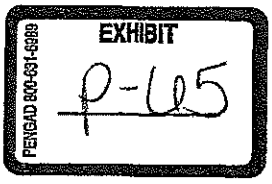
From: Mallows, Susan [PRDUS]
Sent: Sunday, September 28, 2003 12:37 PM
To: Ivo Caers; Katherine Rielly-Gauvin; Marielle Eerdekens; Patrick Sterkens; Peter D'hoore; Vidyasagar Adusumalli
Subject: Autism 10/23

RIS IPP 92503.doc
(1 MB)

Dear Team, Attached is the IPP for pediatrics. Please review this with an eye to autism and return any comments to me by October 3. Thank you - Susan

CAERS



PLAINTIFF'S EXHIBIT 65

Risperdal® (risperidone)

PEDIATRICS

Integrated Project Plan

Johnson & Johnson
PHARMACEUTICAL RESEARCH
& DEVELOPMENT, L.L.C.

Version: September 25, 2003

Replaces the previous version: N/A
Version: 1.0

Table of Contents

IPP

Project Name:	Risperdal
Indication:	Autistic children
Pharmaceutical Dosage form (if applicable):	Available formulations
Pre-IDC Endorsement Date:	June 12, 2003
IDC Date:	October 23, 2003
NPDC Date:	N/A

PROJECT DECISION: Decision to File for Autism in children

Contract Criteria – TIME	**Target Date**	**Allowable Variance**	**Actual Date**
Next Decision Point: Decision to file	October 23, 2003	± 1 mo	
Key Project Deliverables			
RUPP Database Lock	August 12, 2003	± 1 mo	
Marketing Application Filing Date (first G6 core country--US)	December 19, 2003	± 1 mo.	
Marketing Application Approval Date *(first G6 core country--US)*	June 19, 2004	± 1 mo.	
Product Launch Date *(first G6 core country--US)*	July 19, 2004	± 1 mo.	

Contract Criteria – VALUE		
VALUE DRIVERS	**CRITERIA**	**ALLOWABLE VARIANCE**
Target Product Profile *(List 1-3 key target label "must haves" e.g. BID formulation, better efficacy, faster onset of action, better SR profile, side effect)*	➢ Efficacy on Irritability subscale of the ABC vs. placebo in autistic children ➢ Adverse events profile comparable to that in adults with higher incidence of somnolence and possibly weight gain.	Indication wording subject to Med. Comm. input and FDA AC recommendation
Commercial	➢ First pediatric indication for an atypical AP in the US ➢ Halo impact on overall brand ➢ Clear unmet need to have dosing guidance in pediatric population	
Peak Year Sales/ENPV	**$189MM (2007)/$309MM**	

IPP

Contract Criteria - RESOURCE REQUIREMENTS*	*TARGET, $ MM (INTERNAL + OOP)*	*Target, $ MM (OOP)*	Target** FTE#	Allowable Variance** from Target (Int. + OOP)		Total
				OOP	# FTE resources	
Current Budget Year 2003	$5.0	$0.7	17.3	*$0.1MM*	N/A	*$0.1MM*
2004	$1.3	$0.0	5.0	NA	NA	*N/A*
2005	$0.4	$0.0	1.6	NA	NA	*N/A*
Cost to Next Decision Point	N/A	N/A	N/A	NA	NA	*N/A*
Cost to Launch	$6.7	$0.7	23.8	N/A	NA	*$1 MM*

** R&D resource requirements only.*

*** Incremental Headcount: MW = 1 FTE, Document specialist = 1 FTE*

CLINICAL TRIAL SUPPLY REQUIREMENTS*				
Indication	**2003**	**2004**	**2005**	**2006**
N/A				

** Required for Centocor, optional for J&JPRD*

Ivo Caers, PhD CDT Leader Risperdal _____ Date _____

Garry Neil, MD Sr. VP Drug Development, IDC Chair _____ Date _____

1. Executive Summary

Compound Development Leader: Ivo Caers, PhD

Project Management Leader: Susan Mallows

a)—refers to pediatric exclusivity (schizophrenia and bipolar mania)

b)—refers to Autism and Disruptive Behavior Disturbances (DBD)

Project Rationale

Risperdal is the first antipsychotic with specific labeling for the treatment of children in many countries. Additional work is intended to broaden this to all countries incl. US and to strengthen the leading position of Risperdal in the market as indicated below:

a) Risperdal is being studied in pediatrics for schizophrenia and bipolar disorder in order to comply with the FDA Written Request to obtain pediatric exclusivity. The exclusivity will provide additional patent protection of 6 months to the compound, which will extend the compound exclusivity expiry date from Dec. 29, 2007 to June 29, 2008 in the US.

b) In addition, Risperdal has been studied in children with autistic disorder. Two primary efficacy trials have been conducted; one conducted by a consortium of academic investigators with NIMH support (Research Units on Pediatric Psychopharmacology: RUPP study) and a JOI sponsored trial (RIS-CAN-23). An FDA meeting was conducted on April 1, 2003 indicating viability to file with these trials for the indication of the treatment of autistic disorder in children. This file will be suitable for worldwide filing excl. Japan. This indication will be separate from the indication of Disruptive Behavioral Disturbances (DBD) in children, adolescents and adults currently approved in several non-US countries. In those non-US countries where this DBD indication has not been obtained based on the November 2000 file, DBD may still be obtainable with the results of the ongoing study RIS-INT-79, a long-term relapse prevention trial in DBD children and adolescents, to be completed by 4Q2003.

Background

a) Pediatric Patent exclusivity will provide exclusive marketing rights to J&J for an additional 6 months at the end of the compound patent expiry date in the US. To comply, trials must be conducted in accordance with the November 25th, 2002 Written Request from FDA and its subsequent amendment.

b) A request for an Orphan Drug Application was submitted in March 2003 to the Office of Orphan Product Development for the rare condition of autistic disorder in children in the US. Orphan drug status would provide 7 years patent protection

for this indication. At this time, the FDA has turned down this request as the projected patient population covered by this indication is in excess of that required for Orphan Drug status (200,000 patients).

Target Product Profile

a) Critical success will be to obtain the patent exclusivity extension in the US by completing the Written Request requirements in the conduct of trials in adolescent schizophrenia and children/adolescents in bipolar mania.

b) Risperdal is indicated for the treatment of symptoms of autism in children and adolescents.

Risperdal is indicated in conduct and other disruptive behavior disorders in children, adolescents and adults in whom destructive behaviors (e.g. aggression, impulsivity and self-injurious behaviors) are prominent (DBD).

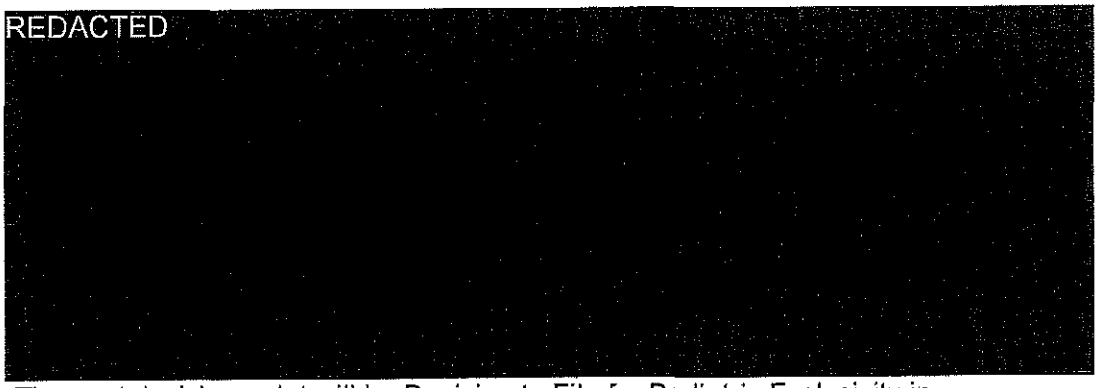
Key Success Factors/Key Issues

a) The critical success factors will hinge on operational aspects of being able to conduct the trials for Pediatric Exclusivity in the time specified by the FDA in the Written Request. Concerns are recruitment of available patient population to enroll into trials for both schizophrenia and bipolar disorder, a suitable number of qualified investigators in the US and worldwide, acceptability of placebo controlled trials by patients and ethics committees. There are no commercial factors that will be applicable here.

b) Successful completion of the autism file with a non-PRD clinical database and successful completion of a public FDA Advisory Committee regarding acceptance of an autism indication.

Next Decision Point

a) REDACTED



The next decision point will be Decision to File for Pediatric Exclusivity in 2Q2007. Critical criteria for next decision point will be successful completion of

the trials as required by the FDA Written Request. All efficacy, safety and PK studies must be completed in accordance with the Written Request.

b) NPDC approval to file Risperdal in autistic children in June 2003.

Development Summary

a) The CNDP will be $52.7MM and CTL will be $57.3MM with submission to be no later than October, 2007 with Pediatric Exclusivity providing 6 months patent extension after the patent expiration date of December 29, 2007 in the US.

b) The CTL for the filing in Autistic disorder in children will be $7.0MM with submission expected to be 4Q2003. Approval, if given priority review, would be by 2Q2004 with launch in 3Q2004.

Asset Valuation

The sales forecast in the US for the 6 month period of the patent exclusivity period indicate $813MM. NPV is $315MM with ENPV of $204MM.

The peak sales forecast for Autism is $189MM WW with $174MM in the US, $12.6MM in EMEA, and $2.5MM in ROW. The NPV is $231MM based on gaining a pediatric indication in the US, impact not as great ex-US as pediatric label has already been obtained.

Contribution to IP (Intellectual Property) for the Compound

a) This will provide 6 months exclusivity in the US for patent protection.

b) None

2. Project Rationale

a) The primary rationale for this project is to obtain six months risperidone product patent extension which will delay the entry of generic oral risperidone in the US by 6 months representing a cumulative additional sales in the US of $ 813MM in 2008.

No additional patent life extension will occur with the following additional formulations such as Risperdal Consta (US patent, Nov 2013) or oral liquid and M-TAB (US patents 2014).

Schizophrenia and bipolar mania both can appear as early as in late childhood and require antipsychotic therapy as much as in adults, although lower doses are often appropriate. Very few studies with antipsychotics in this population have been conducted although the use of Risperdal and other atypical antipsychotics in this population is substantial and these products are 1st line therapy before conventional neuroleptics in view of their better tolerability than conventional neuroleptics. Whereas antipsychotics are primarily studied in acute bipolar mania for the short-term treatment of this condition, its use in schizophrenia is indicated for both acute schizophrenia symptom control and long-term relapse prevention.

b) Autism in children is often accompanied by behavioral symptoms such as severe tantrums, aggression or self-injurious behaviors. No medications are approved for the treatment of these symptoms in autism. An approved pediatric indication and dosing schedule will allow us as well as prescribers to reinforce the appropriate use of atypical antipsychotics in a pediatric population. In addition, it will also serve to maintain Risperdal's leadership position in the Child and Adolescent segment.

