CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209311Orig1s000

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA 209311 (Resubmission/Class 1)
Supporting document/s:	Supporting Document Number 42, Applicant Serial Number 0041
Applicant's letter date:	6/08/2018
CDER stamp date:	6/08/2018 (Type 3 New Dosage Form)
Product:	HLD200 or Methylphenidate Hydrochloride
Indication:	Attention Deficit Hyperactivity Disorder (ADHD)
Applicant:	Ironshore Pharmaceuticals and Development, Inc.
Review Division:	Division of Psychiatry Products
Reviewer:	Deepa B. Rao DVM, MS, PhD
Supervisor:	Ikram Elayan, PhD
Division Director:	Mitchell V. Mathis, MD
Project Manager:	Hiren Patel PharmD, RAC

Memo to File

Following a complete response letter dated July 28, 2017, Ironshore Pharmaceuticals and Development, Inc., is re-seeking approval of their product HLD200 via a Class 1 Resubmission in response to our complete response letter.

There were no new nonclinical studies included with the resubmission.

From a nonclinical perspective, HLD200 remains reasonably safe for approval (see primary review dated 07/11/2017 in DARRTS).

For label updates, we requested that the label be updated to include data from in-vivo studies on the genotoxic potential of methylphenidate (see Section 13.1 under Mutagenesis). The sponsor's response was limited to inclusion of the following sentence: "(b) (4)

Because our request was specific for in-vivo genotoxicity testing, the information was modified to include data available from in vivo mouse bone marrow micronucleus assay available in published literature (Suter et al., 2006). Specifically, under Mutagenesis, the following sentence has been added (see below - highlighted in red) for consistency with other approved labels in this class.

Start of Label Excerpt

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis:
In a lifetime carcinogenicity study carried out in B6C3F1 mice, methylphenidate caused an increase in hepatocellular adenomas and, in males only, an increase in hepatoblastomas, at a daily dose of approximately 60 mg/kg/day. This dose is approximately (b) (4) times the maximum recommended human dose (MRHD) of 100 mg/day given to adults on a (b) (4) mg/m^2 basis. (b) (4) Hepatoblastoma is a relatively rare rodent malignant tumor type. There was no increase in total malignant hepatic tumors. The mouse strain used is sensitive to the development of hepatic tumors, and the significance of these results to humans is unknown.
Methylphenidate did not cause any increases in tumors in a lifetime carcinogenicity study carried out in F344 rats; the highest dose used was approximately 45 mg/kg/day, which is approximately (b) (4) times the MRHD (b) (4) on a (b) (4) mg/m^2 basis. (b) (4)
In a 24-week carcinogenicity study in the transgenic mouse strain p53$^{+/-}$, which is sensitive to genotoxic carcinogens, there was no evidence of carcinogenicity. Male and female mice were fed diets containing the same concentration of methylphenidate as in

the lifetime carcinogenicity study; the high-dose groups were exposed to 60 to 74 mg/kg/day of methylphenidate.

Mutagenesis:
Methylphenidate was not mutagenic in the *in vitro* Ames reverse mutation assay or in the *in vitro* mouse lymphoma cell forward mutation assay. Sister chromatid exchanges and chromosome aberrations were increased, indicative of a weak clastogenic response, in an *in vitro* assay in cultured Chinese Hamster Ovary (CHO) cells. Methylphenidate was negative in vivo in males and females in the mouse bone marrow micronucleus assay.

Impairment of Fertility:
Methylphenidate did not impair fertility in male or female mice that were fed diets containing the drug in an 18-week Continuous Breeding study. The study was conducted at doses up to 160 mg/kg/day, approximately (b) (4)

End of Label Excerpt

References:

Suter, W., Martus,H-J., and Elhajouji, A. 2006. Methylphenidate is not clastogenic in cultured human lymphocytes and in the mouse bone-marrow micronucleus test. Mutation Research. 607, 153-159.

