CLINICAL PHARMACOLOGY REVIEW

NDA:	**205489**
IND:	**109108**
Submission Dates:	**Jan 9th-2015**
Brand Name:	**COTEMPLA XR-ODT (proposed)**
Generic Name:	**Methylphenidate**
Dosage & Strength:	**XR-ODT tablets of 10, 20, and 30 mg strength**
Indication:	**Treatment for ADHD**
Applicant:	**NEOS Therapeutics**
Submission:	**Original NDA[505(b)(2)]**
Division:	**DCP1**
Reviewer:	**Praveen Balimane, Ph.D.**
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Contents

EXECUTIVE SUMMARY 3

1.1 Recommendation 4

1.2 Post-Marketing Studies 5

2 Question Based Review 5

2.1 Are the formulations used for clinical trials different from the planned to-be-marketed formulation? 5

2.2 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug? 6

2.3 What is the proposed dosage form and route of administration? 6

2.4 What is the reported adverse event profile from the Phase 1 (clinical pharmacology formulation) and Phase 3 efficacy study (clinical trial formulation)? 6

2.5 What drugs (substances, products) indicated for the same indication are already approved in the US? 7

2.6 What are the key pharmacokinetic features of the clinical pharmacology formulation? 7

2.7 Can the clinical pharmacology formulation be taken with or without food? 8

2.8 What was the efficacy of the clinical trial formulation demonstrated in a dedicated efficacy study? 8

2.9 What are the sponsor's dosing recommendations for the to-be-marketed formulation? 10

2.10 Did the heavier children get higher doses of clinical trial formulation in Study NT0102.1004? 10

3 Analytical Methods 11

3.1 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters? 11

3.2 Are bioanalytical methods used to assess concentrations of d- and l-methylphenidate acceptable? 11

EXECUTIVE SUMMARY

Neos Therapeutics, Inc. has submitted a New Drug Application (NDA) for Methylphenidate (MPH) Extended Release Orally Disintegrating Tablets (XR-ODT) for the treatment of ADHD via a 505(b)(2) route using Metadate CD ® as the reference listed drug (RLD). The formulation is intended to provide an in vivo extended release profile through the use of both an immediate release (IR) and a delayed/extended-release form of MPH [(b) (4)] The clinical program for this application is based on three phase 1 clinical pharmacology trials (relative bioavailability, food-effect, and pediatric pharmacokinetic trials) and a single clinical efficacy and safety trial (Table 1). Neos is requesting approval for three strengths of Methylphenidate XR-ODT, 10 mg, 20 mg, and 30 mg (equivalent to methylphenidate hydrochloride). The proposed trade name is COTEMPLA XR-ODT.

Table 1: Summary of Clinical Development Program

Trial No.	Trial	Population	Role	Formulation
NT0102.1001	Relative Bioavailability	Adults	To link with RLD, Metadate CD.	Clinical Pharmacology Formulation (Lot: 1E101A)
NT0102.1002	Food Effect	Adults	To assess food effect	Clinical Pharmacology Formulation (Lot: 1E101A)
NT0102.1003	Pediatric Pharmacokinetic	Children and Adolescents (6-17 yr)	[(b) (4)]	Clinical Pharmacology Formulation (Lot: 1E101A)
NT0102.1004	Efficacy and Safety	Children (6-12 yr)	To assess efficacy in children	Clinical Trial Formulation (Lot: 2E116E)

The sponsor developed three formulations in the program, including a clinical pharmacology formulation (Lot: 1E101A), a clinical trial formulation (Lot: 2E116E), and a to-be-marketed formulation (Proposed). The clinical pharmacology formulation (Lot: 1E101A) was used in the relative bioavailability trial, food effect trial, and pediatric pharmacokinetic trial. The clinical trial formulation (Lot: 2E116E) was used in the single efficacy and safety trial. It was identified in the review cycle that all three formulations are significantly different from each other (Table 2) (Refer to OPQ review by David Claffey et. al., signed off on 9/9/2015). The to-be-marketed formulation will have [(b) (4)]% [(b) (4)] (w/w) delayed release and [(b) (4)]% (w/w) [(b) (4)] extended release [(b) (4)] than the clinical trial formulation. In addition, there is about [(b) (4)]% change on the release controlling [(b) (4)] between the clinical pharmacology formulation and the clinical trial formulation. In the development program, no additional bioequivalence study was conducted to bridge the three formulations.