3. Situation Assessment

Market Overview / Trend

In general, the use of antipsychotic medication in children is highly sensitive. Risperdal, an atypical antipsychotic, is a selective monoaminergic antagonist developed by J&J PRD, and was the first first-line atypical antipsychotic to be launched for the treatment of adult schizophrenia in 1993 as the successor to the then standard in conventional (typical) antipsychotic therapy, Haldol (haloperidol). Risperdal can be differentiated from other atypical antipsychotics in terms of its strong safety profile [low incidence of extrapyramidal symptoms (EPS), low TD, low incidence of weight gain], good risk benefit ratio and cost effectiveness (effectiveness in the treatment of positive and negative symptoms with lower acquisition costs compared to other atypicals, and reduced hospitalization).

a) Atypical antipsychotics are standard 1st line therapy in schizophrenia in children and adolescents in the developed countries. In less developed countries, conventional neuroleptics may still prevail. Similar to its efficacy profile in adults, Risperdal can be assumed to be effective in both positive and negative symptoms of schizophrenia in adolescents, as suggested in open studies and in controlled studies such as RIS-INT-35 in which adolescents as young as 15 years were included. Usually, a dose of 2 to 4 mg/day is adequate. The biological basis of schizophrenia is the same for adults as for adolescents.

   Atypical antipsychotics are, together with mood stabilizers, 1st line therapy in children and adolescents with acute bipolar mania. These are either used as monotherapy or as adjunctive therapy to mood stabilizers such as lithium or sodium valproate. The value of antipsychotics in the long-term therapy of bipolar disorder is less established but long-term studies in adult bipolar patients are being conducted with several atypical antipsychotics.

   The pediatric population appears to be more vulnerable to Risperdal induced EPS than adults and therefore requires slow dose titration and usually lower dosing. This population also appears to be more vulnerable to weight gain and somnolence. Risperdal increases prolactin (PRL) in the pediatric population. In the large long-term DBD clinical database, this increased PRL tends to shift towards normal values over time. It rarely leads to clinically relevant adverse events and body growth and sexual maturation do not appear to be affected.

Schizophrenia and bipolar disorder affect about 1% of children and adolescents and 2-3% of the adult population respectively. These disorders gradually start appearing in late childhood to reach the above-mentioned incidences in early adulthood.

Risperdal 2002 sales were $2.14 billion growing 12% over 2001, accounting for 27% antipsychotic market value share and 18% treatment day share. Risperdal is the most prescribed atypical antipsychotic worldwide and in the US it is the most prescribed antipsychotic in the Child and Adolescent (C&A) segment, defined as children ages 0-17 years. In 2002 twenty-two percent (22%) of Risperdal's overall use was in pediatrics. Overall atypical antipsychotics used to treat a variety of conditions in the C&A segment, represented approximately 25%. Risperdal currently holds a leadership position in the child and adolescent market with a 57% share of antipsychotic drug use recorded in 2002.

In the US, the breakdown by disease segment of antipsychotic use in the C&A market, was 22% bipolar, 16% ADHD, 15% schizophrenia, 12% depression and 9% autism. The 2002 usage breakdown for Risperdal in the C&A segment was 21% ADHD, 17% bipolar, 15% autism, 13% schizophrenia, and 12% depression.

In the G-5 European countries, half of Risperdal prescriptions in children and adolescents are for conduct disorders (DBD). Of all antipsychotic use in this population, 17% of prescriptions are for schizophrenia, 15% for other psychoses, 10% for autism whereas only 2% of prescriptions are in bipolar disorder.

b) Autistic Disorder is a rare condition that develops in early childhood and affects approximately 200,000+ children in the U.S. It is characterized by profound and debilitating impairments in social relatedness, behavior patterns and communication. In addition, children with Autistic Disorder commonly exhibit highly disruptive behaviors that interfere with their care, rehabilitation, and social interactions. The Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV) and DSM-IV text revised (DSM-IV TR) classify autism (Autistic Disorder) under PDDs. Autistic Disorder is one of the most severe PDDs.

   About 70% to 75% of autistic children are mentally retarded; up to one third may also have epilepsy. Behaviors such as hyperactivity, self-injurious behavior, aggression towards others, extreme intolerance of change, or stereotypes frequently complicate the management of this condition, although there are no published data on the incidence of these disruptive behaviors within the autistic population. In many cases, the impact of these behaviors may be so severe as to lead to institutionalization. Although behavioral therapy may reduce aggression or self-injurious behavior, it tends to be highly individualized and has not been evaluated in randomized clinical studies.

Currently, no medication has been approved for the treatment of Autistic Disorder. However, medication may enhance benefits from educational, behavioral, and other rehabilitative interventions. The primary goal of drug treatment is to decrease maladaptive target behaviors that may interfere with everyday functioning for affected patients, families or caregivers, and educators. No medications are approved for the treatment of these disruptive behaviors; physicians have historically relied on a variety of psychotropic drugs (e.g., sedatives, antipsychotics) to treat these behaviors. As such, Autistic Disorder represents an area of unmet clinical need.

Disruptive behavior disorders (DBDs) (including conduct disorder, oppositional defiant disorder and DBD not otherwise specified) are some of the most frequently diagnosed conditions in outpatient and inpatient mental health facilities for children and adolescents. The reported prevalence of disruptive behavioral disorders varies for males under 18 years of age from 6–16% and for females of the same age from 2–9%. Prevalence appears to increase in inverse proportion to intellectual level. Reported prevalence, within the population with learning disabilities and other psychiatric disorders, may be as high as 20–64%. There is a high co-morbidity with ADHD (40–70%).

The essential feature of these conditions is a repetitive and persistent pattern of severe and impairing behavior (in terms of both the child and other around them) in which the basic rights of others or major age-appropriate societal norms or rules are violated. It should be noted that these behaviors are much more than simply disobedience; they are severe and impairing to the child, to family life and to society, they interfere with social, academic and professional functioning and, if left untreated, they have long-term consequences for adult behavior, such as antisocial and criminal behaviors. In addition, they are not caused by bad parenting but by a serious psychological condition that can be treated.

There are many different approaches to treating the symptoms of DBD, including drug therapy, behavioral treatment, psychotherapy, cognitive, social and family learning. Virtually every available psychotropic drug has been used for the aggression, agitation, hostility and stereotypical behavior, however with limited success. Prior to Risperdal trials, numerous studies were performed, but the trials were small and not controlled and the data was not strong enough to support drug use in this population.

Stakeholders / Unmet Needs

Psychiatric disorders in children and adolescents are mainly treated by specialists, such as child and adolescent psychiatrists and pediatricians and, to a lesser extent, by GPs who mostly refer children to specialists

Physicians commonly state that safety with the use of antipsychotics in children and adolescents is relatively more important than efficacy. The availability of data and formal approvals are important differentiators to

support Risperdal use in children vs other drugs. A total of 37% of US physicians surveyed said they would increase use of Risperdal in pediatrics as supported by the unrivaled data in this age group.

A key stakeholder group includes patient support groups, mainly comprised of family members of affected children, as they can endorse drug treatment for affected children.

Competition

Competitors in the atypical antipsychotics market include:

- Olanzapine (Zyprexa, Eli Lilly)
- Quetiapine (Seroquel, AstraZeneca)
- Ziprasidone (Geodon, US, Zeldox, U.K. Pfizer)
- Clozapine (Clozaril, Novartis)
- Aripiprazole (Abilify, BMS)

Geographic Variations

Patients in the US tend to be treated at a younger age than their EU counterparts. The EU market is more fragmented than that of the US as seen in the number of antipsychotics with significant sales and the number of diseases treated with antipsychotics.

Risperdal has been licensed for DBD in several European countries, including: Germany, Austria, France, Greece, Iceland, Portugal, Ireland, Estonia, Poland, Turkey, the Czech Republic, Hungary, Australia, Israel, Korea, Mexico, New Zealand, Philippines and South Africa.

4. Target Product Profile

Target Product Vision/Value Proposition	
Product Characteristics	**Target Measure** *
Indication [1]	• Treatment of symptoms of autism in children and adolescents. • Conduct and other disruptive behavior disorders in children, adolescents and adults in whom destructive behaviors (e.g. aggression, impulsivity and self-injurious behaviors) are prominent (Ex-US / Japan).
Population	• Children and adolescents aged 5-17 years old.
Mechanism of Action	• Serotonin-dopamine antagonism
Drug Product • Dosage form • Frequency of administration • Strength	• Oral tablets, oral solution, fast dissolving tablets • Once daily or twice daily • Tablets; 0.25 – 4 mg. 1 mg/ml solution. 0.5 – 2 mg fast dissolving tablets.
Efficacy	• Efficacy on subscale of the ABC vs. placebo in autistic children and adolescents. • Efficacy on the Conduct Problem subscale of the NCBRF vs. placebo in DBD

[1] *The clinical program for obtaining US exclusivity extension will not lead to additional pediatric indications in view of both schizophrenia and bipolar mania already approved.*

IPP	
Safety	
• Clinical	• Adverse events profile comparable to that in adults with higher incidence of somnolence and possibly weight gain.
• Non-Clinical	• No description of preclinical findings specific to pediatrics.
• Tolerability	• No mention in label of possible effect on sexual maturation, brain development or growth. The label may mention that long-term effects of PRL increases are not well known.
Pharmacokinetics & Pharmacology	
REDACTED	REDACTED
• Pharmacodynamics	•
• PK/PD Relationships	• No anticipated PK / PD relationship
• Key Drug Interactions	• As in adult labeling
• Special populations	• Children and adolescents
Health Economics / Quality of Life	• No QoL claims

Key Differentiators: Only approved atypical antipsychotic in pediatric population (Autism and DBD)

** Target Measure = target claims that provides the needed competitive position, are realistically achievable and drive the project strategy and plan.*

5. SWOT Summary

STRENGTHS	WEAKNESSES
• 1st and only atypical licensed for use in children and adolescents • >1000 children and adolescents studied • Established treatment choice in children (EU and US) • Good short and long-term safety data in children • Rapid onset of action, efficacy maintained in the long-term • Child friendly formulations and low dose tablets • Opinion leader advocacy • Global brand recognition	• Transient hyperprolactinemia and somnolence. Some weight gain in children. • Absence of treatment and regulatory guidelines for use in children and adolescents with impairing disruptive behavior • Market potential is unclear • No ability to confirm absence of effect on sexual maturation, brain development in this population
OPPORTUNITIES	**THREATS**
• **Only healthcare company actively pursuing new product labeling in Autism with an antipsychotic** • **Unmet need for safe and effective treatment** • **Compliance programs for patients and caregivers** • **Market potential in Europe in the C&A segment to replace use of conventionals** • **Ongoing clinical trials program to support new indications** • **Co-positioning of Risperdal with Concerta with pediatric specialists** • **Increase comfort level of prescribing physicians to use this product in the pediatric population (overall safety halo effect)**	• **Regulatory aversion to approve the use of antipsychotics for children** • **Influential child and adolescent advocacy groups opposed to the use of antipsychotic medication in children** • **Sensitivity of use in 'mental retardation' population** • **Market and market development potential is unclear** • **Could be conceived as creating an 'indication' for a drug** • **Patent protection only until (2007) with 6 months pediatric exclusivity June 2008 in US.** • **Perception that EPS over the long term leads to irreversible tardive dyskinesia** • **Ability to fulfill FDA Written Request requirements**

6. Key Success Factors & Key Issues

a) Being able to execute the clinical trials in adolescent schizophrenic and child-adolescent bipolar manic patients in accordance with the November 25th 2002 Written Request and its subsequent adaptation and to submit the results no later than December, 2007.

