Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Numbers	**17-577, 18-211, 20-897 (Supplements)**	***Brand Name***	**DITROPAN IR, Syrup, & XL**
OCPB Division (I, II, III)	**DPE II (HFD 870)**	***Generic Name***	**Oxybutynin chloride**
Medical Division	**DRUDP (HFD 580)**	***Drug Class***	**Antimuscarinic**
OCPB Reviewer	**Dhruba J. Chatterjee, Ph.D.**	***Indication(s)***	**Urinary Incontinence**
OCPB Team Leader	**Ameeta Parekh, Ph.D.**	***Dosage Form***	**IR tabs, Syrup & XL tabs**
OCPB Pharmacometrician	**He Sun, Ph.D.**	***Dosing Regimen***	**BID, TID & QD**
Date of Submission	**10/17/2002**	***Route of Administration***	**Oral**
Estimated Due Date of OCPB Review	**3/30/2003**	***Sponsor***	**ALZA (J & J) Corp.**
PDUFA Due Date	**4/17/2003**	***Priority Classification***	**3S**
Division Due Date	**4/10/2003**		

Clin. Pharm. and Biopharm. Information		**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
	"X" if included at filing			
STUDY TYPE		**6**		
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:	X			
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:	**X**			
geriatrics:				
body wt.				
renal impairment:				
hepatic impairment:				
PD:				

Phase 2:				
Phase 3:	**X**			
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	**X**			
Data sparse:	**X**			
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				

Filability and QBR comments		***Comments***
	"X" if yes	
Application filable?	**X**	
Comments sent to firm ?		
QBR questions (key issues to be considered)	**Is there enough PK and or PD information that may be included in the respective labels under pediatrics?**	
Other comments or information not included above	**This is a submission with study reports following PK/PD and efficacy/safety study in pediatric population.**	
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

OCPB Briefing held on 4/11/03, and attended by DJ Chatterjee, A. Parekh,

CC: NDA XX-XXX, HFD-850(Electronic Entry or Lee), HFD-XXX(CSO), HFD-8XX(TL, DD, DDD), CDR (B. Murphy)

Clinical Pharmacology & Biopharmaceutics Review

NDA:	17-577, 18-211, 20-897
Product Trade Name:	DITROPAN Syrup, IR Tablet, XL Tablets
Active Ingredient/s:	Oxybutynin chloride
Indication:	Overactive bladder/urinary incontinence
Submission Dates:	10/17/2002 (pediatric supplemental NDA)
Sponsor:	ALZA Corporation (Johnson & Johnson)
Submission/Priority Type:	Supplement
Reviewer:	Dhruba J. Chatterjee, Ph.D.
Team Leader:	Ameeta Parekh, Ph.D.
Pharmacometrics:	He Sun, Ph.D.

Overall Clinical Pharmacology and Biopharmaceutics Summary

? Following review of the three supplemental NDAs, the main outcome was incorporation of additional information into the DITROPAN (IR, Syrup and XL) labels following use in pediatric population.

? Based on non-parametric analysis of the pharmacokinetic data, pharmacokinetic profiles and parameters were obtained. Those plots and parameter tables are hereby included in the labels for DITROPAN IR tablets, Syrup and XL tablets (please see details under **Clinical Pharmacology**).

? Pharmacokinetic plots and parameter tables were finalized following detailed discussion with the sponsor via teleconference and continuous communication.

Background

Questions addressed in this section:
? What is urinary incontinence?
? What is the pharmacologic rationale for use of this drug?
? What is the regulatory history of this product?
? What are other available alternatives?
? What CPB studies have been submitted in support of this NDA?