From the Office of Clinical Pharmacology (OCP)'s perspective, this program has several deficiencies.

1. No adequate link has been established between the clinical trial formulation and the to-be-marketed formulation. Due to the lack of adequate link, the findings from the efficacy and safety trial based on the clinical trial formulation may not inform the effectiveness of the product intended to be marketed.
2. No adequate link has been established between the to-be-marketed formulation (or clinical trial formulation), and the RLD (Metadate CD ®). Hence, the agency's findings on efficacy and safety of the RLD may not be used to support the approval of the product intended to be marketed.
3. Pediatric pharmacokinetic information obtained with the clinical pharmacology formulation is insufficient to support extrapolation of efficacy findings (based on clinical trial formulation) from children into adolescents and (b) (4) for the to-be-marketed formulation.
4. Food effect findings based on the clinical pharmacology formulation may not inform the food effect on the to-be-marketed formulation. The to-be-marketed formulation contains the (b) (4) amount of release controlling (b) (4) among the three formulations (Table 2). Because the level of interaction between food and the release controlling (b) (4) is unclear, it may not be appropriate to extrapolate the food effect findings from the clinical pharmacology formulation to the to-be-marketed formulation.

Based on OCP's assessment, the following remedy actions are necessary.

- The sponsor should conduct a bioequivalence study to link the to-be-marketed formulation with the clinical trial formulation under fasted condition. It has been shown that the release controlling (b) (4) of the clinical pharmacology formulation is bracketed by the clinical trial formulation and the to-be-marketed formulation (Table 2). Therefore, should bioequivalence be demonstrated between these two formulations i.e. an adequate link established between the to-be-marketed formulation and clinical trial formulation, it will also be sufficient to bridge between the clinical pharmacology formulation and the to-be-marketed formulation. Hence deficiency 1 through 3 can be resolved.
- Food effect on the to-be-marketed formulation should be assessed to address deficiency 4. It can be evaluated by adding one more arm (i.e. to be marketed formulation in fed state) in the above bioequivalence study.

1.1 Recommendation

The Office of Clinical Pharmacology (OCP) has determined that the information provided in the NDA submission does not support approval of the product intended to be marketed. Therefore, OCP recommends a Complete Response action. The sponsor should conduct a bioequivalence study to link the to-be-marketed formulation and the clinical trial formulation under fasted condition. In addition, the food effect on the to-be-marketed formulation should also be assessed.

1.2 Post-Marketing Studies

None

2 Question Based Review

2.1 Are the formulations used for clinical trials different from the planned to-be-marketed formulation?

Yes. The clinical pharmacology formulation (Lot: 1E101A), clinical trial formulation (Lot: 2E116E), and the to-be-marketed formulation are all significantly different from each other. In the development program, there is no additional bioequivalence trial to link the three formulations.

The sponsor developed three formulations in the program, including a clinical pharmacology formulation (Lot: 1E101A), a clinical trial formulation (Lot: 2E116E), and a to-be-marketed formulation (Proposed). The clinical pharmacology formulation was used in the relative bioavailability trial, food effect trial, and pediatric pharmacokinetic trial. The clinical trial formulation was used in the efficacy and safety trial. The difference among the three formulations is summarized in Table 2. The to-be-marketed formulation will have (b) (4)% (b) (4) (w/w) delayed release and (b) (4)% (w/w) (b) (4) extended release (b) (4) than the clinical trial formulation used in the pivotal efficacy study. In addition, there is about (b) (4)% change on the release controlling (b) (4) between the clinical pharmacology formulation and the clinical trial formulation. (OPQ review by David Claffey et. al., signed off on 9/9/2015).