- Sufficient suitable study centers in and ex-US
- Acceptable study design for easy IRB approvals
- Adequate enrollment of patients to complete studies on time
- Trial completions by early 2007 to allow filing no later than November 2007

b) Successful completion of the autism file for US and ex-US filing (excl. Japan) by end 4Q2003.

- Suitability and sufficient quality of NIMH database for incorporation in sNDA / MAA
- Successful QA audits of NIMH study centers (RUPP trial)
- Suitability of RIS-CAN-23, a phase IV study, for sNDA / MAA filing
- Sufficient documentation on validation of efficacy scales used
- Appropriate wording of the indication, to be acceptable to FDA and FDA Advisory Committee
- Successful Advisory Committee meeting

A successful resubmission for DBD in those ex-US / Japan countries that did not accept the November 2000 MAA will depend on a successful outcome of the ongoing RIS-INT-79 trial by 4Q2003.

7. Project Development Strategy

- *Overall Project Strategy*

The overall project strategy of Risperdal in pediatrics is:

1. To obtain a 6 month oral Risperdal exclusivity extension in the US market from Dec. 29, 2007 to June 29, 2008 by submitting a file on Risperdal in adolescent schizophrenia and child/adolescent bipolar mania ≤ December 2007 that fulfills the FDA Written Request of November 25th 2002 and its subsequent adaptations.

The Written Request of November 25th, 2002, requires:

- PK study in pediatric population.
- Double-blind placebo-controlled fixed dose efficacy in adolescent schizophrenia. In case of single flexible dose group study, exclusivity is not obtained in the event of a negative trial.
- Double-blind placebo-controlled fixed dose efficacy in child/adolescent bipolar mania. In case of a single flexible dose group study, exclusivity is not obtained in the event of a negative trial.

- Long-term safety data on 100 patients for at least 6 months.
- These data need to be submitted to the FDA at the latest by November 2007.

2. To have a pediatric indication approved in all countries excl. Japan to allow the reinforcement of the appropriate use of Risperdal in the pediatric population and to maintain or expand our market leadership in the pediatric market segment.
   This indication will either be autism (US, ROW excl Japan) and/or DBD (ROW excl Japan).

The pediatric indication will be based on,

Autism;

- NIMH study in autistic children and adolescents with serious behavioral problems (Part 1: initial 8 week double-blind placebo controlled phase, Part 2: OL: 4 month follow-up phase, Part 3: 8 week double-blind placebo-controlled relapse prevention phase). Both study Parts 1 and 3 showed significant separation vs. placebo on the primary parameter.
- RIS-CAN-23; An 8 week double-blind placebo-controlled study in children with autistic and other pervasive developmental disorders. 70% of these patients were autistic. Risperdal was significantly superior to placebo on the primary parameter.
- Long-term safety data from the NIMH study and from 700 DBD children documented for up to 3 years of Risperdal treatment.

REDACTED

DBD;

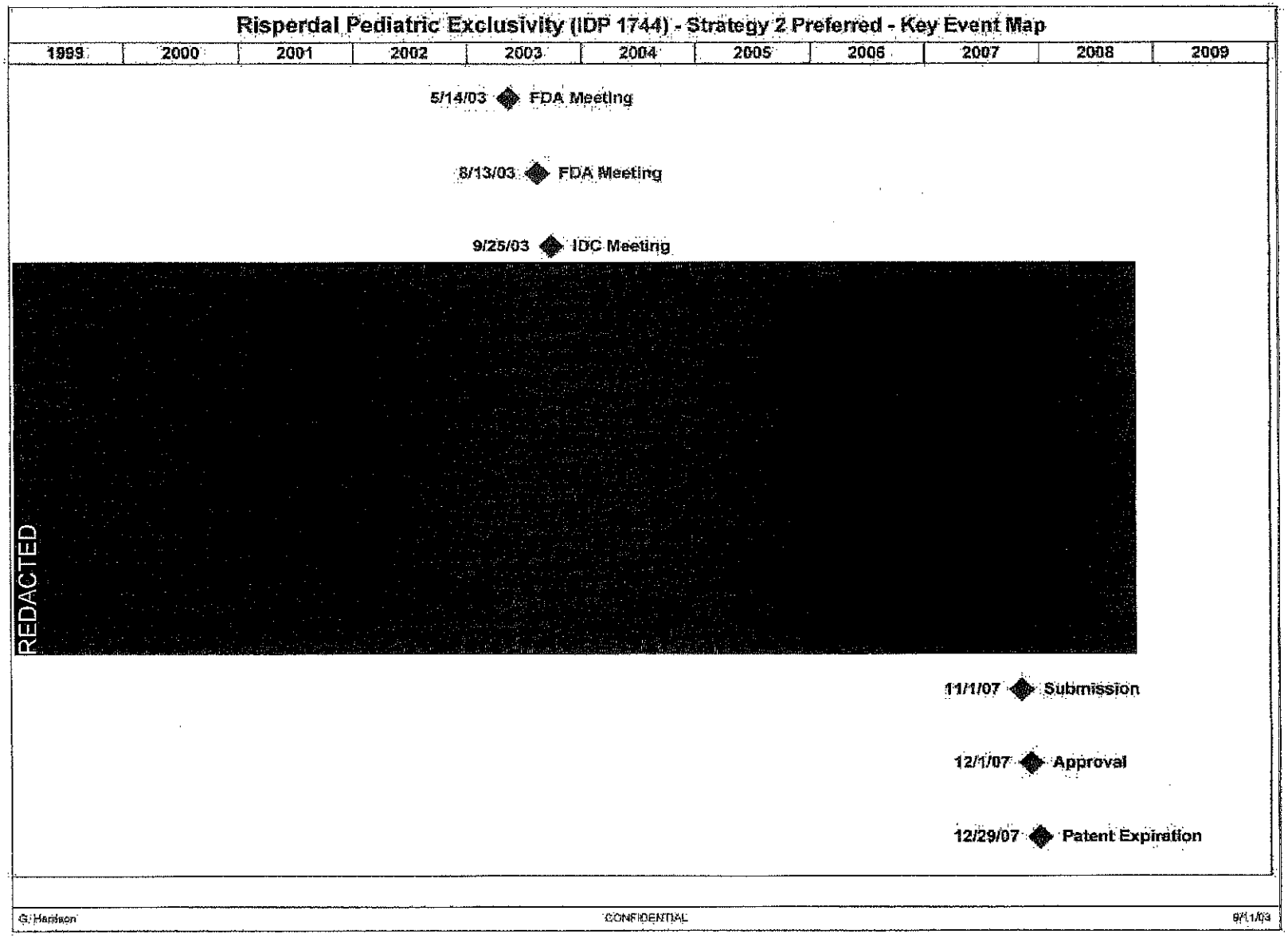
- New file re. submission in 2004 including;
  - November 2000 MAA (2 DB-PC efficacy studies in children, 1 DB-PC efficacy study in adults, long-term safety data).
  - RIS-INT-79, a 6 months double-blind placebo-controlled relapse prevention trial in DBD children and adolescents (Ongoing; topline results 4Q2003).
  - Additional long-term safety data collected since November 2000.

Japan: There is no Risperdal in pediatrics strategy in Japan.

8. Integrated Project Summary

Project Management Leader: Susan Mallows, Titusville, NJ

Project Schedule



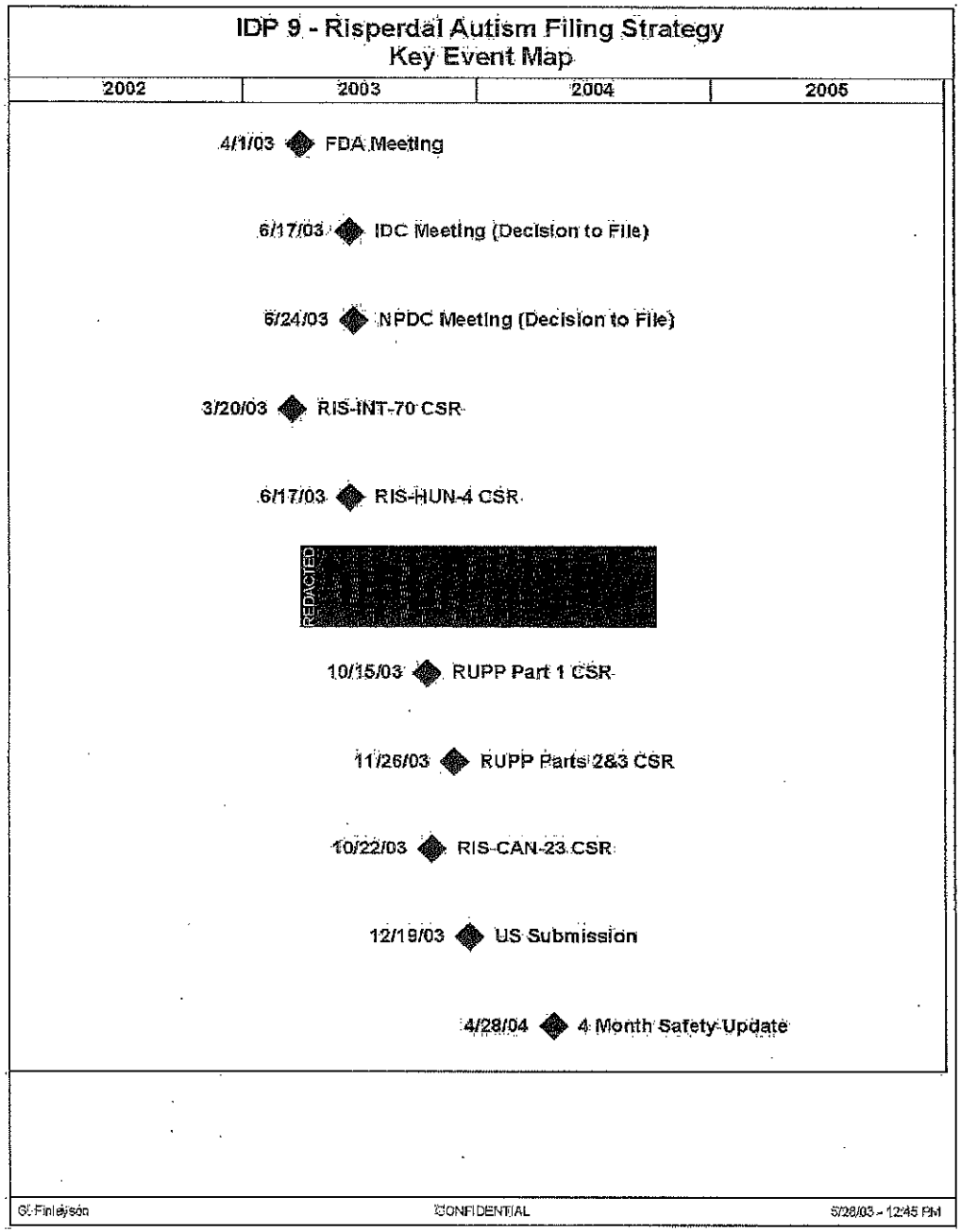


Table 1: Total Costs & Resources Summary (Pediatric Exclusivity) *(R&D costs only)*

R&D	3 Year Estimate			CNDP**		CTL		Cost Drivers	Deviations*
Costs	2003	2004	2005	Baseline	Current	Baseline	Current		
OOP *(millions)*	5.0	10.5	10.2	35.4		36.8			
Internal *(millions)*	3.3	4.6	4.3	17.4		20.5			
TOTAL	14.1	15.9	17.7	62.5		67.2			
# Resources	13.3	18.2	17.1	68.9		81.4		Clinops – Trials and B&R	
Commercial	**3 Year Estimate**			**CNDP**		**CTL**		**Cost Drivers**	**Deviations***
Costs	**2003**	**2004**	**2005**	**Baseline**	**Current**	**Baseline**	**Current**		
OOP	N/A								
Internal									
TOTAL									
# Resources									
Manufacturing	**3 Year Estimate**			**CNDP**		**CTL**		**Cost Drivers**	**Deviations***
Costs	**2003**	**2004**	**2005**	**Baseline**	**Current**	**Baseline**	**Current**		
OOP	N/A								
Internal									
TOTAL									
# Resources									

** If a deviation to the contract exists, explain the deviation and complete the deviation change schedule*
*** Ensure that only costs to the next decision point are captured. Identify the next decision point here.*
See NPD Document User Guide, team resource manager & financial rep to the team for guidance to complete this table.