Morris, SM., Petibone, DM., Lin, WJ., Chen, JJ., Vitiello B., Witt, KL., Marttison, DR. 2012. The genetic toxicity of methylphenidate:a review of the current literature. J Appl Toxicol., 32(10); 756-764.

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/s/

DEEPA B RAO
07/27/2018

IKRAM M ELAYAN
07/30/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA 209311
Supporting document/s:	Supporting Document Number 1, Applicant Serial Number 0000
Applicant's letter date:	9/30/2016
CDER stamp date:	9/30/2016 (Type 3 New Dosage Form)
Product:	HLD200 or Methylphenidate Hydrochloride
Indication:	Attention Deficit Hyperactivity Disorder (ADHD)
Applicant:	Ironshore Pharmaceuticals and Development, Inc.
Review Division:	Division of Psychiatry Products
Reviewer:	Deepa B. Rao DVM, MS, PhD
Supervisor:	Ikram Elayan, PhD
Division Director:	Mitchell V. Mathis, MD
Project Manager:	Martin Yoon PharmD

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 209311 are owned by Ironshore Pharmaceuticals and Development, Inc., or are data for which Ironshore Pharmaceuticals and Development, Inc., has obtained a written right of reference.
Any information or data necessary for approval of NDA 209311 that Ironshore Pharmaceuticals and Development, Inc., does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 209311.

Abbreviations

ADHD	Attention Deficit Hyperactivity Disorder
API	Active Pharmaceutical Ingredient
CNS	Central Nervous System
DR	Delayed Release
ER	Extended Release
HPMC	Hydroxypropylmethylcellulose
IR	Immediate Release
MCC	Microcrystalline cellulose
MPH	Methylphenidate Hydrochloride
MR	Modified Release
NTP	National Toxicology Program
USP	United States Pharmacopeia

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1 Executive Summary

1.1 Introduction

Ironshore Pharmaceuticals and Development, Inc., is seeking approval of HLD200, [a new formulation of methylphenidate hydrochloride (MPH)], via a 505(b)(2) application based on the Ritalin® label, and publically available published literature. The new formulation is an oral MPH Modified Release (MR) Capsule that is designed to allow a delayed release based on coated cores of MPH. The coated cores allow for controlled release of methylphenidate in plasma following an initial delay of approximately 8 to 10 hours. The new proposed dosing regimen is a once-daily evening oral dose in patients ≥ 6 years old diagnosed with Attention Deficit Hyperactivity Disorder (ADHD), up to a maximum dose of 100 mg/day.

1.2 Brief Discussion of Nonclinical Findings

No nonclinical studies were submitted to this NDA.

Nonclinical requirements are met based on the animal studies submitted and reviewed under the reference listed drug (RLD), namely, Ritalin® under NDA 010187. A few animal studies (genotoxicity and carcinogenicity) are supported by publically available literature. The results from all the relevant nonclinical toxicology studies are summarized in the existing label for the RLD.

The proposed label for this sponsor's NDA was modified slightly in the nonclinical sections of the label to reflect the dose differences compared to the RLD (maximum daily dose of 100 mg of HLD200 compared to 60 mg/day for the RLD - see Section 1.3.3).

The active pharmaceutical ingredient (API) for this product (methylphenidate hydrochloride) was originally approved in 1955 with a long history of clinical use. The sponsor's new formulation does not include any novel excipients, and all excipients used are lower than that used in other FDA-approved products for the same oral route of administration.

HLD200 appears reasonably safe for approval from a nonclinical perspective.

1.3 Recommendations

1.3.1 Approvability

Contingent on the negotiation of the label changes with the sponsor, this NDA application is considered to be reasonably safe for approval.

1.3.3 Labeling

Sections 8, 12.1,12.2, and 13 below have been excerpted from the sponsor's submission (Word file titled "(b) (4) Draft Label MS Word" under Module 1.14.1.3).