Table 2: Difference in Formulation between the Clinical Pharmacology Formulation (1E101A), Clinical Trial Formulation (2E116E), and "To-be-Marketed" Formulation

Component	Function	Quantity per 30 mg Strength Tablet (mg)		
		1E101A	2E116E	Proposed
(b) (4)	(b) (4)			
(b) (4)				
Crospovidone				
Sucralose				
Citric Acid (b) (4)				
(b) (4) Grape (b) (4) (b) (4)				
Natural Masking Type Powder (b) (4)				
Lake Blend Purple (b) (4)				
Magnesium Stearate				

2.2 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Neos Therapeutics, Inc. has submitted a New Drug Application (NDA) for Methylphenidate (MPH) Extended Release Orally Disintegrating Tablets (XR-ODT) for the indication of treatment of ADHD via the 505(b)(2) route. The formulation is intended to provide an in vivo extended release profile through the use of both an immediate release (IR) component and a delayed/extended-release form of MPH (b) (4)

The clinical program for this application is based on 3 Phase one clinical pharmacology trials (bioavailability, food-effect, and pediatric PK trials) and a single clinical efficacy and safety trial. The efficacy and safety trial (NT0102.1004) demonstrated efficacy in ADHD for children (ages 6-12 yr) between 20-to-60 mg daily dose levels. Methylphenidate XR-ODT was developed to contain the same dose of methylphenidate base as the RLD in each of the three tablet strengths.

Three different formulations were developed in the program; two of them were used in different clinical trials. Please refer to question 1 regarding the formulation issues in the development program.

2.3 What is the proposed dosage form and route of administration?

The proposed dosage form of the to-be-marketed formulation is XR-ODT tablets (10, 20, and 30mg of (b) (4) and it is to be administered orally.

2.4 What is the reported adverse event profile from the Phase 1 (clinical pharmacology formulation) and Phase 3 efficacy study (clinical trial formulation)?

The adverse event profile was obtained based on the clinical trial formulation from the phase 3 trial and based on the clinical pharmacology formulation from the phase 1 trial. Bioequivalence was not established between the to-be-marketed formulation and the clinical trial formulation (or clinical pharmacology formulation) in the development program. Therefore, the relevance of the safety findings to the to-be-marketed formulation is unclear.

The nature of the AEs reported in the three Phase 1 trials using the clinical pharmacology formulation (NT0102.1001, NT0102.1002, and NT0102.1003) was consistent with the mechanism of action of MPH. The most commonly reported AEs (>5%) included nausea, vomiting, anxiety, nervousness, decreased appetite, headache, heart rate increase, and tachycardia. Based on system organ class (SOC), GI disorders were the most commonly reported AE. The AEs were mostly mild, some moderate, and none were severe or serious. In the study that included a positive control (NT0102.1001), there were no differences in the incidence or severity of AEs between MPH XR-ODT and METADATE CD.

There is limited experience with clinical trial formulation in a single clinical efficacy and safety trial. The most common (≥2% in the clinical trial formulation group and greater than placebo) adverse reactions (causality attributed to study drug by the investigators) reported in the Phase 3 controlled study conducted in 87 ADHD patients (6-12 years of age) were dizziness and trichotillomania.

Thus, overall the clinical trial formulation and clinical pharmacology formulation were well tolerated. No subjects withdrew due to AEs related to the treatment. In general, the nature of the TEAEs reported was consistent with the mechanism of action for these formulations.