Table 2: R&D Costs & Resources by Function (Pediatric Exclusivity) *(R&D costs only)*

	3 Year Estimate			CNDP		CTL		Cost Drivers	Deviations
Costs	2003	2004	2005	Baseline	Current	Baseline	Current		
OOP $									
- Drug Discovery									
- Drug Safety & Surveillance									
- Chem-Pharm	0.1	0.1	0.1	0.4		0.4		CSU	
- Pre-Clinical		0.2	0.1	0.3		0.3			
- Franchises									
- Clinical PK & Pharmacology									
- Clinical Ops - Trials	5.0	10.3	10.0	34.7		35.7		In-Pt trials	
- Clinical Ops – Bio & Informatics									
- Regulatory						0.4		FDA Filing Fee	
- Project and Portfolio Mgmt									
Total OOP $	5.1	10.5	10.2	35.4		36.8			
Internal $									
- Drug Discovery	0	0	0	0		0			
- Drug Safety & Surveillance	0	0	0	0		0			
- Chem-Pharm	0.1	0.1	0.1	0.3		0.3			
- Pre-Clinical	0	0	0	0		0.1			
- Franchises	0.1	0.1	0.1	0.5		0.7			
- Clinical PK & Pharmacology	0.2	0	0	0.6		0.8			
- Clinical Ops – Trials	0.8	1.1	1.3	5.1		6.2			
- Clinical Ops – Bio & Informatics	1.8	2.4	2.2	8.1		8.5			
- Regulatory	0.4	0.8	0.6	2.7		4.0			
- Project and Portfolio Mgmt	0	0	0	0		0			
Total Internal	3.3	4.6	4.3	17.4		20.5			

See team Finance Representative for guidance to complete

Table 2: R&D Costs & Resources by Function (Continued) (Pediatric Exclusivity)*(R&D costs only)*

	3 Year Estimate			Resources to Next Decision Point		Resources to Launch		Resource Drivers	Deviations
Resources	2003	2004	2005	Baseline	Current	Baseline	Current		
Resource FTE's*									
- Drug Discovery	0	0	0	0		0			
- Drug Safety & Surveillance	0	0	0	0		0			
- Chem-Pharm	0.2	0.5	0.5	1.3		1.3			
- Pre-Clinical	0	0.2	0	0.3		0.3			
- Franchises	0.5	0.3	0.3	1.9		2.6			
- Clinical PK & Pharmacology	0.7	0.2	0.1	2.4		3.1			
- –Clinical Trials	7.1	9.5	8.8	32.3		33.6			
- Biometrics & Reporting	3.3	4.2	5	20.1		24.6			
- Regulatory/QA	1.5	3.4	2.3	10.7		16.0			
- Project and Portfolio Mgmt	0	0	0	0		0			
Total Resource FTE's	13.3	18.2	17.1	68.9		81.4			

See team Resource Manager for the team for guidance to complete

* *number of FTE's*

Table 3: R&D Costs and Resources

Contract Deviation Change* – Favorable (Unfavorable) Change

$ in millions

(Pediatric Exclusivity)

R&D	3 Year Estimate			CNDP		CTL		Explanation of Deviation
Costs	2003	2004	2005	Baseline	Current	Baseline	Current	
OOP	N/A							
Internal								
TOTAL								
# Resources								

*Detail of any contract change that results in additional OOP and resource dollars and/or FTE's required, saved or delayed. This could include, but is not limited to trial delays, change in protocol and recruitment issues.

Table 1: Total Costs & Resources Summary (Autism) *(R&D costs only)*

R&D	3 Year Estimate			CNDP**		CTL		Cost Drivers	Deviations*
Costs	2003	2004	2005	Baseline	Current	Baseline	Current		
OOP	1.0	0	0	1.0		1.0			
Internal	4.4	1.3	0.4	6.0		6.0			
TOTAL	5.4	1.3	0.4	7.0		7.0			
# Resources	17.3	5.0	1.6	23.8		23.8			
Commercial	**3 Year Estimate**			**CNDP**		**CTL**		**Cost Drivers**	**Deviations***
Costs	2003	2004	2005	Baseline	Current	Baseline	Current		
OOP	N/A								
Internal									
TOTAL									
# Resources									
Manufacturing	**3 Year Estimate**			**CNDP**		**CTL**		**Cost Drivers**	**Deviations***
Costs	2003	2004	2005	Baseline	Current	Baseline	Current		
OOP	N/A								
Internal									
TOTAL									
# Resources									

** If a deviation to the contract exists, explain the deviation and complete the deviation change schedule*

Table 2: R&D Costs & Resources by Function (Autism) *(R&D costs only)*

	3 Year Estimate			CNDP		CTL		Cost Drivers	Deviations
Costs	2003	2004	2005	Baseline	Current	Baseline	Current		
OOP $									
- Drug Discovery									
- Drug Safety & Surveillance									
- Chem-Pharm									
- Pre-Clinical									
- Clinical PK & Pharmacology	0.4			0.4		0.4			
- Clinical Ops – Trials	0.3			0.3		0.3			
- Clinical Ops – Bio & Informatics									
- Regulatory	0.4			0.4		0.4		FDA Filing Fee/ Advisory committee	
- Project and Portfolio Mgmt									
Total OOP $	1.0			1.0		1.0			
Internal $									
- Drug Discovery									
- Drug Safety & Surveillance									
- Chem-Pharm									
- Pre-Clinical									
- Clinical PK & Pharmacology	0.2	0.1		0.3		0.3			
- Clinical Ops – Global Dev. Franchise	0.3	0.1		0.4		0.4			
- Clinical Ops – Bio & Informatics	2.9	0.6		3.4		3.4			
- Regulatory	1.0	0.5	0.4	1.9		1.9			
- Project and Portfolio Mgmt									

Total Internal	4.4	1.3	0.4	6.0		6.0			

Table 2: R&D Costs & Resources by Function (Continued) (Autism) *(R&D costs only)*

	3 Year Estimate			Resources to Next Decision Point		Resources to Launch		Resource Drivers	Deviations
Resources	**2003**	**2004**	**2005**	**Baseline**	**Current**	**Baseline**	**Current**		
Resource FTE's*									
- **Drug Discovery**									
- **Drug Safety & Surveillance**									
- **Chem-Pharm**									
- **Pre-Clinical**									
- **Franchises**									
- **Clinical PK & Pharmacology**	0.9	0.2		1.1		1.1			
- **Global Dev. Franchise**	1.0	0.5		1.5		1.5			
- **Biometrics & Reporting**	11.4	2.2		13.55		13.55			
- **Regulatory/QA**	4.0	2.1	1.6	7.7		7.7			
- **Project and Portfolio Mgmt**									
Total Resource FTE's	14.1	2.7	1.2	23.83		23.83			

See team Resource Manager for the team for guidance to complete

* *number of FTE's*

Table 3: R&D Costs and Resources

Contract Deviation Change* – Favorable (Unfavorable) Change

$ in millions

(Autism)

R&D	3 Year Estimate			CNDP		CTL		Explanation of Deviation
Costs	2003	2004	2005	Baseline	Current	Baseline	Current	
OOP	N./A							
Internal								
TOTAL								
# Resources								

*Detail of any contract change that results in additional OOP and resource dollars and/or FTE's required, saved or delayed. This could include, but is not limited to trial delays, change in protocol and recruitment issues

Risk Assessment – Pediatric Exclusivity

Key Risks	Description of Risk	Mitigation Plan
Technical/Regulatory		
REDACTED		
Low technical risk if placebo controlled trial conducted	Trial results can be positive or negative	Successful completion of trials
High A.E. rates might result from doses up to 6 mg thus > 50% patients discontinue in active treatment group	Decreased enrollment FDA will not accept trial, regardless of outcome, for pediatric exclusivity	Continue SCH 231 as is and have WR amended to include positive outcome as acceptable for pediatric exclusivity (FDA agreed to this). Ensure that down titration is included in the protocol and measures are taken to prevent early drop out.
REDACTED		
Operational		
REDACTED		
Insufficient patient recruitment to complete trials in order to submit on schedule	History of slow enrollment in SCH 231 schizophrenia trial	Increase number of investigators, broaden country participation, advertising campaign;
Adequate diagnosis of disease state	Ensure appropriate patients enrolled	Validated scales to be used, investigator training regarding diagnosis
Commercial		
None—6 months patent extension being sought, no label changes regarding indication to be made	No indication for schizophrenia or bipolar mania in children and adolescents	Description of efficacy trials in adolescents with schizophrenia and bipolar mania to be included in label in Clinical Trials Section.

