

- statistically significant increase in morphological transformation at 1 dose (MD) of (b) (4) in non-statistically significant dose-responsive manner from LD with no HD data due to cell toxicity
- Degradants of olopatadine, (b) (4) (b) positive in the SHE Cell Transformation assay in a non-GLP study

**Study no.:** Alcon TDOC-0001870 (Technical Report E-04-003)

**Volume # and page #:** volume 57, pages 1-45

**Conducting laboratory and location:** (b) (4)

**Date of study initiation:** February 13, 2004 (March 19, 2004 report date)

**GLP compliance:** no (spirit of GLP and draft OECD guidance)

**QA reports:** yes ( ) no ( x )

**Drug lot # and % purity:** (b) (4) (olopatadine degradant) – lot # 10489:030 and (b) (4) %  
(b) (4) (olopatadine degradant) – lot # M-Ref 9502 and (b) (4) %

### Methods

Strains/species/cell line: Syrian Hamster Embryo cells

Doses used in definitive study: Low (LD), MD (mid), and HD (high) doses of 15, 35, & 50 ug/mL (b) (4) and 10, 90, & 170 ug/mL (b) (4)

Basis of dose selection: dose range finding studies – 9 doses from (b) (4)

Negative controls: culture medium

Positive controls: benz[a]pyrene at 5 ug/mL

Incubation and sampling times: 7 days

### Results:

Study validity:

- not valid as non-GLP, but conducted in spirit of GLP and draft OECD guidance re protocol
- 3 doses
  - HD > 50% decreased relative plating efficiency (RPE)
  - LD RPE similar to negative control
  - MD
- reference to methods using guideline SHE Cell morphological transformation assay protocol (e.g., pH 6.65-6.75, plate for expected 25-45 colonies per plate at end of incubation period, 25-45 dishes per treatment group, 3 doses in transformation assay)
- criteria for positive response – for transformation assay, 2 doses with statistically

significant increases in morphological transformation frequency or 1 dose with statistically significant increase in mutation frequency with a statistically significant trend test

Study outcome:

- (b) (4) positive as 2 doses (LD & MD) with statistically significant increases in morphological transformation frequency compared to negative control (see table)
  - MD increase in morphological transformation frequency, but not statistically significant
- (b) (4) positive as 1 dose with statistically significant increase in morphological frequency compared to negative control and apparent dose response increase from LD to MD (see table)
  - HD had no viable cells (only 2 doses)
- sponsor considered results equivocal and of questionable value
  - (b) (4) data no dose responsive
  - (b) (4) data not statistically significant for trend test
  - non-GLP study
  - opinion that assay is not adequately validated for use in regulatory decisions
- Degradants of Olopatadine, (b) (4) are positive in the SHE Cell Morphological Transformation assay

SHE Cell Assay with Degradants (b) (4)					
	negative control	positive control	low dose	mid dose	high dose
MT frequency (%) (b)	0.2 (100% RPE)	1.9* (126% RPE)	1.9* (109% RPE)	0.8 (72% RPE)	1.7* (17% RPE)
MT frequency (%) (b)	0.5 (100% RPE)	1.9* (93% RPE)	0.8 (100% RPE)	1.6* (49% RPE)	ND (0% RPE)

\* - statistically significant  
 MT – morphological transformation  
 ND – not determined as nothing to count  
 RPE – relative plating efficiency

**6) Study title:** Mammalian Erythrocyte Micronucleus Test Using a Combined Solution Containing (b) (4) and AL-4943A (Olopatadine)

**Key findings:**

- combined doses of (b) (4) and AL-4943A (Olopatadine) negative in single dose mouse bone marrow micronucleus at dose ratio of (b) (4) respectively
  - (b) (4) and 22, 73, and 220 mg/kg olopatadine

- test results not considered adequate for assessment of genotoxic potential of olopatadine degradant, (b) (4), based on this spiking study as (b) (4) was not tested individually at adequate doses (e.g., frank toxicity or limit dose of 2000 mg/kg)

**Study no.:** TDOC-0000653 (Alcon Technical Report N-03-064)

**Volume # and page #:** volume 57, pages 1-58

**Conducting laboratory and location:** (b) (4)

**Date of study initiation:** July 28, 2003 (November 26, 2003 report date)

**GLP compliance:** yes (USFDA, USEPA, UK, Japan, OECD)

- except for concentration analysis of dosing formulations (conducted by sponsor) and stability of test article (not conducted)