2.5 What drugs (substances, products) indicated for the same indication are already approved in the US?

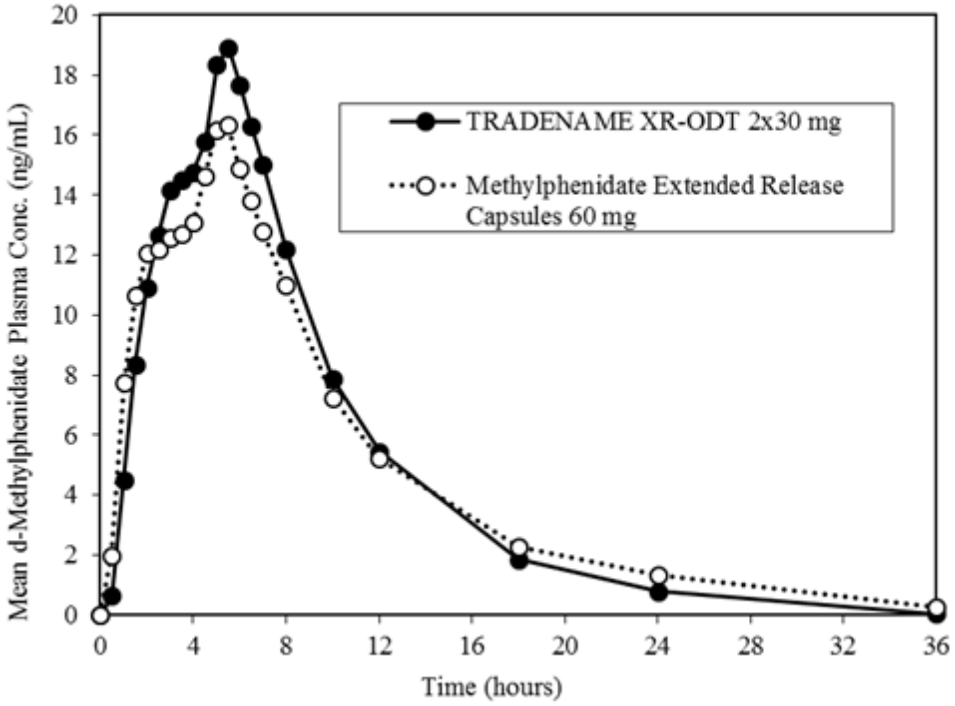
Other previously approved methylphenidate extended-release products indicated for the treatment of ADHD are Aptensio ®, Concerta ®, Ritlain LA ®, Focalin ®, Metadate CD ®, and Quillivant ®.

2.6 What are the key pharmacokinetic features of the clinical pharmacology formulation?

The clinical pharmacology formulation (1E101A) was used in the three pharmacokinetic trials (relative bioavailability trial, food effect trial, and pediatric pharmacokinetic trial).

Based on the relative bioavailability trial ((NT0102.1001), the PK profile of the clinical pharmacology formulation was similar to the reference listed drug (RLD), Metadate® CD. Following a single, 60 mg (2x30 mg qd) oral dose in healthy adult subjects in a crossover study under fasting conditions, *d*-methylphenidate (*d*-MPH) mean (±SD) peak plasma concentration occurred at a median time of 5.0 hours after dosing. The terminal T1/2 was 4 hr. The shape of the mean PK profile demonstrated the typical dual peak with the 1st shoulder at around 2 hr followed by the Cmax at around 5 hr.

Figure 1: Mean *d*-Methylphenidate Plasma Concentration-Time Profiles for Clinical Pharmacology Formulation (Filled Circle) vs. METADATE CD (Empty Circle)



2.7 Can the clinical pharmacology formulation be taken with or without food?

Yes. However food effect trial was conducted using clinical pharmacology formulation (1E101A) and not the to-be-marketed formulation. The high-fat, high-calorie food causes only minor changes in PK of d-methylphenidate. The Cmax for d-methylphenidate is decreased by 12.6% while the AUCinf increases by 11%. These would not be considered as clinically important changes.