Risk Assessment – Autism

Key Risks	Description of Risk	Mitigation Plan
Technical		
Indication for Autism has not been granted previously	FDA will not take position on the indication	Conduct Clinical Advisory Board meetings with KOLs
Advisory committee to be scheduled by FDA	As above	As above and prepare for and submit AC outline and presentation one month after filing.
Validity of scales	FDA not familiar with ABC scale and question pseudo-specificity of scale	Consult with Clinical Advisory Board and submit documentation to FDA on scales as soon as possible
Operational		
Dependent on NIMH for data from the RUPP study	Quality of the data not completely ascertained yet, trial conduct may be dissimilar from PRD trials	Thorough review of RUPP DB, PRD QA to audit Investigator sites as if they were PRD sponsored trials
Commercial		
Competitor filing for Autism ahead of Risperdal	Risperdal would no longer be 1st AP to have pediatric label. This would impact halo effect and ultimately forecast.	Ensure submission filing by year end 2003

9. Asset Valuation (Autism)

Key Forecast Assumptions - US

Price

Gross price per mg:	$3.74
Mgs per day:	1.8
Discount rate:	13.4%
Peak Year Sales	$174 MM
Share at Peak Sales Year	49%
Peak Year	2007

Market Share Rationale

- Utilized Risperdal Dementia Launch as an analog for Autism indication; factored share impact against Risperdal Base Share
- Seroquel pediatric launch in Q1-05
- Assumes Geodon obtains oral solution formulation in Q4-03

Product Exclusivity

Patent Expiry:	Q2 2008 (pediatric exclusivity)
Generic Entry:	Q3 2008

Key Forecast Assumptions – G5

Price

Gross price per mg:	$0.57 (G5 wtd. Average)
Mgs per day:	1.0
Discount rate:	2.0%
Peak Year Sales	$8 MM
Share at Peak Sales Year	80%
Peak Year	2007

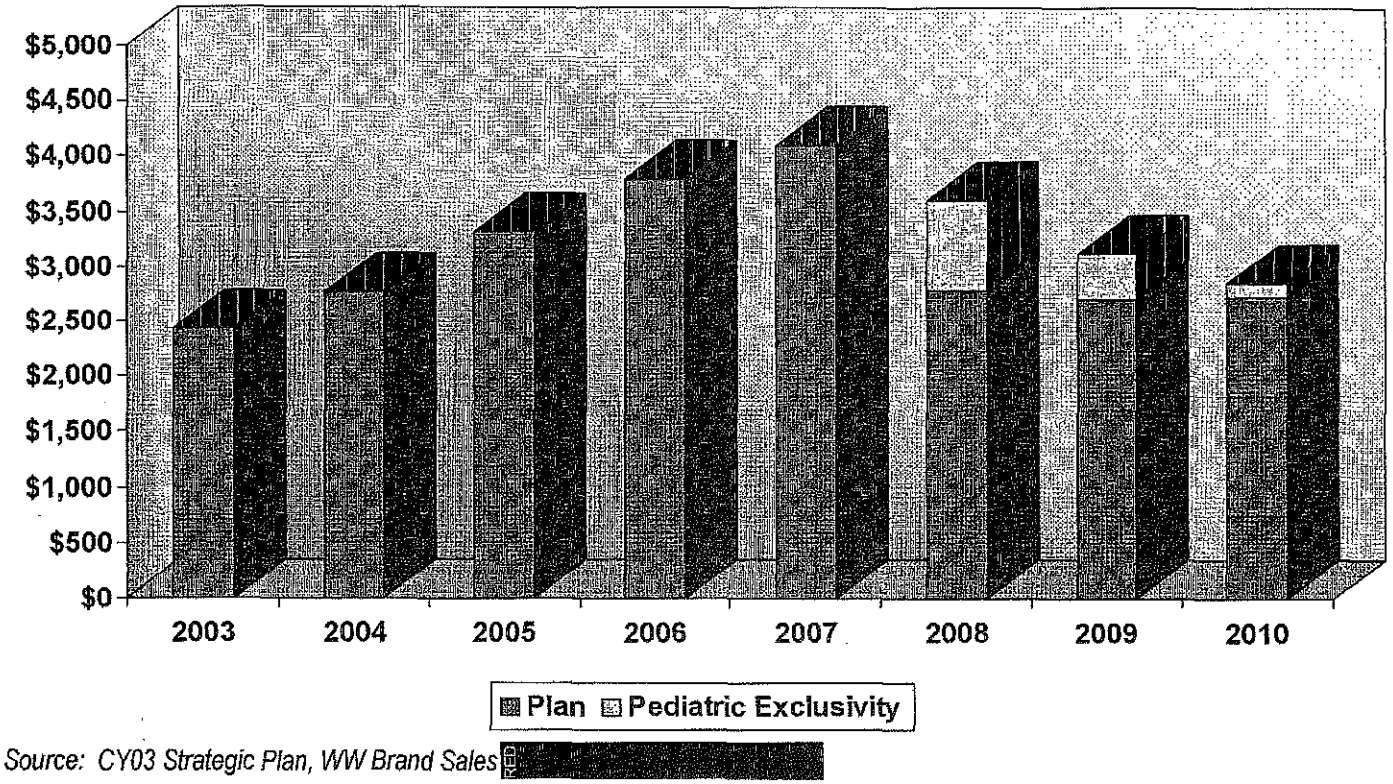
Market Share Rationale

- Risperdal only antipsychotic with Autism indication and leader in the field with 37% current market share
- Halo effect from other Conduct Disorders

Product Exclusivity

Patent Expiry:	Q4 2007
Generic Entry:	Q1 2008

Risperdal Strategic Plan Sales through 2010



Source: CY03 Strategic Plan, WW Brand Sales

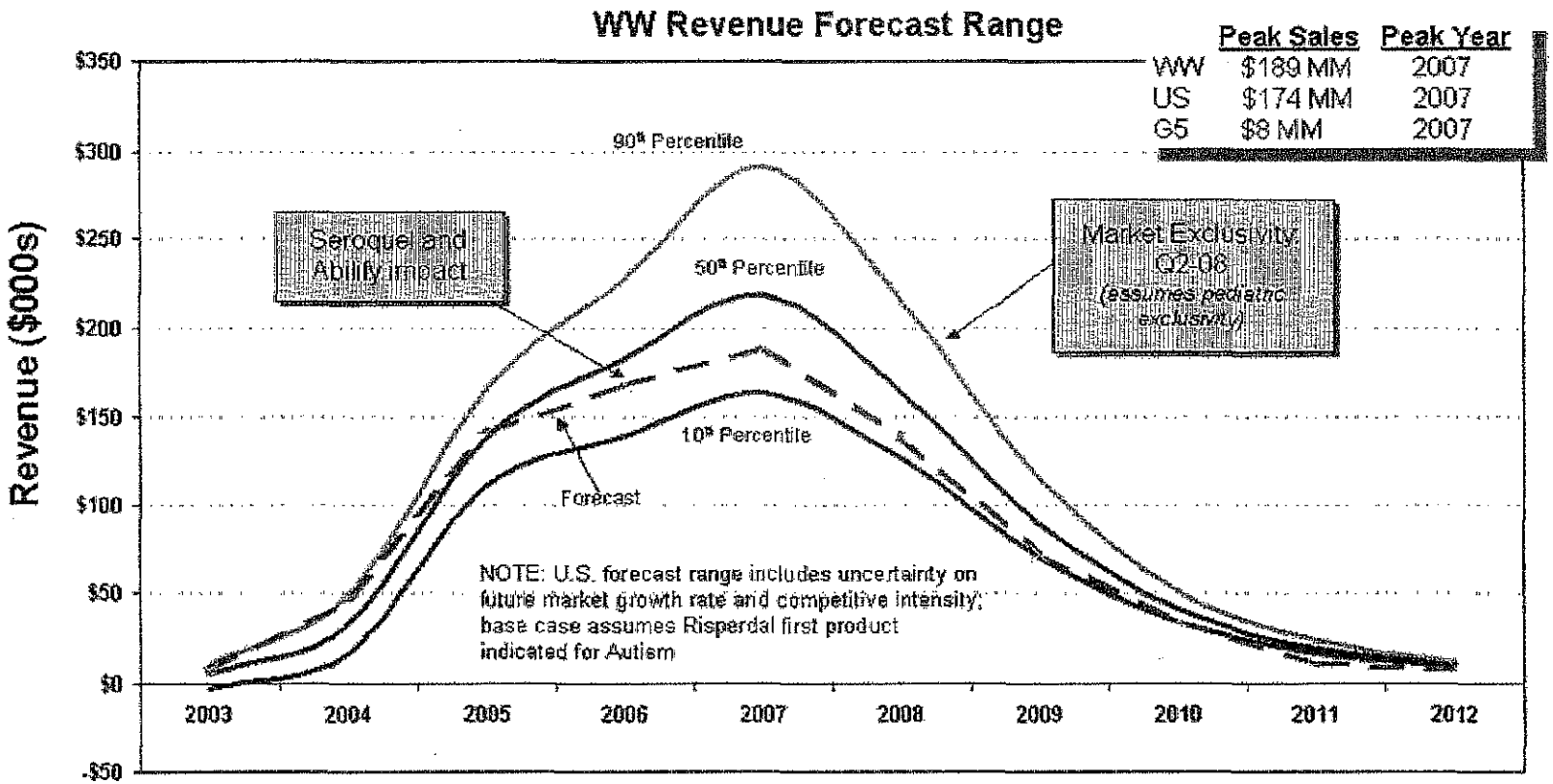
Autism Valuation Summary

($ millions)

Expected Value (with technical success) **$309**

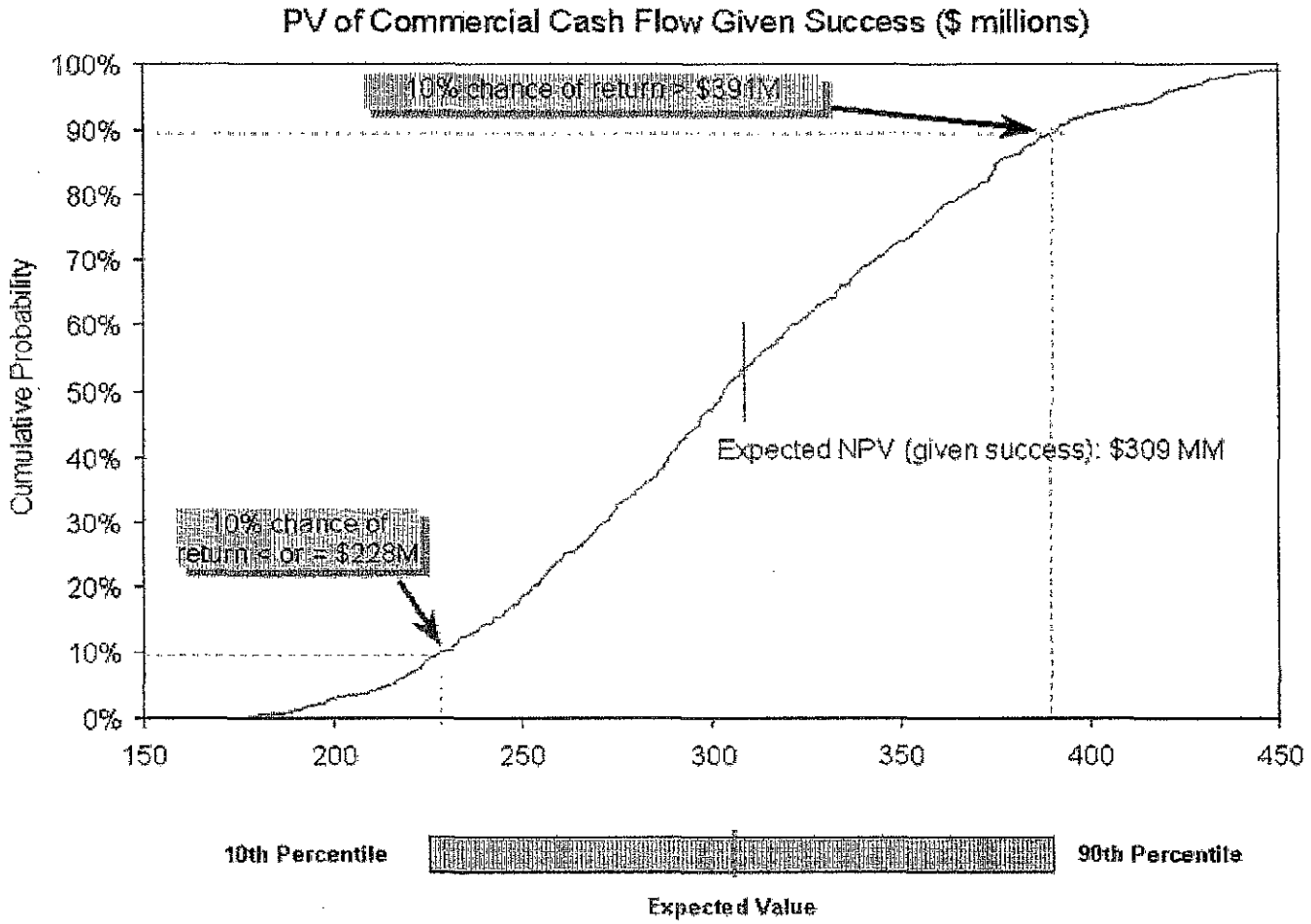
Given Technical Success	Base Case	50/50 Values	10/90 Values	90/10 Values
Peak Year Net Trade Sales	$ 189	$ 218	$ 164	$ 291
Peak Sales Year	2007			
J&J Net Present Value	$ 270	$ 303	$ 228	$ 391
Internal Rate of Return	2194%			
Cost to Next Decision Point	$ 5			
Cost to Launch	$ 5			
M&S Cost [Launch Year]	$ 12			