**QA reports:** yes ( x ) no ( )

**Drug lot # and % purity:** olopatadine: lot # AL-4943A-09 and 99.5%

(b) (4) lot # (b) (4) (b) (4)

## Methods

Strains/species/cell line: male and female ICR mice

Doses used in definitive study: (dosing solution with ratio of (b) (4) olopatadine and (b) (4))

- untreated and vehicle control (dose volume 30 mL/kg) groups
  - 10 mice/sex ( 5 for 24 hour and 48 hour bone marrow collection periods
- 30 mg/kg (LD) – 5 mice/sex for 24 hour evaluation at dose volume of 3 mL/kg
- 100 mg/kg (MD) – 5 mice/sex for 24 hour evaluation at dose volume of 10 mL/kg
- 300 mg/kg (HD) – 15 mice/sex for 24 hour and 48 hour evaluation with 5 extra/sex at dose volume of 30 mL/kg
- positive control of 50 mg/kg – 5/sex for 24 hour evaluation at dose volume of 30 mL/kg
- actual doses
  - LD – 22 mg/kg olopatadine and (b) (4)
  - MD – 73 mg/kg olopatadine and (b) (4)
  - HD – 220 mg/kg olopatadine and (b) (4)

Basis of dose selection:

- pilot toxicity study by intraperitoneal administration using dosing solutions with ratio of (b) (4) olopatadine and (b) (4)
  - 2 male mice at a single dose of 240 mg/kg at 20 mL/kg dose volume, 360 mg/kg at dose volume of 30 mL/kg, and 480 mg/kg at dose volume of 40 mL/kg
  - 2 male mice at 2 single doses (2 hours apart) with total dose of 720 mg/kg at a total dose volume of 30 mL/kg
  - 5 male and 5 female mice at 2 single doses of 0 mg/kg (vehicle AA79FD) at a total dose volume of 40 mL/kg and 960 mg/kg at a total dose volume of 40 mL/kg
- mice observed for clinical signs of toxicity for 3 days and weighed on days 1 and 3 after dose administration
  - 1 mouse at 480 mg/kg, 2 mice at 720 mg/kg and all mice at 960 mg/kg found

- dead on day 1 post dosing
- clinical signs in surviving mice
  - lethargy and piloerection in all survivors
  - prostration and irregular at 360 and 480 mg/kg
  - body weight changes
    - 240 mg/kg - -3.3% day 1 and -1% day 3
    - 360 mg/kg - -4.3% day 1 and +2.2% day 3
    - 480 mg/kg - -6.4% day 1 and -12.8% day 3
    - vehicle control - +1.4% (males) and + 2.6% (females) day 3

Negative controls: untreated and vehicle AA79FD (0.01% benzalkonium chloride, (b) (4) EDTA, (b) (4) Povidone, (b) (4) NaCl, (b) (4) dibasic sodium phosphate, and water)

Positive controls: 50 mg/kg cyclophosphamide monohydrate (CP) in sterile water  
- 30 mL/kg of 1.67 mg/mL concentration

Incubation and sampling times:

- bone marrow from distal femur collected at 24 hours (untreated control, vehicle control, LD, MD, and positive control groups)
- bone marrow from distal femur collected at 48 hours (untreated control, vehicle control, and HD groups)

**Results:**

Study validity:

- duplicate slides per mouse
- scored in blind evaluation
- evaluate 2000 polychromatic erythrocytes (PCEs) per animal for presence of micronuclei (MN)
- note proportion of PCEs to total erythrocytes for 1000 erythrocytes
- valid study
  - negative controls MN/PCE ratio not greater than 0.5% (5/1000)
  - positive control MN/PCE ratio statistically significant increase

Study outcome:

- adequate dose for this test based on pilot toxicity study data and treatment-related clinical signs observed in definitive study that included mortality at HD (see table)
- no increase in micronuclei due to treatment
- combined doses of (b) (4) and AL-4943A (Olopatadine) negative in single dose mouse bone marrow micronucleus at dose ratio of (b) (4) and (b) (4) respectively
  - 3, 10 and 30 mg/kg (b) (4) and 22, 73, and 220 mg/kg olopatadine
- test results not considered adequate for assessment of genotoxic potential of olopatadine degradant, (b) (4) based on this spiking study as (b) (4) was not tested individually at adequate doses (e.g., toxicity or limit dose of 2000 mg/kg)

Definitive Micronucleus Study - Clinical Signs Following a Single Dose Administration of Two Combined Test Articles, AL-4943A and (b) (4) in ICR Mice

Treatment	Observation	Number of Animals With Observed Signs/Total Number of Animals Dosed		Number of Animals Died/Total Number of Animals Dosed	
		Males	Females	Males	Females
Negative Control Untreated	Normal	10/10	10/10	0/10	0/10
Vehicle (30 mL/kg)	Piloerection	10/10	10/10	0/10	0/10
AL-4943A (b) (4) 30 mg/kg (10 mg/mL x 3 mL/kg)	Lethargy Piloerection	5/5 5/5	5/5 5/5	0/5	0/5
100 mg/kg (10 mg/mL x 10 mL/kg)	Lethargy Piloerection	5/5 5/5	5/5 5/5	0/5	0/5
300 mg/kg (10 mg/mL x 30 mL/kg)	Lethargy Piloerection Convulsions Irregular breathing	14/15 14/15 2/15 14/15	14/15 14/15 1/15 14/15	1/15	1/15
Cyclophosphamide 50 mg/kg (1.67 mg/mL x 30 mL/kg)	Normal	5/5	5/5	0/5	0/5

-Summary of Bone Marrow Micronucleus Analysis Following a Single Dose Administration of Two Combined Test Articles, AL-4943A and (b) (4) in ICR Mice

Treatment	Sex	Time (hr)	Number of Mice	PCE/Total Erythrocytes (Mean +/- SD)	Change from Control (%) <sup>2</sup>	Micronucleated Polychromatic Erythrocytes	
						Number per 1000 PCEs (Mean +/- SD)	Number per PCEs Scored <sup>1</sup>
<b>Negative Control (Untreated)</b>							
	M	24	5	0.460 ± 0.04	—	0.9 ± 0.42	9 / 10000
	F	24	5	0.476 ± 0.06	—	0.4 ± 0.22	4 / 10000
<b>Vehicle specified by the sponsor</b>							
30 mL/kg	M	24	5	0.530 ± 0.04	15	0.1 ± 0.22	1 / 10000
	F	24	5	0.497 ± 0.07	4	0.4 ± 0.42	4 / 10000
<b>AL-4943A(b) (4)</b>							
30 mg/kg	M	24	5	0.463 ± 0.07	1	0.6 ± 0.22	6 / 10000
	F	24	5	0.503 ± 0.06	6	0.6 ± 0.22	6 / 10000
100 mg/kg	M	24	5	0.481 ± 0.04	5	0.7 ± 0.45	7 / 10000
	F	24	5	0.518 ± 0.05	9	0.6 ± 0.42	6 / 10000
300 mg/kg	M	24	5	0.462 ± 0.03	0	0.5 ± 0.35	5 / 10000
	F	24	5	0.482 ± 0.07	1	0.3 ± 0.27	3 / 10000
<b>CP</b>							
50 mg/kg	M	24	5	0.357 ± 0.04	-22	33.5 ± 5.68	*335 / 10000
	F	24	5	0.399 ± 0.11	-16	24.2 ± 4.52	*242 / 10000
<b>Negative Control (Untreated)</b>							
	M	48	5	0.506 ± 0.04	—	0.7 ± 0.57	7 / 10000
	F	48	5	0.456 ± 0.03	—	0.5 ± 0.35	5 / 10000
<b>Vehicle specified by the sponsor</b>							
30 mL/kg	M	48	5	0.490 ± 0.05	-3	0.7 ± 0.27	7 / 10000
	F	48	5	0.529 ± 0.04	16	0.6 ± 0.42	6 / 10000
<b>AL-4943A(b) (4)</b>							
300 mg/kg	M	48	5	0.473 ± 0.06	-7	0.7 ± 0.27	7 / 10000
	F	48	5	0.469 ± 0.06	3	0.6 ± 0.22	6 / 10000