2.8 What was the efficacy of the clinical trial formulation demonstrated in a dedicated efficacy study?

Yes, efficacy was established using the clinical trial formulation. However efficacy trial used a formulation (2E116E) that is considered significantly different from the to-be-marketed formulation. Bioequivalence was not established between the to-be-marketed formulation and the clinical trial formulation. Therefore, the relevance of the efficacy and safety findings based on the clinical trial formulation to the to-be-marketed formulation is unclear at present.

Efficacy and safety study (NT0102.1004) demonstrated efficacy in ADHD for children (ages 6-12 yr) between 20-to-60 mg daily dose levels. It was a randomized, multicenter, double-blind, placebo-controlled, parallel group study of NT0102 methylphenidate polistirex extended-release oral disintegrating tablets (equivalent to 20, 30, 40,or 60 mg of methylphenidate hydrochloride) in children (ages 6-12 years) with attention-deficit

hyperactivity disorder. The primary objective of this study was to determine the efficacy, safety, and tolerability of the NT0102 MPP XR ODT in children with ADHD in a laboratory classroom setting.

The clinical trial formulation was administered in an open-label, 4-week, stepwise dose optimization period (from 20- to 30- to 40- and up to 60 mg per day) to determine the optimal dose, followed by a 1-week dose-stabilization period, then a double-blind, parallel group treatment period during which subjects received either clinical trial formulation at the optimal dose, or matching placebo, administered once daily for 7 days (at home for the first 6 days, and in the laboratory classroom setting on the 7th day). Efficacy measures include the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) and the Permanent Product Measure of Performance (PERMP). Subjects were assessed at baseline (pre-dose), and 1, 3, 5, 7, 10, 12, and 13 hours post-dose on the testing day (Visit 8). Specifically, the primary objective was to evaluate the efficacy of NT0102 compared to placebo as measured by the SKAMP-Combined post-dose score averaged across the test day for active drug versus placebo. The treatment average score is defined as the mean daily average across the 7 post-dose measurements.

The results of this study demonstrated the efficacy of the clinical trial formulation for the primary endpoint (the SKAMP-Combined score averaged over the classroom test day). The SKAMP-Combined score averaged over the classroom testing day was 25.3 for the placebo group and 14.3 in the clinical trial formulation treated group; the symptom severity was greater in the placebo group. The LS mean difference was -11.04, which was statistically significant ($p<0.0001$).

Table 3: Efficacy Results from Study NT0102.1004

Primary Analysis Results for the SKAMP-Combined Averaged Over the Classroom Testing Day (N=82)

	SKAMP-Combined (Full Analysis Set) N=82	SKAMP-Combined (Per Protocol Set) N=80	SKAMP-Attention (Full Analysis Set) N=82	SKAMP-Deportment (Full Analysis Set) N=82
LS Mean (95% CI)				
NT0102	14.3 (12.2, 16.4)	14.6 (12.4, 16.7)	7.7 (6.7, 8.7)	6.7 (5.2, 8.1)
Placebo	25.3 (23.0, 27.6)	25.9 (23.5, 28.3)	12.2 (11.1, 13.4)	12.8 (11.3, 14.3)
Difference	-11.04 (-13.9, -8.20)	-11.29 (-14.2, -8.42)	-4.49 (-5.91, -3.08)	-6.13 (-7.97, -4.28)
P-value	<0.0001	<0.0001	<0.0001	<0.0001

Abbreviations: CI= confidence interval, LS Mean=least squares mean, SKAMP=Swanson, Kotkin, Agler, M-Flynn, and Pelham

2.9 What are the sponsor's dosing recommendations for the to-be-marketed formulation?

The sponsor has proposed the following dosing recommendations for the to-be-marketed formulation:

For patients 6 years [redacted], recommended starting dose is [redacted] mg given orally once daily in the morning. Dosage may be [redacted] weekly in increments of [redacted] mg to [redacted] mg per day. Daily dosage above [redacted] mg is not recommended.