Proposed changes are underlined and italicized in blue below. It should be noted that the following label changes documented in this review are work-in- progress changes to the most updated version of the label, and may not reflect the finalized label (pending at this time) accurately.

Start of Label Excerpt

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

(b) (4)

Risk Summary

(b) (4) published studies report on the use of methylphenidate (b) (4) (b) (4) are insufficient to inform any drug-associated risks. No teratogenic effects were observed in embryo-fetal development studies with oral administration of methylphenidate to rats and rabbits during organogenesis at doses up to 2 and (b) (4) 9 times the maximum recommended human dose (MRHD) of 100 mg/day given to adolescents on a mg/m^2 basis, respectively.; (b) (4). However, spina bifida was observed in rabbits at a dose 31 (b) (4) times the MRHD given to adolescents. A decrease in pup body weight was observed in a pre-and post-natal development study with oral administration of methylphenidate to rats throughout pregnancy and lactation at doses (b) (4) 3.5 times the MRHD given to adolescents [see Data].

The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2% to 4% and of miscarriage is 15% to 20% of clinically recognized pregnancies.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

CNS stimulant medications, such as (b) (4) ™, can cause vasoconstriction and thereby decrease placental perfusion. No fetal and/or neonatal adverse reactions have been reported with the use of therapeutic doses of methylphenidate during pregnancy; however, premature delivery and low birth weight infants have been reported in amphetamine-dependent mothers.

Data

Animal Data

In studies conducted in rats and rabbits, methylphenidate was administered orally at doses of up to 75 and 200 mg/kg/day, respectively, during the period of organogenesis.

Teratogenic effects (increased incidence of fetal spina bifida) were observed in rabbits at the highest dose, which is approximately (b) (4) 31 times the (b) (4) maximum recommended human dose (MRHD) of 100 mg/day given to adolescents on a mg/m^2 basis. The no effect level for embryo-fetal development in rabbits was 60 mg/kg/day ((b) (4) 9 times the MRHD given to adolescents on a mg/m^2 basis). There was no evidence of specific teratogenic activity in rats, although increased incidences of fetal skeletal variations were seen at the highest dose leve (b) (4) 6 times the MRHD given to adolescents on a mg/m^2 basis), which was also maternally toxic. The no effect level for embryo-fetal development in rats was 25 mg/kg/day (2 times the MRHD given to adolescents on a mg/m^2 basis).

(b) (4)

8.3 Lactation

Risk Summary

Limited published literature, based on breast milk sampling from five mothers, reports that methylphenidate is present in human milk, which resulted in infant doses of 0.16% to 0.7% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 1.1 and 2.7. There are no reports of adverse effects on the breastfed infant and no effects on milk production. Long-term neurodevelopmental effects on infants from CNS stimulant exposure are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for (b) (4) ™ (b) (4) ™ and any potential adverse effects on the breastfed infant from or from the underlying maternal condition.

Clinical Considerations

Monitor breastfeeding infants for adverse reactions, such as agitation, insomnia, anorexia, and reduced weight gain.

8.4 Pediatric Use

The safety and effectiveness of (b) (4) ™ in (b) (4) 6 years of age have not been (b) (4)

The safety and effectiveness of (b) (4) ™ have been established in (b) (4) ages 6 to 17 years (b) (4) 2 adequate and well-controlled clinical studies *[see Clinical Studies (14)]*; pharmacokinetic data in (b) (4) adults (b) (4) and safety information from other methylphenidate products. The long-term efficacy of methylphenidate in (b) (4) has not been established.

Long-Term Suppression of Growth

Juvenile Animal Toxicity Data

Rats treated with methylphenidate early in the postnatal period through sexual maturation demonstrated a decrease in spontaneous locomotor activity in adulthood. A

deficit in acquisition of a specific learning task was observed in females only. The doses at which these findings were observed are at least 2.5 times the maximum recommended human dose (MRHD) of 100 mg/day given to children on a mg/m^2 basis.