<sup>1</sup>\*Statistically significant, p ≤ 0.05 (Kastenbaum-Bowman Tables)

<sup>2</sup>PCE/Total Erythrocytes Percent Change from Negative Control = ((Treatment group + Negative control) - 1) X 100

7) Study title: Mammalian Erythrocyte Micronucleus Test of and AL-4943A (Olopatadine) and (b) (4)

Key findings:

- combined doses of (b) (4) and AL-4943A (Olopatadine) negative in single dose mouse bone marrow micronucleus study at dose ratio of 8% and 92%, respectively
  - (b) (4) mg/kg (b) (4) and 28, 92, and 276 mg/kg olopatadine

- test results not considered adequate for assessment of genotoxic potential of olopatadine degradant, (b) (4) based on this spiking study as (b) (4) was not tested individually at adequate doses (e.g., frank toxicity or limit dose of 2000 mg/kg)

**Study no.:** TDOC-0001783 (Alcon Technical Report N-04-068)

**Volume # and page #:** volume 58, pages 1-106

**Conducting laboratory and location:** (b) (4)

**Date of study initiation:** May 3, 2004(October 5, 2004 report date)

**GLP compliance:** yes (USFDA, USEPA, UK, Japan, OECD)

- except for concentration analysis of dosing formulations and stability of test article

**QA reports:** yes ( x ) no ( )

**Drug lot # and % purity:** olopatadine: AL-4934A-09, 99.5%

(b) (4) (b) (4) (AA92AM), (b) (4)

## Methods

Strains/species/cell line: male and female ICR mice

Doses used in definitive study: (dosing solution with ratio of (b) (4) olopatadine and (b) (4))

- untreated and vehicle control (dose volume 30 mL/kg) groups
  - 10 mice/sex (5 for 24 hour and 48 hour bone marrow collection periods)
- 30 mg/kg (LD) – 5 mice/sex for 24 hour evaluation at dose volume of 3 mL/kg
- 100 mg/kg (MD) – 5 mice/sex for 24 hour evaluation at dose volume of 10 mL/kg
- 300 mg/kg (HD) – 15 mice/sex for 24 hour and 48 hour evaluation with 5 extra/sex at dose volume of 30 mL/kg
- positive control of 50 mg/kg – 5/sex for 24 hour evaluation at dose volume of 30 mL/kg
- 6 toxicokinetic animals/sex/test article treatment groups for blood sampling at 0.5 and 1 hour after dosing
- actual doses
  - LD – 28 mg/kg olopatadine and (b) (4)
  - MD – 92 mg/kg olopatadine and (b) (4)
  - HD – 276 mg/kg olopatadine and (b) (4)

Basis of dose selection:

- pilot toxicity study by intraperitoneal administration using dosing solutions with ratio of (b) (4) olopatadine and (b) (4)
  - 5 mice/sex at a single dose of 240 mg/kg at 20 mL/kg dose volume, 360 mg/kg at dose volume of 30 mL/kg, and 480 mg/kg at dose volume of 40 mL/kg
  - 5 mice/sex at 2 single doses (2 hours apart) with total dose of 720 mg/kg at a total dose volume of 30 mL/kg
  - 5 mice/sex at 2 single doses of 0 mg/kg (vehicle AA92AN) at a total dose volume of 40 mL/kg and 960 mg/kg at a total dose volume of 40 mL/kg
- mice observed for clinical signs of toxicity for 3 days and weighed on days 1 and 3 after dose administration

- all mice at 480, 720, & 960 mg/kg found dead within 3 days post dosing
- clinical signs in surviving mice
  - lethargy in all survivors
  - piloerection and tremors in all mice at 360 mg/kg
  - crust eyes in 4/5 females and cool to the touch in 2/5 females at 360 mg/kg
- body weight changes
  - 240 mg/kg - -1.8% day 1 and -0.9% day 3 (males) and -0.4% day 1 and 0% day 3 (females)
  - 360 mg/kg - -2.7% day 1 and -10.3% day 3 (males) and -4.0% day 1 and -4.9% day 3 (females)
  - vehicle control - +2.8% (males) and +3.0% (females) day 3

