ethyl acetate	1-10% or 13.5 -135 µg	141-78-6 2414	Used in gelatins and puddings at 200 ppm or 20mg/d. Maximum possible exposure from Zyrtec chewable tablets is <0.135 mg. Therefore acceptable.	148
Ethyl butyrate		105-54-4 2427	Present in candy at 98 ppm or 98 µg/g and chewing gum at 1400 ppm or 1400 µg/g, i.e. 882 µg/d and 12.6 mg/d, respectively. Maximum possible exposure from Zyrtec chewable tablets is <0.135 mg. Therefore acceptable.	6.5-93.3
Ethyl caprylate	<1% or <13.5 µg	106-32-1 2449	Present in chewing gum at 60 ppm or 60	40

			µg/g or 0.54 mg/d. Maximum possible exposure from Zyrtec chewable tablets is <0.0135 mg. Therefore acceptable.	
Ethyl decylate		110-38-3 2432	Present in baked goods at 23 ppm or 23 µg/g or 1.38 mg/d. Maximum possible exposure from Zyrtec chewable tablets is <0.0135 mg. Therefore acceptable.	102
Ethyl isobutyrate		97-62-1 2428	Present in baked goods at 200 ppm or 200 µg/g or 12.0 mg/d. Maximum possible exposure from Zyrtec chewable tablets is <0.0135 mg. Therefore acceptable.	889
Ethyl isovalerate		108-64-5 2463	Present in chewing gum at 430 ppm or 430 µg/g or 3.87 mg/d. Maximum possible exposure from Zyrtec chewable tablets is <0.0135 mg. Therefore acceptable.	287
Ethyl laurate		106-33-2 2441	<u>Methyl</u> laurate has been used in transdermal controlled release film at doses up to 17.6% (N020489). Ethyl Laurate is present in chewing gum at 39 ppm or 351 µg/d. Maximum possible exposure from Zyrtec chewable tablets is <0.0135 mg. Therefore acceptable.	26 based on ethyl laurate in chewing gum.
Ethyl propionate	1-10% or 13.5 -135	105-37-3 2526	Present in ice cream/ices at 40 ppm	~30,000

	µg		or 40 µg/g or 4000 µg/d. Maximum possible exposure from Zyrtec chewable tablets is <0.135 mg. Therefore acceptable.	
Geranyl propionate	<1% or <13.5 µg	105-90-8 2517	Present in chewing gum at 70 ppm or 70 µg/g or 630 µg/d. Maximum possible exposure from Zyrtec chewable tablets is <0.0135 mg. Therefore acceptable.	~47
trans-2-Hexenol		928-95-0 2562	Present in baked goods at 4.1 ppm or 4.1 µg/g or 246 µg/d. Maximum possible exposure from Zyrtec chewable tablets is <0.0135 mg. Therefore acceptable.	18.2
cis-3-hexenyl butyrate		16491-36-4 3402	Present in candy at 10 ppm and 5 ppm in gelatins and puddings or 90 or 500 µg/d, respectively. Maximum possible exposure from Zyrtec chewable tablets is <0.0135 mg. Therefore acceptable.	6.67-37
cis-3-hexenyl acetate		3681-71-8 3171	Present in baked goods at 0.6 ppm or 0.6 µg/g or 36 µg/d. Maximum possible exposure from Zyrtec chewable tablets is <0.0135 mg. Therefore acceptable.	2.67
trans-2-Hexenyl acetate		2497-18-9 2564	Present in baked goods at 1.7 ppm or 1.7 µg/g or 102 µg/d. Maximum possible exposure from Zyrtec chewable tablets is	7.55

			<0.0135 mg. Therefore acceptable.	
Hexelic alcohol		111-27-3 2567	Present in ice cream/ices at 26 ppm or 26 µg/g or 2.6 mg/d. Maximum possible exposure from Zyrtec chewable tablets is <0.0135 mg. Therefore acceptable.	192.6
4-hydroxy-2,5-dimethyl-3(2H) furanone		3658-77-3 3174	Present in baked goods and candy at 10 ppm or 90-600 µg/d. Maximum possible exposure from Zyrtec chewable tablets is <0.0135 mg. Therefore acceptable.	6.7-44.5
Isoamyl acetate		628-63-7 2055	Present in chewing gum at 2700 ppm or 2700 µg/g or 24.3 mg/d. Maximum possible exposure from Zyrtec chewable tablets is <0.0135 mg. Therefore acceptable.	1800
Isoamyl propionate		105-68-0 2082	Present in chewing gum at 750 ppm or 750 µg/g or 6.75 mg/d. Maximum possible exposure from Zyrtec chewable tablets is <0.0135 mg. Therefore acceptable.	500
Lauric acid		143-07-7 2614	Present in baked goods at 39 ppm or 39 µg/g or 351 µg/d. Maximum possible exposure from Zyrtec chewable tablets is <0.0135 mg. Therefore acceptable.	26
Maltodextrin	>50% or >675 µg	9050-36-6	Used in amounts of 729 mg for oral powder (N019669, Questran® or	540