WW Autism Revenue Forecast

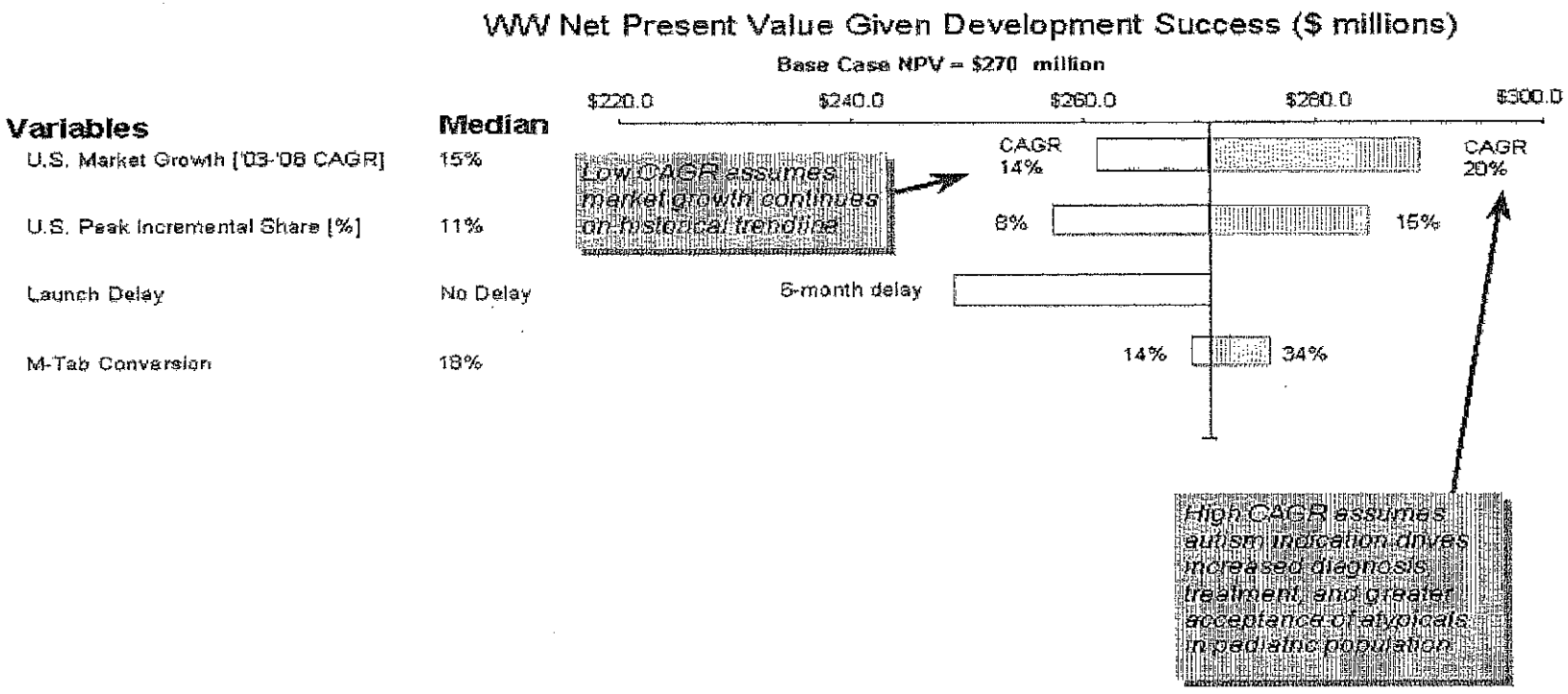


-Upside potential if Seroquel does not achieve a pediatric indication for Schizophrenia
-Additional upside if indications drive increased diagnosis, treatment and acceptance of atypical antipsychotics in pediatric population

Distribution of Commercial Value Given Technical Success - Autism



Sensitivity Analysis of Commercial Value Given Technical Success - Autism



10. Functional Plan Summary

Regulatory/Clinical

- **Clinical Leader: Marielle Eerdekens, MD**
- **Regulatory Leader: Sagar Adusumalli, PhD**

EXECUTIVE SUMMARY

On 25 November 2002, FDA issued a formal Written Request (WR), pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act, for J&JPRD to submit information from RISPERDAL® trials in pediatric patients with (1) schizophrenia and (2) acute mania associated with bipolar disorder. The WR detailed the following requirements for obtaining pediatric exclusivity:

(1) Collect pharmacokinetic data in a single indication to provide information pertinent to dosing in the relevant pediatric age group.

(2) Conduct an acute (6-8 week), randomized, double-blind, placebo-controlled, fixed-dose efficacy and safety study in adolescent schizophrenia (ages 13-17 years).

(3) Conduct an acute (≥3 weeks), randomized, double-blind, placebo-controlled, fixed-dose efficacy and safety study in pediatric mania associated with bipolar disorder (ages 10-17 years).

(4) Conduct a separate, longer-term (≥6 months exposure) safety study (e.g., open-label extension of the controlled efficacy study) in a single indication at or above the dose/doses identified as effective in an adequately designed efficacy trial.

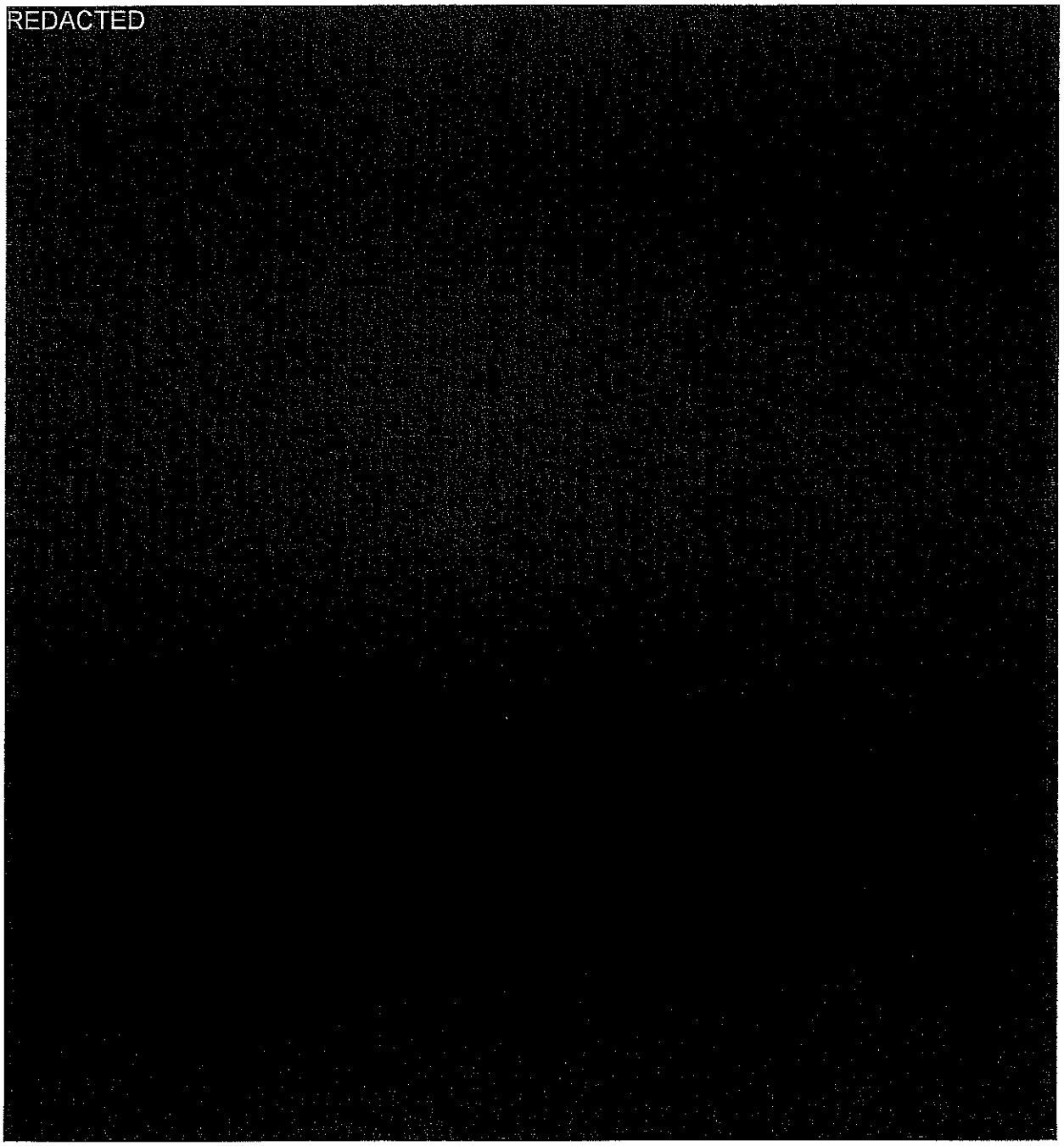
To qualify for pediatric exclusivity, requirements must be completed and all supporting documents submitted within 5 years of the receipt of the WR (25 November 2007; subsequently modified to 25 December 2007). If granted, pediatric exclusivity would confer an additional 6 months of exclusivity to the existing patient for RISPERDAL® Tablets, thereby extending the patent expiration date from December 2007 to June 2008.