Negative controls: untreated and vehicle AA92AN (0.01% benzalkonium chloride, (b) (4) disodium EDTA, (b) (4) Povidone, (b) (4) NaCl, (b) (4) dibasic sodium phosphate, and water)

Positive controls: 50 mg/kg cyclophosphamide monohydrate (CP) in sterile water  
- 30 mL/kg of 1.67 mg/mL concentration

Incubation and sampling times:

- bone marrow from distal femur collected at 24 hours (untreated control, vehicle control, LD, MD, and positive control groups)
- bone marrow from distal femur collected at 48 hours (untreated control, vehicle control, and HD groups)

**Results:**

Study validity:

- duplicate slides per mouse
- scored in blind evaluation
- evaluate 2000 polychromatic erythrocytes (PCEs) per animal for presence of micronuclei (MN)
- note proportion of PCEs to total erythrocytes for 1000 erythrocytes
- valid study
  - negative controls MN/PCE ratio not greater than 0.5% (5/1000) except for untreated males with value of 0.9%
  - positive control MN/PCE ratio statistically significant increase

Study outcome:

- marginally adequate dose for this test based on pilot toxicity study data and treatment-related clinical signs observed in definitive study in animals at only HD of lethargy and piloerection (see table)
- no increase in micronuclei due to treatment
- combined doses of (b) (4) and AL-4943A (Olopatadine) negative in single dose mouse bone marrow micronucleus at dose ratio of (b) (4) and (b) (4), respectively
  - 2, 8 and (b) (4) and 28, 92, and 276 mg/kg olopatadine
- test results not considered adequate for assessment of genotoxic potential of

olopatadine degradant<sup>(b) (4)</sup> based on this spiking study as <sup>(b) (4)</sup> was not tested individually at adequate doses (e.g., toxicity or limit dose of 2000 mg/kg)

**Definitive Micronucleus Study - Clinical Signs Following a Single Dose Administration of AL-4943A and <sup>(b) (4)</sup> in ICR Mice**

Treatment	Observation*	Number of Animals With Clinical Signs/Total Number of Animals Dosed		Number of Animals Died/Total Number of Animals Dosed	
		Males	Females	Males	Females
Untreated	Normal	10/10**	10/10**	0/10	0/10
Vehicle specified by Sponsor at 30 mL/kg	Normal	10/10**	10/10**	0/10	0/10
AL-4943-A <sup>(b) (4)</sup> 30 mg/kg (actual: 29 mg/kg)	Normal	5/5	5/5	0/5	0/5
100 mg/kg (actual: 96 mg/kg)	Normal	5/5	5/5	0/5	0/5
300 mg/kg (actual: 288 mg/kg)	Lethargy Piloerection	15/15*** 15/15***	15/15*** 15/15***	0/15	0/15
Cyclophosphamide 50 mg/kg	Normal	5/5	5/5	0/5	0/5

\*Observations of animals assigned for toxicokinetic evaluation are not presented

\*\* Five animals/sex/group for each of the 24 and 48 hour time point

\*\*\* Five animals/sex/group for each of the 24 and 48 hour time point and 5 extra contingency animals in case deaths occurred during treatment

**Summary of Bone Marrow Micronucleus Analysis Following a Single Dose Administration of AL-4943A and (b) (4) in ICR Mice**