However, in section [redacted] the sponsor has [redacted]

2.10 Did the heavier children get higher doses of clinical trial formulation in Study NT0102.1004?

Study NT0102.1004 was an efficacy study in children between the ages of 6 yr to 12 yr designed as a flexible-dosing study. Clinical trial formulation was used in the trial. It had open-label dose-optimization period (4 weeks) with an initial dose of 20 mg of clinical trial formulation once daily in the morning. The dose could be titrated on a weekly basis from 20 mg, to 30 mg, to 40 mg, and up to 60 mg until an optimal dose or the maximum dose of 60 mg/day was reached. Thus, each patient received the final optimized dose (anywhere between 20 to 60 mg per day) based on individual tolerability and efficacy (i.e. clinical response).

However, the study failed to show any dependence of final optimized dose on body-weight. As is evident from the table below, there was no correlation between patients weight to the final optimized dose. Thus, the heavier children were neither on higher doses nor the lighter children on lower doses. Please refer to Biostatistics review for full details.

Table 4: Final Optimized Dose (mg) vs. Patient Weight (kg) in Study NT0102.1004

Final optimized dose (mg)	N (number of patients)	Weight in kg (mean ± sd)
20	11	39.5 ± 18.1
30	21	35.2 ± 10.9
40	22	33.4 ± 10.4
60	28	38.1 ± 13.3

This suggests that a weight-based optimization of dose is not required in the clinic.

3 Analytical Methods

3.1 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters?

Yes.
The active moiety, d- and l-methylphenidate was appropriately measured in biological fluids.

3.2 Are bioanalytical methods used to assess concentrations of d- and l-methylphenidate acceptable?

Yes.
A fully validated bioanalytical method was used for sample analysis and it was acceptable. The bioassay information is summarized in Table 9.

Table 5: Bioanalytical Method

Parameter	Results
Method Summary	Human plasma was analyzed for *d-threo*-MPH and *l-threo*-MPH according to (b) (4) procedure (b) (4) Validation, effective 31 January 2011. The method was validated for a range of 0.250 to 50.0 ng/mL for *d-threo*-MPH, and 0.0100 to 2.00 ng/mL for *l-threo*-MPH, based on the analysis of 0.100 mL of plasma. Human plasma containing MPH and the IS, (b) (4) was extracted with an organic solvent after basification (liquid-liquid extraction). After evaporation and reconstitution, an aliquot of the extract was injected on a Sciex API 5000 LC-MS-MS equipped with an HPLC column. The peak area of the m/z 234→84 chiral MPH product ion was measured against the peak area of the m/z 237→84 chiral (b) (4) IS product ion. Quantitation was performed using separate weighted ($1/x^2$ for *d-threo*-MPH and 1/x for *l-threo*-MPH) linear least squares regression analyses generated from calibration standards prepared immediately prior to each run.
Analyte	*d-threo*-MPH *l-threo*-MPH
IS	(b) (4)
Method Description	Liquid-liquid extraction with analysis/detection by LC-MS-MS equippied with an high-performance liquid chromatography (HPLC) column.
Limit of Quantitation (ng/mL)	0.250 to 50.0 ng/mL for *d-threo*-MPH 0.0100 to 2.00 ng/mL for *l-threo*-MPH
Average Recovery of Drug (% Mean)	*d-threo* -MPH Peak Area 93.17% at 0.250 ng/mL 90.13% at 5.00 ng/mL 95.75% at 50.0 ng/mL *l-threo* -MPH Peak Area 89.04% at 0.0100 ng/mL 89.81% at 0.200 ng/mL 95.24% at 2.00 ng/mL