Urinary incontinence, the involuntary loss of urine, is a clinical condition. Urinary incontinence affects all age groups and is particularly common in the elderly. Overactive bladder is one cause of urinary incontinence. Overactive bladder is a condition characterized by involuntary detrusor contractions during the bladder filling phase, which may be spontaneous or provoked, and which the patient cannot suppress. Overactive bladder causes troublesome symptoms, which result in a significant impairment of normal social functioning. These symptoms include frequency, nocturia, urgency, and urge incontinence. Uncontrolled bladder contractions give the feeling of urgency, and exaggerated sense of needing to urinate. In turn, urgency causes frequency and nocturia; voiding at abnormally reduced intervals. Urgency may lead to urge incontinence if the sphincter mechanism is unable to resist the uncontrolled bladder contraction. Patients may have any combination of these symptoms. Frequency may be a primary symptom of the underlying disease or may be secondarily self-induced to avoid incontinence. Frequency and urgency mean that patients must make frequent visits to the toilet, so that daily activities are conditioned by the need to be near a toilet. Sleeping patterns are disrupted when these symptoms occur at night.

Urinary incontinence is not solely due to overactive bladder. Stress urinary incontinence, particularly common in women, is a type of urinary incontinence in which the urethral closure mechanism is compromised and urine escapes when intra-abdominal pressure increases sufficiently. Leakage may also occur as a result of a combination of overactive bladder and the compromised urethral closure mechanism. Patients sometimes present with symptoms of both urge and stress incontinence, called mixed incontinence. Mixed incontinence is common in women, especially older women. Involuntary loss of urine associated with overdistension of the bladder is termed overflow incontinence. Overflow incontinence may be caused by an underactive or acontractile detrusor, or may be due to bladder outlet or urethral obstruction leading to overdistension and overflow. Urine loss may be caused by factors outside the lower urinary tract, such as, chronic impairment of physical or cognitive functioning, or both, a condition termed as functional incontinence. Urine loss may also occur without any warning or sensory awareness, such as, in paraplegics and in some patients without overt neurologic dysfunction.

Normal bladder contractions are mediated primarily through cholinergic muscarinic receptor stimulation. These receptors are believed to control normal bladder contractions, and possibly play a major role in overactive bladders. Hence, antimuscarinic drugs have

almost become a standard of therapy for overactive bladder. However, a most common side effect of these class of drugs is dry mouth (due to its effect on the salivary glands).

Several drug therapies including antimuscarinics, antispasmodics, tricyclic antidepressants and estrogen are available to treat the disease. Besides oxybutynin, tolterodine (another antimuscarinic) is available in the market as IR (DETROL) and extended release (DETROL LA) formulations.

Oxybutynin is a competitive muscarinic receptor antagonist. Oxybutynin has been available as IR tablets and syrup. More recently, an extended release formulation for oxybutynin (Ditropan XL) once-daily dosing was approved by the FDA in December, 1998. In the current application, the sponsor has presented clinical and clinical pharmacology related information following clinical studies in the pediatric population (1 – 15 year old). Based on this information, sponsor seeks pediatric dosing and PK information included in the labels for the IR tablets, syrup and XL formulations.

Clinical Pharmacology Studies

There were two clinical and clinical pharmacology studies undertaken by the sponsor for safety, efficacy, pharmacokinetics and pharmacodynamic assessment of Ditropan immediate release (IR) tablets, syrup and extended release (XL) formulation in the age appropriate pediatric population.

Design of the Two Clinical Studies

Study C-2000-042-01. This was a multicenter, 24-week treatment duration, open label, multiple-dose level, dose-response and safety study of oxybutynin (administered either as Ditropan XL, Ditropan tablets, or Ditropan syrup) in 116 pediatric subjects diagnosed with detrusor hyperreflexia due to neurogenic conditions and aged 6 to 15 years. The dose-effect (urodynamic) and concentration-effect (urodynamic) of oxybutynin chloride were evaluated. A PK study was conducted in a sub section of 42 patients at steady state: 12 on Ditropan syrup, 11 on Ditropan tablets, and 19 on Ditropan XL (QD, BID or BID).

Study C-2000-043-00. This was multicenter, open label, repeated dose, multiple-dose level, minimum 2-week treatment duration, pharmacokinetic (PK) and pharmacodynamic (PD [urodynamic]) study of Ditropan syrup in 16 pediatric patients diagnosed with detrusor hyperreflexia due to neurogenic conditions and aged one to five years. The steady state PK profiles and the dose-effect (urodynamic) and concentration-effect (urodynamic) of Ditropan syrup were evaluated.