Treatment	Sex	Time (hr)	Number of Mice	PCE/Total Erythrocytes (Mean +/- SD)	Change from Control <sup>2</sup> (%)	Micronucleated Polychromatic Erythrocytes	
						Number/1000 PCEs (Mean +/- SD)	Number/PCEs Scored <sup>1</sup>
Untreated	M	24	5	0.495 ± 0.04	---	0.9 ± 0.22	9 / 10000
	F	24	5	0.473 ± 0.01	---	0.5 ± 0.00	5 / 10000
Vehicle specified by the Sponsor							
30 mL/kg	M	24	5	0.450 ± 0.02	-9	0.6 ± 0.42	6 / 10000
	F	24	5	0.497 ± 0.05	5	0.4 ± 0.42	4 / 10000
AL-4943A (b) (4)							
30 mg/kg (actual: 29 mg/kg)	M	24	5	0.494 ± 0.07	0	0.7 ± 0.45	7 / 10000
	F	24	5	0.483 ± 0.03	2	0.7 ± 0.27	7 / 10000
100 mg/kg (actual: 96 mg/kg)	M	24	5	0.462 ± 0.03	-7	0.5 ± 0.35	5 / 10000
	F	24	5	0.456 ± 0.04	-4	0.3 ± 0.27	3 / 10000
300 mg/kg (actual: 288 mg/kg)	M	24	5	0.476 ± 0.09	-4	0.7 ± 0.27	7 / 10000
	F	24	5	0.454 ± 0.04	-4	0.2 ± 0.27	2 / 10000
Cyclophosphamide							
50 mg/kg	M	24	5	0.350 ± 0.04	-29	16.8 ± 5.81	*168 / 10000
	F	24	5	0.341 ± 0.04	-28	20.2 ± 7.52	*202 / 10000
Untreated							
	M	48	5	0.489 ± 0.05	---	0.3 ± 0.27	3 / 10000
	F	48	5	0.437 ± 0.06	---	0.5 ± 0.35	5 / 10000
Vehicle specified by the Sponsor							
30 mL/kg	M	48	5	0.485 ± 0.06	-1	0.7 ± 0.27	7 / 10000
	F	48	5	0.453 ± 0.05	4	0.4 ± 0.42	4 / 10000
AL-4943A (b) (4)							
300 mg/kg (actual: 288 mg/kg)	M	48	5	0.464 ± 0.03	-5	0.5 ± 0.50	5 / 10000
	F	48	5	0.475 ± 0.06	9	0.4 ± 0.22	4 / 10000

<sup>1</sup>\*Statistically significant, p ≤ 0.05 (Kastenbaum-Bowman Tables)

<sup>2</sup>PCE/Total Erythrocytes Percent Change from Negative Control = ((Treatment group ÷ Negative control) - 1) X 100

**Conclusions:**

Based on the results of the seven genotoxicity assays, (b) (4) were determined to be genotoxic in the mouse lymphoma and SHE cell assays. These degradants, as well as (b) (4) should be considered genotoxic degradants/impurities and controlled as indicated (see recommendation).

**Recommendation:**

Based on the positive genotoxicity results of (b) (4) (Mouse Lymphoma Assays and Syrian Hamster Embryo Assays), olopatadine degradants (b) (4) (b) as well as (b) (4) structural analog and structural alert, (b) (4) should be controlled to levels of <0.1% of active ingredient or the sponsor should or conduct a carcinogenicity assay with the isolated impurities.

Gary P. Bond, Ph.D., DABT  
Reviewing Pharmacologist

C. Joseph Sun, Ph.D.  
Supervisory Pharmacologist

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/s/

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Gary Bond  
6/14/05 10:09:29 AM  
PHARMACOLOGIST

Joseph Sun  
6/15/05 10:05:59 AM  
PHARMACOLOGIST  
I concur.

**DIVISION OF PULMONARY DRUG PRODUCTS**  
**REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA**  
**Chemistry Consult**