In a study conducted in young rats, methylphenidate was administered orally at doses of up to 100 mg/kg/day for 9 weeks, starting early in the postnatal period (Postnatal Day 7) and continuing through sexual maturity (Postnatal Week 10). When these animals were tested as adults (Postnatal Weeks 13-14), decreased spontaneous locomotor activity was observed in males and females previously treated with ≥ 50 mg/kg/day (approximately ≥ 2.5 times the MRHD of 100 mg/day given to children on a mg/m^2 basis), and a deficit in the acquisition of a specific learning task was seen in females exposed to the highest dose (5 times the MRHD of 100 mg/day given to children on a mg/m^2 basis). The no effect level for juvenile neurobehavioral development in rats was 5 mg/kg/day (0.25 times the MRHD of 100 mg/day given to children on a mg/m^2 basis). The clinical significance of the long-term behavioral effects observed in rats is unknown.

8.5 Geriatric Use

(b) (4)™ has not been studied in patients over 65 years of age.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Methylphenidate HCl is a central nervous system (CNS) stimulant. The exact mode of therapeutic action in ADHD is not known.

12.2 Pharmacodynamics

Methylphenidate is a racemic mixture comprising the *d*- and *l*-isomers. The *d*-isomer is more pharmacologically active than the *l*-isomer. Methylphenidate is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis:
In a lifetime carcinogenicity study carried out in B6C3F1 mice, methylphenidate caused an increase in hepatocellular adenomas and, in males only, an increase in hepatoblastomas, at a daily dose of approximately 60 mg/kg/day. This dose is approximately (b) (4) times the maximum recommended human dose (MRHD) of 100 mg/day given to (b) (4) on a (b) (4) mg/m^2 basis. (b) (4) Hepatoblastoma is a relatively rare rodent malignant tumor type. There was no increase in total malignant hepatic tumors. The mouse strain used is sensitive to the development of hepatic tumors, and the significance of these results to humans is unknown.

Methylphenidate did not cause any increases in tumors in a lifetime carcinogenicity study carried out in F344 rats; the highest dose used was approximately 45 mg/kg/day, which is approximately [redacted] times the MRHD ([redacted] on a [redacted] mg/m^2 basis.
In a 24-week carcinogenicity study in the transgenic mouse strain p53 [redacted], which is sensitive to genotoxic carcinogens, there was no evidence of carcinogenicity. Male and female mice were fed diets containing the same concentration of methylphenidate as in the lifetime carcinogenicity study; the high-dose groups were exposed to 60 to 74 mg/kg/day of methylphenidate.

Mutagenesis:
Methylphenidate was not mutagenic in the *in vitro* Ames reverse mutation assay or in the *in vitro* mouse lymphoma cell forward mutation assay. Sister chromatid exchanges and chromosome aberrations were increased, indicative of a weak clastogenic response, in an *in vitro* assay in cultured Chinese Hamster Ovary (CHO) cells. [redacted]

Impairment of Fertility:
Methylphenidate did not impair fertility in male or female mice that were fed diets containing the drug in an 18-week Continuous Breeding study. The study was conducted at doses up to 160 mg/kg/day, approximately [redacted] the [redacted] recommended dose on a [redacted] mg/m^2 basis, [redacted].

End of Label Excerpt

*This is to be updated pending response from the sponsor.

2 Drug Information

2.1 Drug

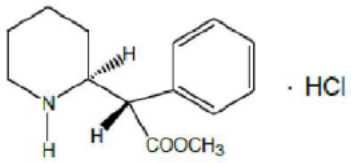
CAS Registry Number
298-59-9

Generic Name
Methylphenidate Hydrochloride United States Pharmacopeia (USP)
Code Name
Methylphenidate Hydrochloride Modified Release Capsules, HLD200

Chemical Name
2-Piperidineacetic acid, α-phenyl-, methyl ester, hydrochloride(R*,R*)-(±)-