[Please refer to Medical Officer's Review for details of the study designs, and table below]

Table 1 Tabular Listing of Submitted Clinical Investigations

Study No. Study Title	Study Design Status	No. Sites/Country	No. Patients/Sex Age Range Race	No. Patients Treatment Dose/Route/Regimen
C-2000-042-01 A Phase 3, multicenter, open-label, 24-week treatment duration, open label, multiple-dose level, dose response, safety study of oxybutynin chloride (administered either as Ditropan XL, Ditropan tablets, or Ditropan syrup) pediatric subjects aged 6 to 15 years and diagnosed with detrusor hyperreflexia due to neurogenic conditions.	Multicenter Open-label Uncontrolled Ongoing- data through November 9, 2001 was submitted as an interim report	24 sites/USA (100 of all enrolled patients and 56 of the Initial Cohort patients) and Netherlands (6 of all enrolled patients and 4 of the Initial Cohort patients)	116 pediatric patients (55 male and 61 female) with 60 in the Initial Cohort (29 male and 31 female) Range: 4 - 16 yr <6 yr=5 6-10 yr=67 11-15 yr=43 >15 yr=1 PK substudy was conducted in 42 pediatric patients 74 Caucasian 17 African American 23 Hispanic 1 Asian 1 Other	116 pediatric patients on a total daily dose of 10 or 15 mg oxybutynin chloride (administered either as Ditropan XL, Ditropan tablets, or Ditropan syrup). In the Initial Cohort of 60 patients, 17 were exposed to Ditropan syrup, 13 to Ditropan tablets and 31 to Ditropan XL. (Note: one patient switched formulation after enrollment from Ditropan syrup to Ditropan XL and was exposed to more than one formulation) PK substudy was conducted in 42 patients: 12 on Ditropan syrup, 11 on Ditropan tablets, and 19 on Ditropan XL
C-2000-043-00 A multicenter, open-label, repeated dose, multiple-dose level, minimum 2-week treatment duration, pharmacokinetic and pharmacodynamic study of Ditropan syrup in patients aged one to five years and diagnosed with detrusor hyperreflexia due to neurogenic conditions	Multicenter Open-label Uncontrolled Completed	4 sites/USA (6 patients) and Netherlands (10 patients)	16 pediatric patients (11 male and 5 female) Range: 1-5 yr. (1yr.=1; 2yr.=5; 3 yr.=4; 4yr.=4; 5yr.=2) 12 Caucasian 1 African American 3 Hispanic 0 Asian	16 patients on Ditropan syrup with their total daily dose ranging from 3.6 to 9 mg/day. Their total daily dose was split into two, three or four doses per day. 1 patient was on 3.6 mg/day split into 3 doses 1 patient was on 4 mg/day split into 2 doses 1 patient was on 4.5 mg/day split into 3 doses 1 patient was on 5 mg/day split into two doses 1 patient was on 5 mg/day split into four doses 1 patient was on 5.1 mg/day split into 3 doses 5 patients were on 6 mg/day split into 3 doses 3 patients were on 7.5 mg/day split into 3 doses 2 patients were on 9 mg/day split into 3 doses

Source: Modified from December 2001 submission, pg 53.2/8, 53. 2/78, 53.2/81, 53.2/130, 53.13/1, 53.13/246, and 53.14/325-326

PK Assessment Methods and Results

Following administration of all the three dosage forms and determination of serum levels of the parent drug and metabolite, comprehensible PK parameter tables and PK profiles were constructed. For the purposes of simplicity and practicability, mean profiles were determined. This was done by averaging out sampling time points and plotting the dose normalized (to 5 mg BID or TID) concentration levels of each patient against those time points. For Ditropan IR tablets and syrup, the steady state AUC and C_{max} were determined from pooled data and reported in the parameter table. Following such analysis, the plots and parameter tables generated were included in the respective product labels.

Additionally, parametric analysis was also performed with the aid of Non-Linear Mixed Effect Modeling (NONMEM) using the average PK information as the base model.