			cholestyramine for treatment of primary hypercholesterolemia). Present at >50% of 1.35 mg (assuming worst case scenario of 100% maltodextrin = 1.35 mg), which is well below the marketed dose. Therefore acceptable.	
Methoxy phenyl butanone	<1% or <13.5 µg	104-20-1 2672	Present in candy at 28 ppm or 28 µg/g or 252 µg/d. Maximum possible exposure from Zyrtec chewable tablets is <0.0135 mg. Therefore acceptable.	18.7
Methyl anthranilate	10-50% or 135 - 675 µg	134-20-3 2682	Present in chewing gum at 2200 ppm or 2200 µg/g or 19.8 mg/d. Maximum possible exposure from Zyrtec chewable tablets is <675 µg/d. Therefore acceptable.	29
Modified corn starch		9005-25-8	Used in amounts of 115.84 mg/tablet/d in oral tablets (N019835, Zyrtec tablets). Maximum possible exposure from Zyrtec chewable tablets is <675 µg/d. Therefore acceptable.	170
Phenyl ethyl isobutyrate	<1% or <13.5 µg	103-48-0 2862	Present in candy at 13 ppm or 13 µg/g or 117 µg/d. Maximum possible exposure from Zyrtec chewable tablets is <0.0135 mg. Therefore acceptable.	8.6

Phenyl ethyl propionate		122-70-3 2867	Present in baked goods at 16 ppm or 16 µg/g or 960 µg/d. Maximum possible exposure from Zyrtec chewable tablets is <0.0135 mg. Therefore acceptable.	71.1
Propylene glycol		57-55-6 2940	Used in Claritin® syrup (1000 mg/d, N020641, an antihistamine). Maximum possible exposure from Zyrtec chewable tablets is <0.0135 mg. Therefore acceptable.	74,000
Propylene glycol alginate		9005-37-2 2941	Used at 75 mg/scoop in oral powder (N019669, Questran® or cholestyramine for treatment of primary hypercholesterolemia). Maximum possible exposure from Zyrtec chewable tablets is <0.0135 mg. Therefore acceptable.	5555

The safety of the ingredients in \_\_\_\_\_ grape flavor is shown above. They all have acceptable margins of safety for oral use compared to accepted use in various food products and approved drug products.

**Recommendations:**

1. The proposed use of Betadex (up to \_\_\_\_\_ mg in children ages 2-11 yrs and \_\_\_\_\_ mg in adults and children ages 12 and over) is acceptable. In addition, presence of \_\_\_\_\_ in betacyclodextrin at NMT \_\_\_\_\_ is within the acceptable federal EPA drinking water limits with a safety factor of ~12. However, due to the carcinogenic potential of \_\_\_\_\_ the limit should be set as low as technically feasible.
2. The proposed use of \_\_\_\_\_ Artificial Grape flavor is acceptable.

**Appendix:**

The following response letter to GRAS notice letter for betacyclodextrin can be found at the attached url (<http://www.cfsan.fda.gov/~rdb/opa-g074.html>).

## Agency Response Letter GRAS Notice No. GRN 000074

Gerhard Schmid, Ph.D.  
Wacker Biochem Corporation  
3301 Sutton Road  
Adrian, MI 49221

Re: GRAS Notice No. GRN 000074

Dear Dr. Schmid:

The Food and Drug Administration (FDA) is responding to the notice, dated March 23, 2001, that you submitted in accordance with the agency's proposed regulation, proposed 21 CFR 170.36 (62 FR 18938; April 17, 1997; Substances Generally Recognized as Safe (GRAS)). The Office of Food Additive Safety (OFAS; formerly the Office of Premarket Approval) received the notice on March 28, 2001 and designated it as GRAS Notice No. GRN 000074.

The subject of your notice is beta-cyclodextrin. The notice informs FDA of the view of Wacker Biochem Corporation (Wacker Biochem) that beta-cyclodextrin is GRAS, through scientific procedures, for use as a flavor carrier or protectant as described in the table below.

Food Category	Maximum Level of Use
Baked goods prepared from dry mixes Breakfast cereal Chewing gum Compressed candies	2 percent
Gelatins and puddings Flavored coffee and tea Processed cheese products Dry mix for beverages	1 percent
Flavored savory snacks and crackers	0.5 percent
Dry mixes for soups	0.2 percent

In the notice, Wacker Biochem reports that a panel of individuals (Wacker Biochem's GRAS panel) evaluated the data and information that are the basis for Wacker Biochem's GRAS determination. Wacker Biochem considers the members of its GRAS panel to be qualified by scientific training and experience to evaluate the safety of substances added to food. Wacker Biochem's GRAS panel evaluated published and unpublished data and information concerning the manufacture, intended use, and safety of beta-cyclodextrin and concluded that Wacker

Biochem's beta-cyclodextrin product that meets appropriate food grade specifications and is manufactured in accordance with good manufacturing practices is generally recognized as safe.