**IND/NDA: 21-861**

**Date of Consult Request:** February 2, 2005

**Date of Submission:** December 21, 2004

**Reviewer:** Gary P. Bond, Ph.D., DABT

**Date Completed:** June 1, 2005

**Sponsor:** Alcon Research Ltd.

**Drug Name:** Patanase (olapatadine HCl)

**Class:** antihistamine and mast cell stabilizer

**Route of administration:** intranasal

**Daily Dose:** 0.6% olapatadine as single doses of 2x 100 ul spray/nostril BID

**Response to Chemistry Consult as Requested by Craig M. Bertha**

**Description of the Consult**

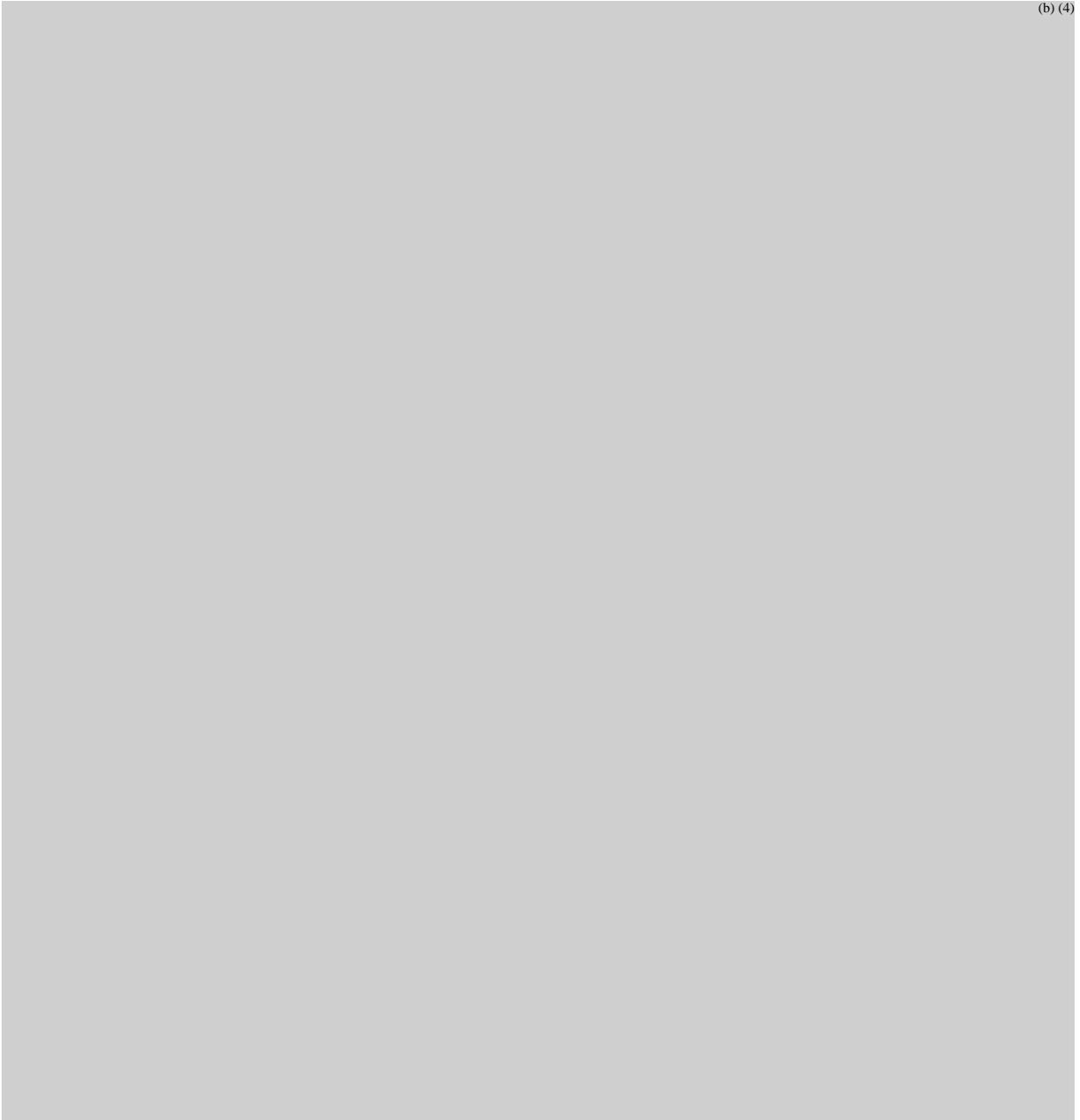
This consult request is for the evaluation of the toxicological assessment tests of biological reactivity for various packaging components. Testing for biological reactivity was conducted using *in vitro* and *in vivo* tests according to ISO 10993 in GLP studies that were audited for quality assurance purposes.

**Review and Evaluation:**

The following packaging components were tested:

(b) (4)

(b) (4)



(b) (4)

**Conclusion** – For all tests, all components were negative for biological reactivity in valid studies according to ISO 10993, consistent with USP sections 87 & 88.

**Recommendation** – The packaging components tested for biological reactivity [redacted] (b) (4)  
[redacted]  
[redacted] tested negative according to ISO 10993, consistent with USP sections 87 & 88.

Gary P. Bond, Ph.D., DABT  
Reviewing Pharmacologist

C. Joseph Sun, Ph.D.  
Supervisory Pharmacologist

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/s/

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Gary Bond  
6/1/05 02:24:17 PM  
PHARMACOLOGIST

Joseph Sun  
6/2/05 12:43:19 PM  
PHARMACOLOGIST  
I concur.