Standard Curve Concentrations (ng/mL)	*d-threo* -MPH 0.250, 0.500, 2.50, 5.00, 10.0, 25.0, 45.0, and 50.0 ng/mL *l-threo* –MPH 0.0100, 0.0200, 0.100, 0.200, 0.400, 1.00, 1.80, 2.00 ng/mL
LLOQ Concentration (ng/mL)	*d-threo* -MPH LLOQ 0.250 ng/mL *l-threo* –MPH LLOQ 0.0100 ng/mL
LLOQ Intra-Batch Precision Range (% CV)	*d-threo*-MPH: 2.2% to 3.3% *l-threo*-MPH: 8.9% to 13.5%
LLOQ Intra-Batch Accuracy Range (% Bias)	*d-threo*-MPH: -4.0% to 4.4% *l-threo*-MPH: -11.9% to 22.0%
LLOQ Inter-Batch Precision (% CV)	*d-threo*-MPH: 4.5% *l-threo*-MPH: 18.2%
LLOQ Inter-Batch Accuracy (% Bias)	*d-threo*-MPH: -0.4% *l-threo*-MPH: 1.0%
QC Concentrations (ng/mL)	*d-threo* -MPH QC Low 0.750 ng/mL QC Medium 10.0 ng/mL QC High 40.0 ng/mL *l-threo* –MPH QC Low 0.0300 ng/mL QC Medium 0.400 ng/mL QC High 1.60 ng/mL
QC Intra-Batch Precision Range (% CV)	*d-threo*-MPH: 1.0% to 2.4% *l-threo*-MPH: 0.9% to 6.4%

Parameter	Results
QC Intra-Batch Accuracy Range (% Bias)	*d-threo*-MPH: -4.8% to 10.8% *l-threo*-MPH: -4.4% to 3.7%
QC Inter-Batch Precision Range (% CV)	*d-threo*-MPH: 1.5% to 4.5% *l-threo*-MPH: 2.8% to 4.8%
QC Inter-Batch Accuracy Range (% Bias)	*d-threo*-MPH: -3.5% to 6.1% *d-threo*-MPH: -1.3% to 2.7%
Dilution QC Intra-Batch Precision (% CV)	*d-threo*-MPH: 3.9% *l-threo*-MPH: 3.6%
Dilution QC Intra-Batch Accuracy (% Bias)	*d-threo*-MPH: 5.6% *l-threo*-MPH: 8.0%
Bench-Top Stability (Hrs)	24 hour bench top Stability for d and *l-threo*-MPH extracted from Human K2-EDTA Plasma at a storage Temperature = 1 °C
Stock Stability (Days)	203 days at 4°C for stock solution MPH HCl Salt in Acetonitrile/Water (1:1)
Processed Stability (Hrs)	22 hrs at room temperature for stock solution MPH HCl Salt in Acetonitrile/Water (1:1)
Freeze-Thaw Stability (Cycles)	5 freeze-thaw cycles for *d-threo*-MPH 4 freeze-thaw cycles for *l-threo*-MPH
Long-Term Storage Stability (Days)	22 hrs at room temperature and 203 days at 4°C
Dilution Integrity	Up to 250 ng/mL, diluted 10-fold
Assay Selectivity Range (% Bias)	*d-threo*-MPH: -2.8% to 0.4% *l-threo*-MPH: -15.0% to -6.0%
Detection Specificity	Six different individual lots of blank human plasma were analyzed to identify any interference at the retention times of *d-threo*-MPH, *l-threo*-MPH, or the IS. The peak response at the retention time of the analyte and IS must be ≤20.0% and ≤5.0%, respectively, of the peak response of the LLOQ standard analyzed in the same run. Detection specificity was acceptable for this method.

Abbreviations: API = active pharmaceutical ingredient; CV = coefficient of variation; EDTA = ethylenediaminetetraceticacid; HPLC = high pressure liquid chromatography; hrs = hours; IS = internal standard; LC = liquid chromatography; LLOQ = lower limit of quantitation; MPH = methylphenidate; MS = mass spectrometry; QC = quality control;

(b) (4)

Source: NT0102-1001 1004259; NT0102-1002 3006311; NT0102-1003 3007054

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