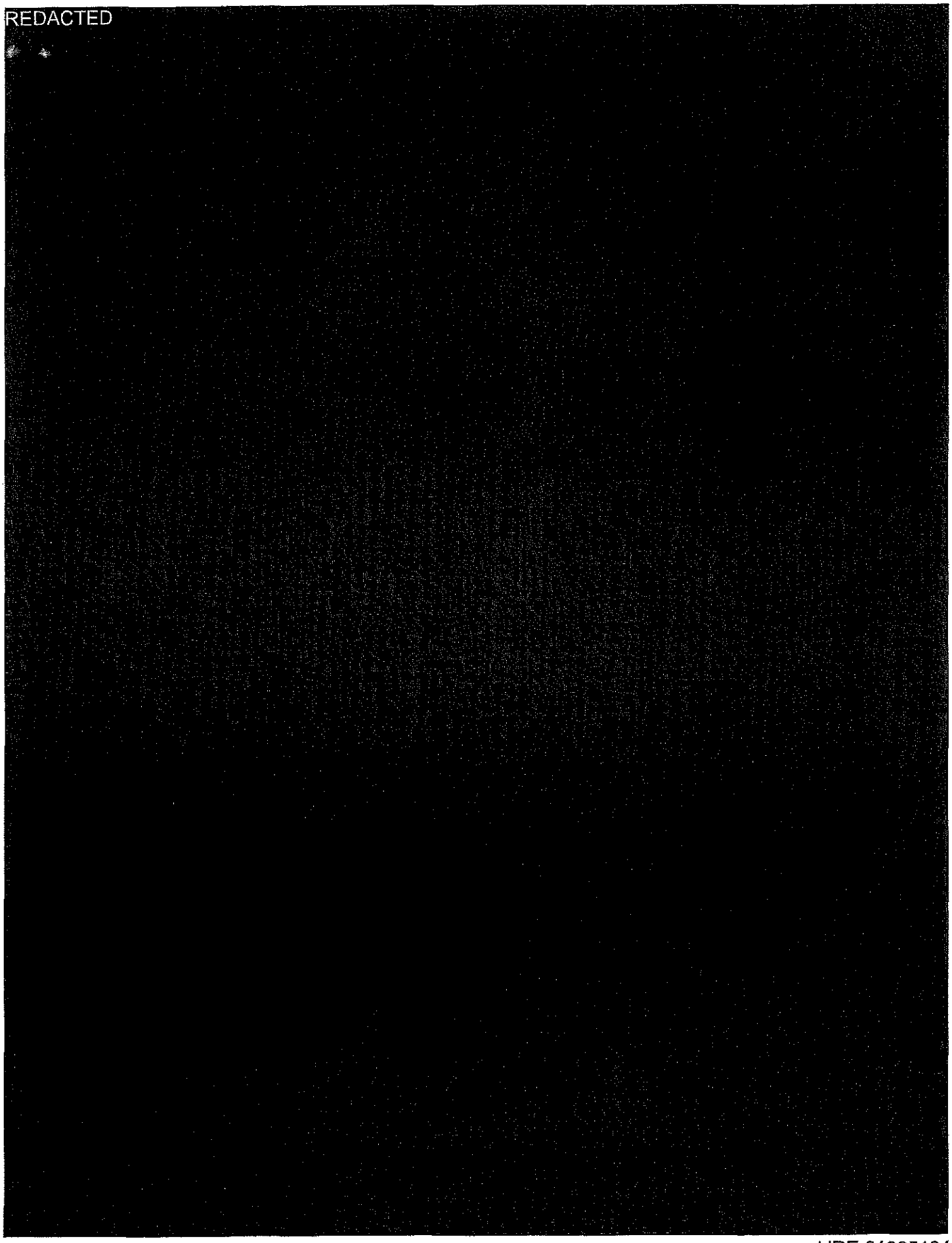
The objective of this interim review is to select the optimal scenario for obtaining pediatric exclusivity with RISPERDAL® in the treatment of adolescent schizophrenia and pediatric mania associated with bipolar disorder. Management feedback and decisions on three proposed scenarios will be made at the following meetings:

- Regulatory Stage gate (5 June 2003)
- IDC (25 September 2003)
- NPDC (10 October 2003)

Key Findings

In 1999, FDA updated the previous Guidance to Industry, "Qualifying for Pediatric Exclusivity under Section 505A of the Federal Food, Drug, and Cosmetic Act" (http://www.fda.gov/cder/guidance/2891fnl.htm). As specified in the WR for RISPERDAL® (25 November 2002), the sponsor's proposed changes to the WR and the reasons for the proposed changes should be submitted to FDA; the sponsor will be notified in writing if any changes to the WR are agreed upon by the Agency.




REDACTED

REDACTED

Plan to Execute Strategy

Regulatory Authority Meetings

- Clinical: REDACTED

  Request amendment to WR (August 2003).

US Regulatory Filings

- IND: Response to 14 May 2003 meeting requests

  REDACTED

  New protocol for placebo-controlled, fixed/flexible dose trial in adolescent schizophrenia (Scenarios 2-3 only, September 2003)

  Supplemental New Drug Application (December 2007)

EU (G5) Regulatory Filings (not applicable)

Japan Regulatory Filings (not applicable)

General (none planned)

Commercial

- **Global Marketing Leader: Katie Rielly-Gauvin**

  See sections 3 and 9 of this document

Project Management

- **Project Management Leader: Susan Mallows**

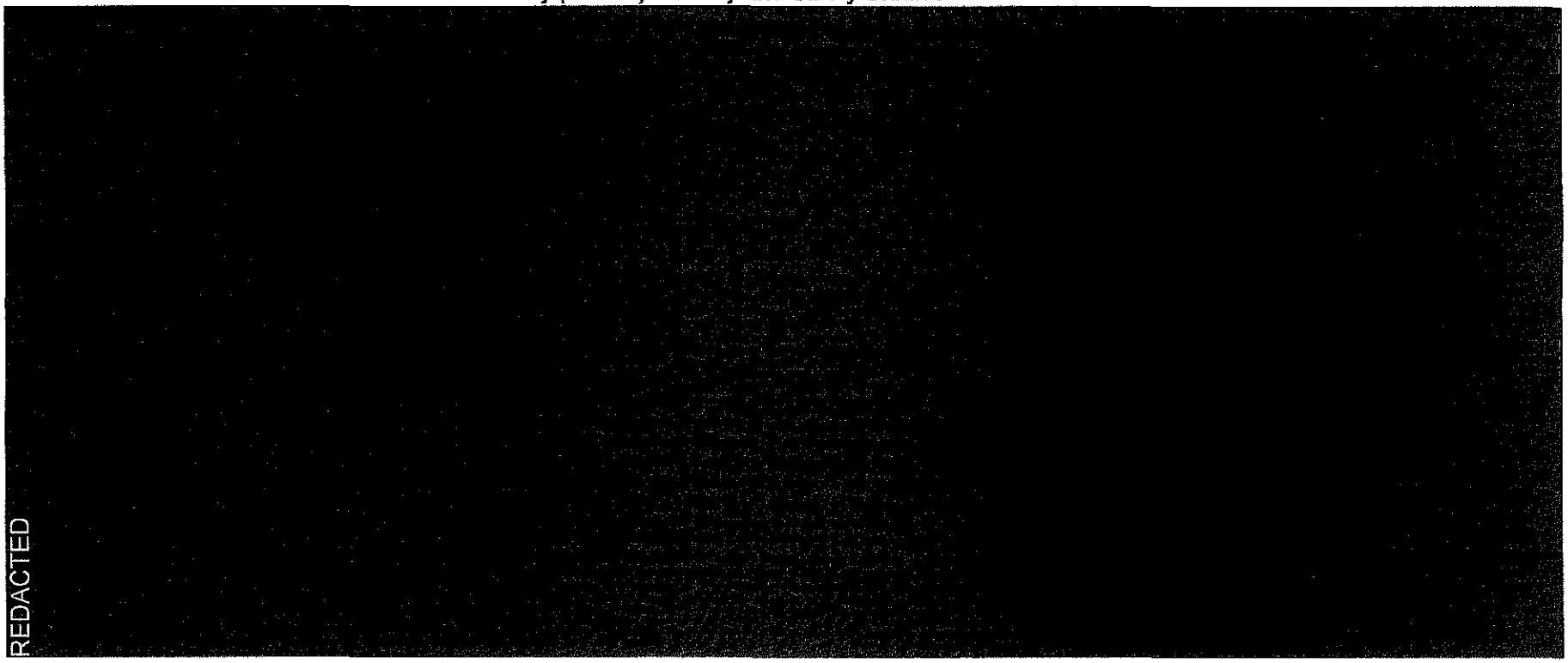
See Section 8 of this document

Chem-Pharm: Not applicable

Preclinical: Not applicable

An overview of proposed studies follows:

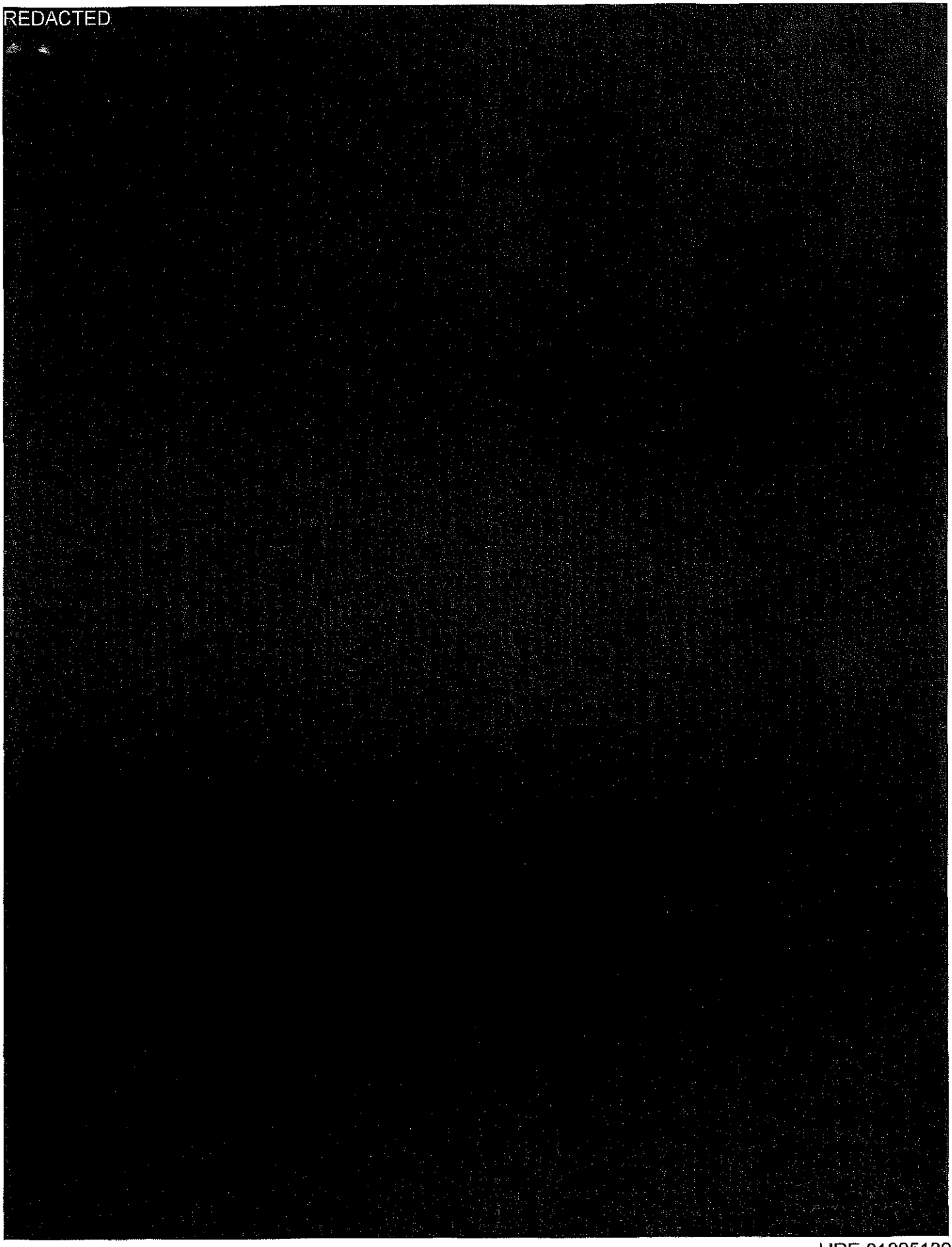
- **Primary (Pivotal) Efficacy and Safety Studies**