Molecular Formula/Molecular Weight
$C_{14}H_{19}NO_2HCl$/ 269.76 g/mol

Structure or Biochemical Description



Pharmacologic Class
Central Nervous System (CNS) Stimulant

2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA 010187 (This is the RLD)
Product Name: Ritalin® Tablet
Sponsor: Novartis Pharmaceuticals Corp
Indication: ADHD
Status: Active (Approved Dec 5, 1955)

NDA 21259
Product Name: Metadate® CD (Methylphenidate hydrochloride)
Sponsor:UCB Inc.
Indication: ADHD
Status: Approved April 3, 2001

IND 118074
Product Name: Methylphenidate hydrochloride Capsule
Sponsor: Ironshore Pharmaceuticals and Development Inc.
Indication: ADHD
Status: Active

DMF (b) (4)
Product Name: Methylphenidate Hydrochloride, USP
Sponsor: (b) (4)
Indication: Type II
Status: Active

DMF (b) (4)
Product Name: (b) (4)
Sponsor: (b) (4)
Indication: Type IV
Status: Active

DMF (b) (4)
Product Name: (b) (4)
Sponsor: (b) (4)
Indication: Type III
Status: Active

DMF (b) (4)
Product Name: (b) (4)
Sponsor: (b) (4)
Indication: Type III
Status: Active

DMF (b) (4)
Product Name: (b) (4)
Sponsor: (b) (4)
Indication: Type III
Status: Active

2.3 Drug Formulation

MPH MR Capsules consist of (b) (4) each unit capsule containing either 20 mg, 40 mg, 60 mg, 80 mg or 100 mg of active. The composition of the MPH MR Capsules is shown in the tables below:

Table 1: Composition of Methylphenidate HCl MR Capsules ([redacted]) for 20 mg, 40 mg and 60 mg Strengths (excerpted from the sponsor's submission)

Component and Quality Standard (and Grade if applicable)	Function	IID Oral Route (mg)[1]	Quantity per Unit (mg) and % Composition					
			20 mg	%	40 mg	%	60 mg	%
Methylphenidate Hydrochloride, USP	Active Ingredient	----------	20.00	[redacted]	40.00	[redacted]	60.00	[redacted]
Microcrystalline Cellulose, [redacted] NF	[redacted]	[redacted]	[redacted]					
[redacted]								
Ethylcellulose, [redacted] NF								
Hydroxypropyl Cellulose [redacted] NF								
Dibutyl Sebacate, NF								
Magnesium Stearate [redacted] NF								
Methacrylic Acid Copolymer Type B, NF[2]								
Mono- and Di-Glycerides, NF								
Polysorbate 80, NF								
Talc [redacted] USP								
[redacted]								
Total Capsule Weight		--------	**163.42**	**NA**	**311.85**	**NA**	**472.28**	**NA**

NA = not applicable; NF = National Formulary; USP = United States Pharmacopeia
[1]FDA's Inactive Ingredient Database (IID)
[2]Methacrylic Acid Copolymer Type B, NF is also referred to as [redacted]

Table 2: Composition of Methylphenidate HCl MR Capsules ((b) (4)) for 80 mg and 100 mg Strengths (excerpted from the sponsor's submission)

Component and Quality Standard (and Grade if applicable)	Function	IID Oral Route (mg)[1]	Quantity per Unit (mg) and % Composition			
			80 mg	%	100 mg	%
Methylphenidate Hydrochloride, USP	Active Ingredient	----------	80.00	(b) (4)	100.0	(b) (4)
Microcrystalline Cellulose, (b) (4) NF	(b) (4)					(b) (4)
(b) (4)						
Ethylcellulose (b) (4) NF						
Hydroxypropyl Cellulose (b) (4) NF						
Dibutyl Sebacate, NF						
Magnesium Stearate (b) (4) (b) (4), NF						
Methacrylic Acid Copolymer Type B, NF[2]						
Mono- and Di-Glycerides, NF						
Polysorbate 80, NF						
Talc ((b) (4) , USP						
						(b) (4)
Total Capsule Weight		--------	**608.71**	**NA**	**749.13**	**NA**