NDA 21-day Pharmacology fileability check list

NDA No: 21-861

Date of submission: Dec 27, 2004

Date of 45-day fileability meeting: 2/10/05

Date of check list:

(1) On its face, is the pharm/tox section of the NDA organized in a manner to allow substantive review? Yes

(2) On its face, is the pharm/tox section of the NDA legible for review? Yes

(3) Are final reports of all required and requested preclinical studies submitted in this NDA?

	Yes	No	NA
Pharmacology	( X )	( )	( )
ADME	( X )	( )	( )
Toxicology (duration, route of administration and species specified)			
acute	( X )	( )	( )
subchronic and chronic studies	( X )	( )	( )
reproductive studies	( X )	( )	( )
carcinogenicity studies	( X )	( )	( )
mutagenicity studies	( X )	( )	( )
special studies	( X )	( )	( )
others	( X )	( )	( )
EA (items 7, 8, 9, 10, 11 and 15)	( )	( )	( )

(4) If the formulation to be marketed is different from the formulation used in the toxicology studies, is repeating or bridging the studies necessary?

Yes already done – included for review in NDA

If yes, has the applicant made an appropriate effort to repeat the studies using the ‘to be marketed’ product, to bridge the studies or to explain why such repetition or bridging should not be required? Yes

(5) Are the proposed preclinical labeling sections (carcinogenesis, mutagenesis and impairment of fertility, pregnancy category and over dosage) appropriate (including human dose multiples expressed in either mg/m<sup>2</sup> or comparative systemic exposure levels) and in accordance with 201.57? Yes, on cursory review they appear acceptable.

(6) Has the applicant submitted all special studies/data requested by the Division prior to the submission including but not limited to pre-NDA discussion? Yes

(7) On its face, does the route of administration used in the pivotal toxicity studies appear to be the same as the intended clinical route? **Yes, for toxicity studies, carcinogenicity studies were oral as were reprotoxicity studies. No IN carcinogenicity studies are required unless preneoplastic changes seen in chronic toxicity studies.**

(8) Has the applicant submitted a statement(s) that all of the toxicity studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations? **Upon cursory review, studies appear to be GLP.**

(9) Has the applicant submitted any studies or data to address any impurity or extractable issues (if any)? **Yes**

(10) Are there any outstanding preclinical issues? **No**

(11) From a preclinical perspective, is this NDA fileable? **Yes**

If "yes", should any additional information/data be requested? **No**

NDA 45-day Planning Timeline

NDA NO: 21861

Date of 45-day planning meeting: 2/10/05

Date of planning timeline: 2/10/05

User Fee Due Date: October 27, 2005

Final review completion date:

Milestone Date  
To be Determined

Pharmacology and ADME

Toxicology

General toxicity studies

Carcinogenicity studies and mutagenicity studies

a. Statistical consult request for CA studies

b. Submission of CA studies for CAC's concurrence

Reproductive studies

Special studies and Others

Labeling

EA

Review Pharmacologist/Toxicologist: Jui Shah, Ph.D.

Team Leader: Tim McGovern, Ph.D.

HFD-570/Division File

HFD-570/Reviewer

HFD-570/Team Leader

The purpose of the 45-day NDA planning meeting are multiple and include the following:

- (1) follow-up on any outstanding filing issues
- (2) identify any necessary consults
- (3) identify needed information not usually provided in the pharm/tox section
- (4) apprise other team members of significant pharm/tox issues that have been identified
- (5) plan subsequent team meetings
- (6) develop the time line for the completion of the pharm/tox review

By the 45-day planning meeting, the milestone dates for the NDA review as shown in the attachment (45-day planning timeline) should also be completed. Milestone dates may be modified due to changes in workload or other circumstances. In such situations, discuss with your team leader anticipated delays in completing the review and set a revised schedule.

The 45-day pharmacology fileability check list and the planning timeline should be placed in the division file within 60 days of the NDA submission.

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/s/

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Jui Shah  
2/17/05 07:34:55 AM  
PHARMACOLOGIST

Timothy McGovern  
2/17/05 07:43:40 AM  
PHARMACOLOGIST  
I concur.