**(C) – Complete (Defined as the availability of topline data), (O) – Ongoing, (P) – Planned*

Phase	Status* (C, O, or P)	Study Identifier	Study Population	Primary Endpoint(s)	Dose & Regimen	Number of Subjects			Treatment Duration (Days/ weeks/ months)		
						Placebo	Drug	Active Compar	DB	OLE	Total
3	P	RIS-BIM-302	Children (10-12 yrs) and adolescents (13-17 yrs) with manic or mixed episodes of bipolar I disorder	Safety: incidence of adverse events	3-6 mg/day OD or BID		Max.200			9 wks	

Study Title, Objective and Design:
Title: The sustained efficacy and safety of risperidone in the treatment of children and adolescents with manic or mixed episodes of bipolar I disorder: a follow-up trial to RIS-BIM-301
Objective: To assess safety profile of risperidone in children and adolescents with bipolar mania during 9 wks treatment. Additionally efficacy will be documented.
Design: open-label, multicenter trial.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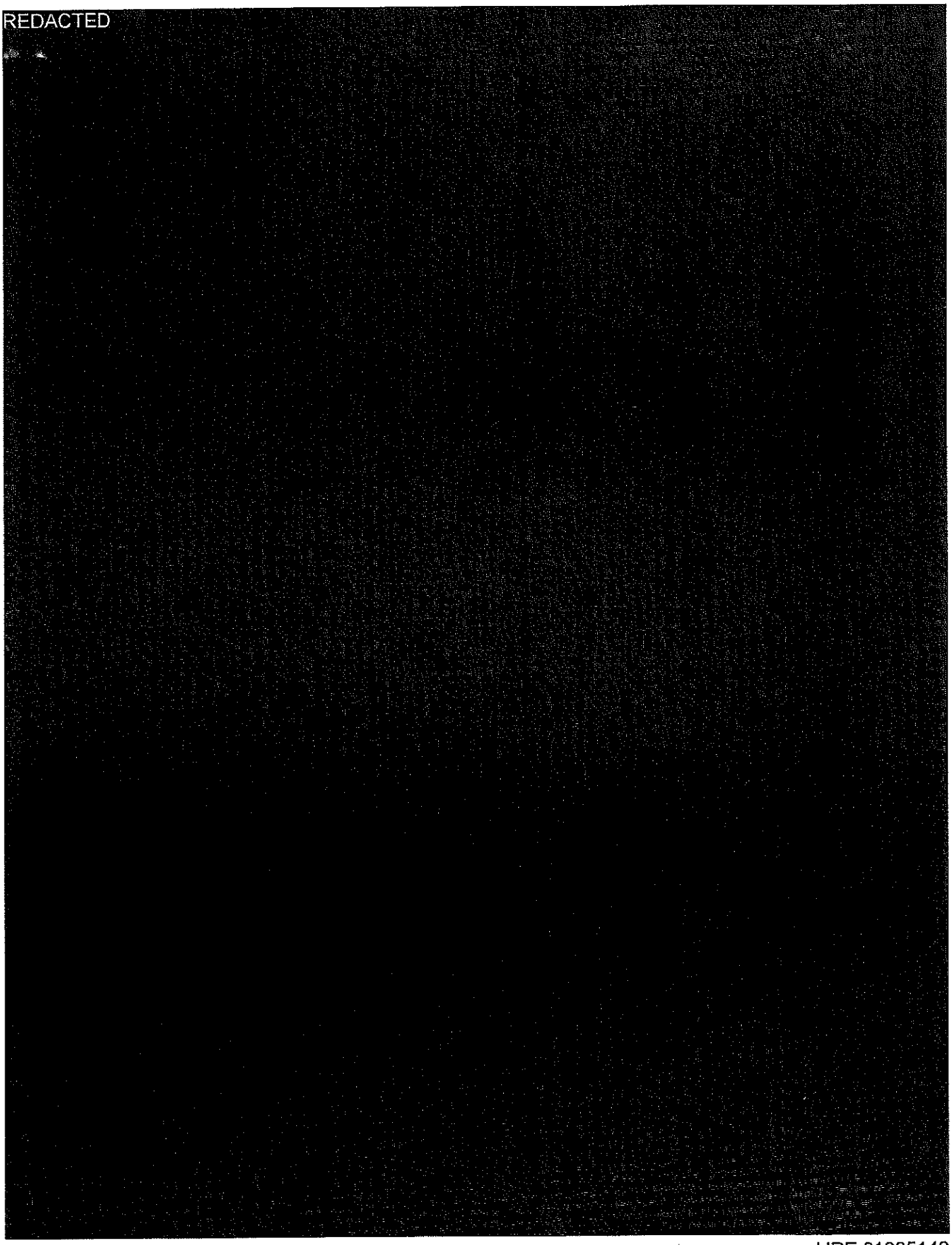
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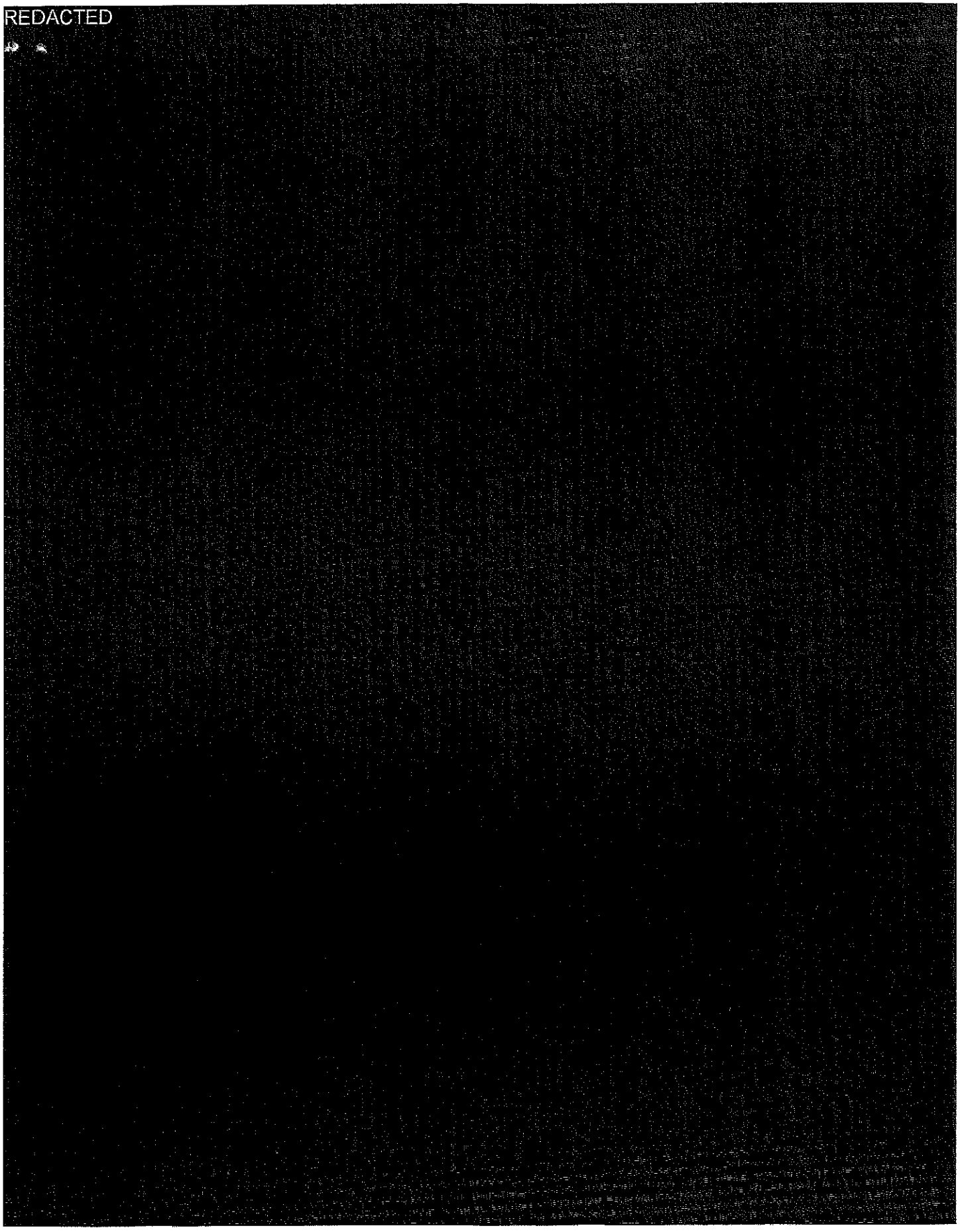
REDACTED

Attachment: History of Key Decisions

History of Key Decisions (Peds)

Date	Decision forum	Decision	Synopsis of Contract
Dec. 12, 2000	DCC	• Start 1 adolescent schizophrenia trial for label purposes and 1 pediatric Pk study	• 1 US trial for label purposes, submission in 4Q02 • 1 additional trial to start after WR
Aug. 28, 2002	IDC	• OK to file bipolar mania in US	• Team to return to IDC with pediatric plan after WR

Additional program history:

- March 2000: FDA does not accept filing for Risperdal in DBD (multiple diagnosis, unclear indication ...)
- Oct. 2000: Submitted study protocol in schizophrenia for label purposes (RIS-USA-231)
- Dec. 2001: FDA issues Lilly's WR: schizophrenia + bipolar mania

REDACTED

- Nov. 2002: FDA issues Janssen's WR
- May 2003: Meeting with FDA on WR requirements

History of Key Decisions (Autism)

Date	Decision Forum	Decision	Synopsis of Contract
Apr. 15	pre-IDC	OK to start filing preparation process	Prior to NPDC endorsement

Add. Program history

- Risperdal in DBD approved in 20 countries ex-US incl. Germany and France. Not in others because no long-term efficacy data (e.g. UK) or indication not suitable (US).
- April 1, 2003 meeting with FDA. RUPP study, RIS-CAN-23, REDACTED and DBD safety database = suitable package to file in autistic children. Advisory Committee required for indication wording and approval.
- March 2003; request for Orphan drug review (< 200,000 children in US)

Available Reference Document

Target Core Data Sheet

Clinical Supporting Documentation

- Clinical Functional Plan
- Investigators Brochure
- Clinical Stage Gate Review Minutes
- Competitive Labels
- SBA
- Clinical Summaries

Regulatory Supporting Documentation

- Regulatory Functional Plan
- Regulatory Stage Gate Review Minutes

Commercial Supporting Documentation

- Commercial Functional Plan
- Commercial Stage Gate Review Minutes

Project Management Supporting Documentation

- Project Management Functional Plan
- Project Management Stage Gate Review Minutes
- High level cross-functional project schedule