NA = not applicable; NF = National Formulary; USP = United States Pharmacopeia
[1]FDA's Inactive Ingredient Database (IID)
[2]Methacrylic Acid Copolymer Type B, NF is also referred to as (b) (4)

2.4 Comments on Novel Excipients

There are no novel excipients in this new formulation. All listed excipients are lower than that used in other FDA-approved products (compared to FDA's Inactive Ingredient Database – IID – as listed in Tables 1 and 2 above; see chemistry review for more details) for the same oral route of administration.

2.5 Comments on Impurities/Degradants of Concern

A toxicological assessment of the levels of elemental impurities (b) (4)) in the RLD product in relation to Permitted Daily Exposures (PDEs) under the RLD (see DARRTS under NDA 010187 dated October 16, 2013).

2.6 Proposed Clinical Population and Dosing Regimen

Patients diagnosed with ADHD aged ≥ 6 years.

2.7 Regulatory Background

The corresponding IND for this NDA is IND 118074 owned by the same sponsor - Ironshore Pharmaceuticals and Development, Inc.

3 Studies Submitted

No nonclinical studies have been submitted with this NDA.

4 Pharmacology

4.1 Primary Pharmacology

The mechanism of action of methylphenidate in ADHD is not entirely understood, although it is known to block the reuptake and enhance release of dopamine and norepinephrine in the mammalian brain, an effect that increases dopamine and norepinephrine levels in the synaptic cleft.

11 Integrated Summary and Safety Evaluation

Ironshore Pharmaceuticals and Development, Inc., is seeking approval of HLD200, [a new formulation of methylphenidate hydrochloride (MPH)] via a 505(b)(2) application based on the Ritalin® label (NDA 010187), and publically available published literature.

The new formulation is an oral MPH Modified Release (MR) Capsule that is designed to allow a delayed release based on coated cores of MPH. The delayed release (DR) and extended release (ER) coated cores allow for controlled release of methylphenidate following an initial delay of approximately 8 to 10 hours.

The proposed dosing regimen is a once-daily evening oral dose in patients ≥ 6 years old diagnosed with Attention Deficit Hyperactivity Disorder (ADHD), up to a maximum dose of 100 mg/day (compared to a maximum daily dose of 60 mg for the RLD).

The RLD for the sponsor's drug under NDA 010187 was originally approved in 1955.

Based on the long history of clinical use of the API, the information found in the labeling of the RLD (NDA 010187), publically available literature, and the use of known

excipients and at amounts lower than in other FDA-approved products for the same route, HLD200 appears reasonably safe for approval from a nonclinical perspective.

12 References

Toxicology and Carcinogenesis Studies of Methylphenidate Hydrochloride (CAS No. 298-59-9) in F344/N rats and B6C3F_1 mice (Feed Studies). National Toxicology Program. Technical Report Series. No.439. July 1995. NIH Publication No. 95-3355.

Freeman GB., Reichelderfer D., Athey PM., Graves SW., Yarrington JT., and Hejtmancik M. Toxicity Evaluation of Methylphenidate Hydrochloride in Transgenic Mice. Conducted by Battelle for the National Institute of Environmental Health Sciences, July 1996.

Suter, W., Martus, H-J., and Elhajouji,A. Methylphenidate is not clastogenic in cultured human lymphocytes and in the mouse bone-marrow micronucleus test. Mutation Research 607, 153-159, 2006.

L5178Y $TK^{+/-}$ Mouse Lymphoma Cell Forward Mutation Assay of NTP Chemical # 563326. Conducted by SRI International for Environmental Protection Agency.March 1983.

Teo, SK., San, RH., Wagner, VO., Gudi,R., Stirling, D.I., Thomas,S.D., Khetani, V.D. D-Methylphenidate is non-genotoxic in in vitro and in vivo assays. Mutation Research 537, 67-79, 2003.

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