Assuming constant values for volume of distribution and clearance, rate of absorption was parameterized for each formulation. Post-hoc simulation for individual subjects led to individual PK parameters. Mean of those PK parameters were determined, which very closely matched parameters obtained following non-parametric determination (results of the NONMEM analysis is not included in this review). Please see Attachment 1.

For the sake of simplicity in comprehension, the average PK profiles and parameters (non-parametric) are presented in the proposed product label, as follows:

[Note: The following plots and tables were finalized following detailed discussion with the sponsor via teleconference and continuous communication.]

DITROPAN IR Tablets and Syrup:

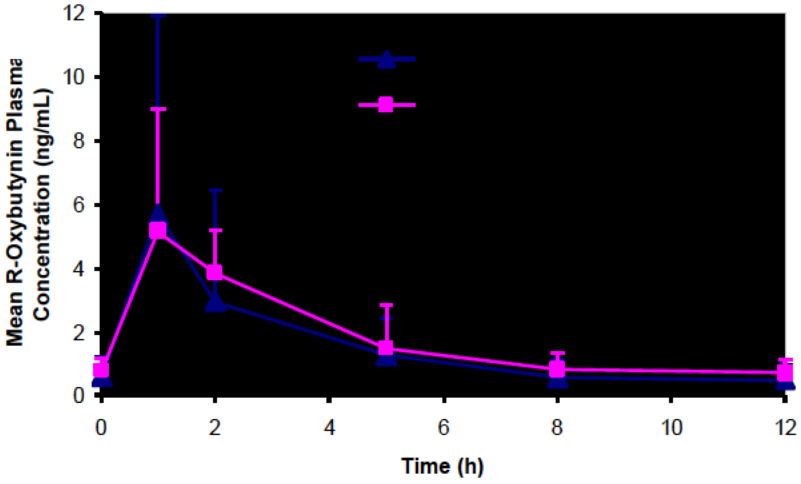


Figure 1. *Mean steady-state (?SD) R-oxybutynin plasma concentrations following administration of total daily Ditropan dose of 5 mg to 30 mg (0.21 mg/kg to 0.77 mg/kg) in children 5-15 years of age – Plot represents all available data normalized to the equivalent of Ditropan 5 mg BID or TID at steady state*

Table 2a

Mean ± SD R- and S-Oxybutynin and R- and S-Desethyloxybutynin Pharmacokinetic Parameters In Children Aged 5-15 Following Administration of 7.5 mg to 15 mg Total Daily Dose of Ditropan Tablets (N=11)

All Available Data Normalized to An Equivalent of Ditropan Tablets 5 mg BID or TID at Steady State

	R-Oxybutynin	S-Oxybutynin	R- Desethyloxybutynin	S- Desethyloxybutynin
C_{max}*(ng/mL)	6.1± 3.2	10.1 ± 7.5	55.4 ± 17.9	28.2 ± 10.0
T_{max} (hr)	1.0	1.0	2.0	2.0
AUC** (ng hr/mL)	19.8 ± 7.4	28.4 ± 12.7	238.8 ± 77.6	119.5 ± 50.7

*Reflects C_{max} for pooled data

**$AUC_{0\text{-end of dosing interval}}$

Table 2b

Mean ± SD R- and S-oxybutynin and R- and S-desethyloxybutynin Pharmacokinetic Parameters In Children Aged 5-15 Following Administration of 5 mg to 22.5 mg Total Daily Dose of Ditropan Syrup (N=12)

All Available Data Normalized to An Equivalent of Ditropan Syrup 5 mg BID or TID at Steady State

	R-Oxybutynin	S-Oxybutynin	R- Desethyloxybutynin	S- Desethyloxybutynin
C_{max}* (ng/mL)	5.7 ± 6.2	7.3 ± 7.3	54.2 ± 34.0	27.8 ± 20.7
T_{max} (hr)	1.0	1.0	1.0	1.0
AUC** (ng hr/mL)	16.3 ± 17.1	20.2 ± 20.8	209.1 ± 174.2	99.1 ± 87.5

*Reflects C_{max} for pooled data

**$AUC_{0\text{-end of dosing interval}}$

DITROPAN XL Tablets:

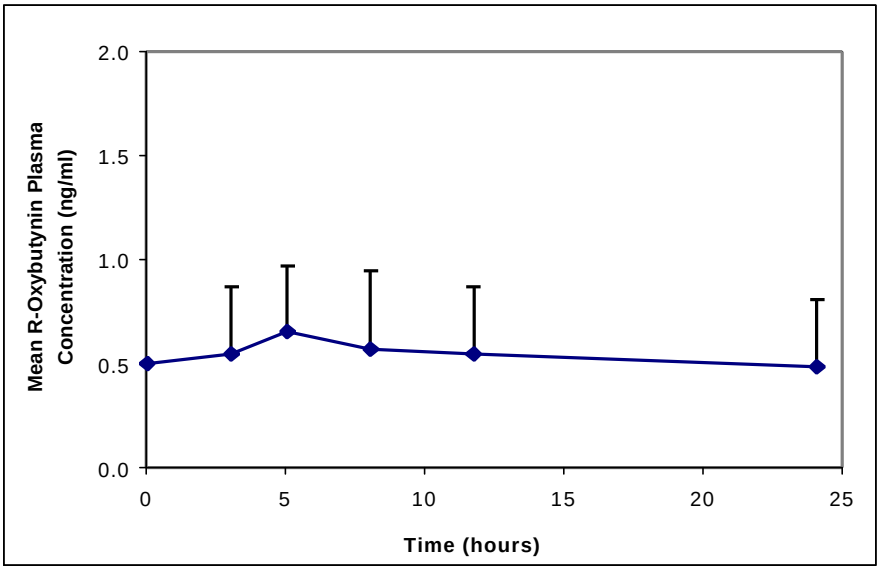


Figure 2. *Mean steady state (±SD) R-oxybutynin plasma concentrations following administration of 5 to 20 mg Ditropan XL once daily in children aged 5-15. - Plot represents all available data normalized to an equivalent of Ditropan XL 5 mg once daily*

Table 3

Mean R- and S-Oxybutynin and R- and S-Desethyloxybutynin Pharmacokinetic Parameters in Children Aged 5-15 Following Administration of 5 to 20mg Ditropan XL Once Daily (N=19): All Available Data Normalized To An Equivalent of Ditropan XL 5 mg Once Daily

	Mean ± SD		Mean ± SD
	C_{max} (ng/mL)	T_{max} (hr)	AUC (ng.hr/mL)
R-Oxybutynin	0.7 ± 0.4	5.0	12.8 ± 7.0
S-Oxybutynin	1.2 ± 0.8	5.0	23.7 ± 14.4
R- Desethyloxybutynin	6.8 ± 3.5	5.0	125.1 ± 66.7
S- Desethyloxybutynin	3.8 ± 2.2	5.0	73.6 ± 47.7

Reviewer's Comments:

- Note that the T_{max} values above are obtained from the mean PK profiles presented in the plots above.
- The above PK information is inserted into the product label for the first time for DITROPAN (IR tablets, Syrup and XL). Inclusion of this information may be useful for a physician while prescribing this product in the pediatric population.

Analytical Methodology

The sponsor used a sensitive and rapid stereoselective LC/MS/MS assay method to determine the serum concentrations of R and S oxybutynin and R and S desethyloxybutynin (primary active metabolite).

The method showed good sensitivity, linearity and specificity. Recovery vales for the molecules of interest were generally above 80%. All inter-day and intra-day accuracy and precision C.V. values were generally < 5% (all < 10%). Higher deviation values were observed at the lower limits of quantification (as expected).

Overall, the analytical methodology and results were acceptable for CPB purposes.