Wacker Biochem's notice describes generally available information about the identity, characteristic properties, and functionality of beta-cyclodextrin. Beta-cyclodextrin (Chemical Abstracts Service Registry No. 7585-39-9) is a cyclic, alpha-(1-4)-linked maltooligosaccharide consisting of seven glucose units. Due to the three-dimensional arrangement of the glucose units, the inner side of the torus-like cyclodextrin molecule is less polar than the outer side. This property enables cyclodextrins to form inclusion complexes with various organic compounds and forms the basis for the applications of cyclodextrins in foods.

Wacker Biochem's notice describes generally available information about the method of manufacture of beta-cyclodextrin. Cyclodextrins (including alpha-, beta-, and gamma cyclodextrins) are formed when bacterial-derived amylolytic enzymes (cyclodextrin-glycosyltransferases (CGTase); EC 2.4.1.19; Chemical Abstracts Service Registry No. 9030-09-5) degrade starch by a cyclization reaction. Beta-cyclodextrin is physically isolated from the enzymatic reaction mixture by the addition of a suitable organic solvent (i.e., toluene), which forms an insoluble complex with the cyclodextrin.<sup>(1)</sup> Wacker Biochem's notice states that toluene is added as a complexant to precipitate formed beta-cyclodextrin. Beta-cyclodextrin manufactured by Wacker Biochem meets the specifications for food-grade beta-cyclodextrin in the Food Chemicals Codex (FCC) 4th edition, (First Supplement), including a lead specification of not more than one part per million.

Wacker Biochem's notice describes published studies conducted with beta-cyclodextrin. These studies include 52-week toxicity studies in rats and dogs, carcinogenicity studies in mice and rats, and a 3-generation reproductive toxicity study in rats with a teratology phase. Wacker Biochem notes that these data have previously been reviewed by the Joint Food and Agriculture Organization/World Health Organization's (FAO/WHO) Expert Committee on Food Additives (JECFA) (Refs. 1 and 2). JECFA considered the No Observed Adverse Effect Level (NOAEL) in a 1-year toxicity study in the dog was 1.25 percent beta-cyclodextrin in the diet (equal to 470 mg/kg body weight/day). JECFA applied a 100-fold safety factor to this NOAEL and allocated an acceptable daily intake (ADI) of 0-5 mg/kg body weight/day for beta-cyclodextrin, equivalent to 300 mg per person per day (mg/p/day) for a 60 kg person.

In an amendment dated August 31, 2001, Wacker Biochem informed FDA that beta-cyclodextrin has been marketed in the U.S. since 1996 and that the actual amount of beta-cyclodextrin that is being used in the food industry is less than 50 tons per year. This information, combined with the knowledge that the population of the U.S. is approximately 285 million persons, and an assumption that only 10 percent of that population are "eaters" of beta-cyclodextrin, leads to an estimate of dietary exposure of approximately 4 mg/p/day for mean consumers and 9 mg/p/day at the 90th percentile.

Based on the information provided by Wacker Biochem, as well as other information available to FDA, the agency has no questions at this time regarding Wacker Biochem's conclusion that beta-cyclodextrin is GRAS under the intended conditions of use. The agency has not, however, made its own determination regarding the GRAS status of the subject use of beta-cyclodextrin. As always, it is the continuing responsibility of Wacker Biochem to ensure that food ingredients that

the firm markets are safe, and are otherwise in compliance with all applicable legal and regulatory requirements.

In accordance with proposed 21 CFR 170.36(f), a copy of the text of this letter, as well as a copy of the information in your notice that conforms to the information in proposed 21 CFR 170.36(c)(1), is available for public review and copying on the Office of Food Additive Safety's homepage on the Internet (at <http://www.cfsan.fda.gov/~rdb/opa-gras.html>).

Sincerely,  
/s/  
Alan M. Rulis, Ph.D.  
Director  
Office of Food Additive Safety  
Center for Food Safety and Applied Nutrition

### References

1. WHO (1993). Safety evaluation of certain food additives and contaminants. WHO Food Additives Series 32:173-193, World Health Organization, Geneva
2. WHO (1996). Safety evaluation of certain food additives and contaminants. WHO Food Additive Series 35:257-268, World Health Organization, Geneva

---

<sup>(1)</sup>As you discussed by telephone with OFAS representatives on July 13, 2001, the monograph for beta-cyclodextrin in the Food Chemicals Codex lists both \_\_\_\_\_ as solvents that can be used. A study conducted by the National Toxicology Program reports that \_\_\_\_\_ is carcinogenic in B6C3F1 mice, causing increased incidences of hepatocellular carcinomas in males and females and increased incidence of hepatocellular adenomas in females. To minimize the potential that residues of \_\_\_\_\_ would be present in food products that contain beta-cyclodextrin, FDA recommends that \_\_\_\_\_ not be used. In that telephone conversation, you confirmed that Wacker Biochem does not use \_\_\_\_\_

**APPEARS THIS WAY  
ON ORIGINAL**

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

/s/

-----  
Jui Shah  
1/30/04 10:23:07 AM  
PHARMACOLOGIST

Timothy McGovern  
1/30/04 11:14:40 AM  
PHARMACOLOGIST  
I concur.

**APPEARS THIS WAY  
ON ORIGINAL**