Labeling

Following review of this application, a significant body of CPB information was obtained in pediatric patients (for this first time with this product) and hence, including that in the

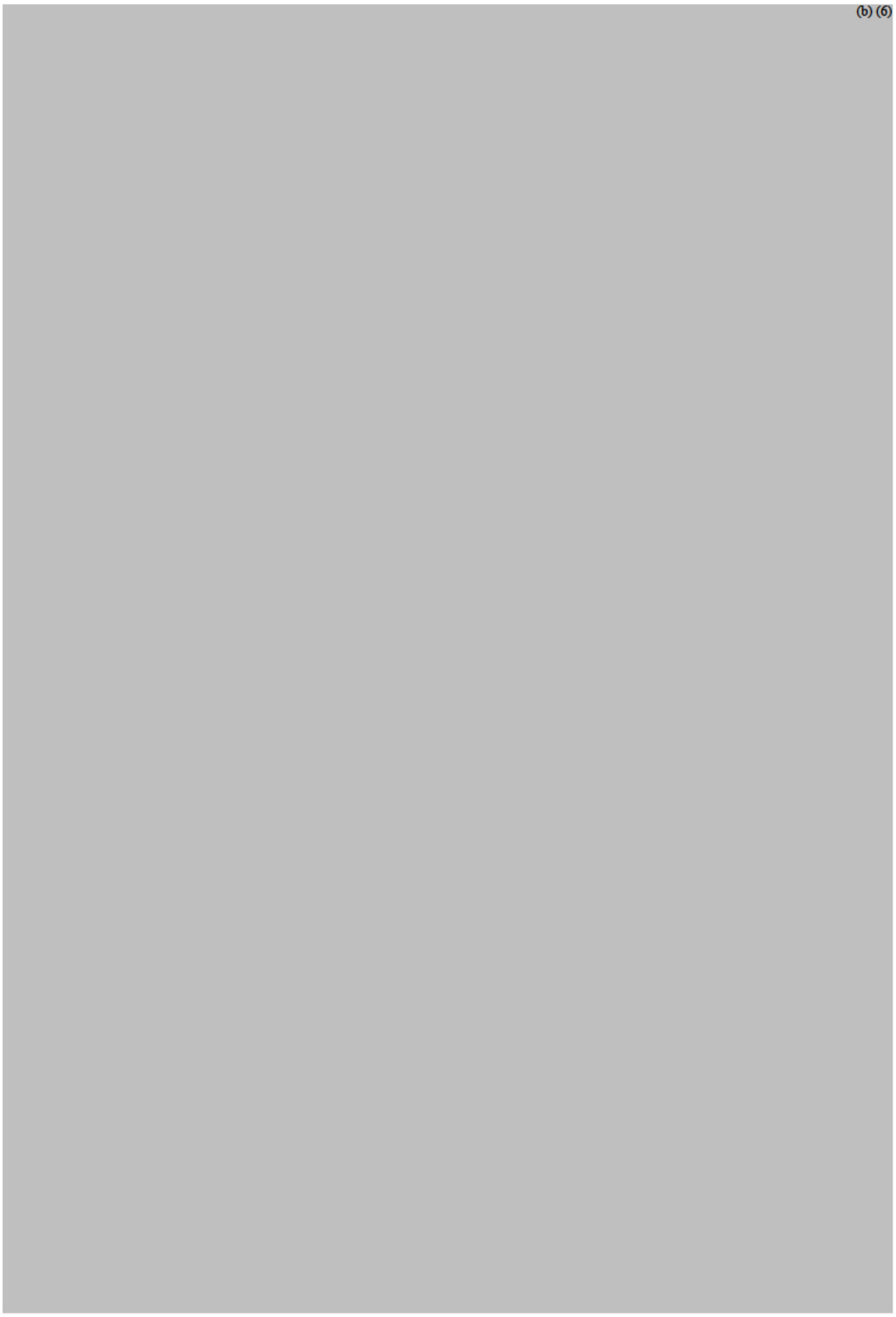
product label was one of the primary objective of a review of this NDA Supplement. The following are excerpts of DITROPAN IR tablet, syrup and XL labels that is ***only relevant*** to OCPB (with proposed changes on the final version):

(b) (4)

7 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Attachment 1

The following are individual observed and fitted plasma concentration vs. time profiles for pediatric subjects administered with IR tablets, syrup and XL tablets (using parametric method using NONMEM; N = 42).



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/s/

Dhruba Chatterjee
4/11/03 05:00:26 PM
BIOPHARMACEUTICS
DFS Worked!
Final Review

Ameeta Parekh
4/14/03 12:29:18 PM
BIOPHARMACEUTICS
I concur