Assessing Bioequivalence for Generic Extended Release Formulations

APSARD 2020 Annual Meeting

Symposium: ***Are differences in long-acting stimulant formulations clinically meaningful?***

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Office of Generic Drugs | CDER | U.S. FDA

Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Outline

1. General principles of bioequivalence (BE) for generic approval
2. BE recommendations for Attention-Deficit/Hyperactivity Disorder (ADHD) Products
3. Use of partial AUC (pAUC) for BE
4. Case study: methylphenidate transdermal extended release (ER) film

AUC = area under the concentration-time curve

General Framework for ANDAs

- Approval of generic drug starts with a listed drug – generally an innovator product approved under 505(c)
- An ANDA relies on FDA's finding of safety and effectiveness for listed drug
- Requires demonstration of "sameness" of a number of characteristics + additional information to permit reliance on the reference listed drug (RLD)

Generic drugs are now approximately 90% of the prescription drugs dispensed in the U.S.

NDA vs. ANDA Review Process

New Drug NDA Requirements	Generic Drug ANDA Requirements
1. Chemistry	1. Chemistry
2. Manufacturing	2. Manufacturing
3. Controls	3. Controls
4. Labeling	4. Labeling
5. Testing	5. Testing
6. Animal Studies	
7. Clinical Studies	6. Bioequivalence (BE)
8. Bioavailability	

ANDA: abbreviated new drug application; NDA: new drug application

Generic Drug Substitutability

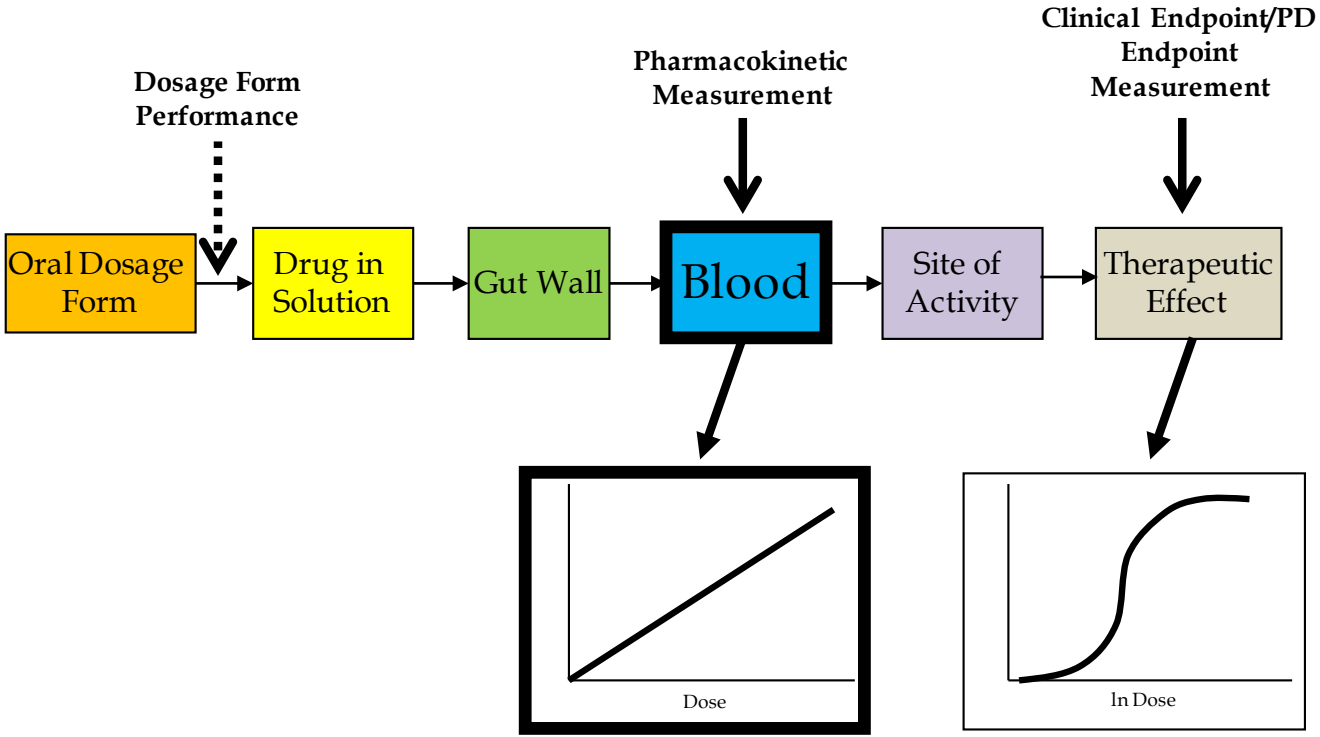
In relation to the RLD, generic products are expected to be:

- Pharmaceutically Equivalent
  - The same active ingredient, dosage form, strength, route of administration and meet the same compendial standards (strength, quality, purity, and identity)
- Bioequivalent
  - No significant difference in the rate and extent of absorption of the active ingredient at the site of action
- Therapeutic Equivalence
  - Approved drug products that are pharmaceutical equivalents for which bioequivalence has been demonstrated, and that can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.

Therapeutic Equivalence = Pharmaceutical Equivalence + BE

In Vivo BE Approaches for Systemic Drug Products

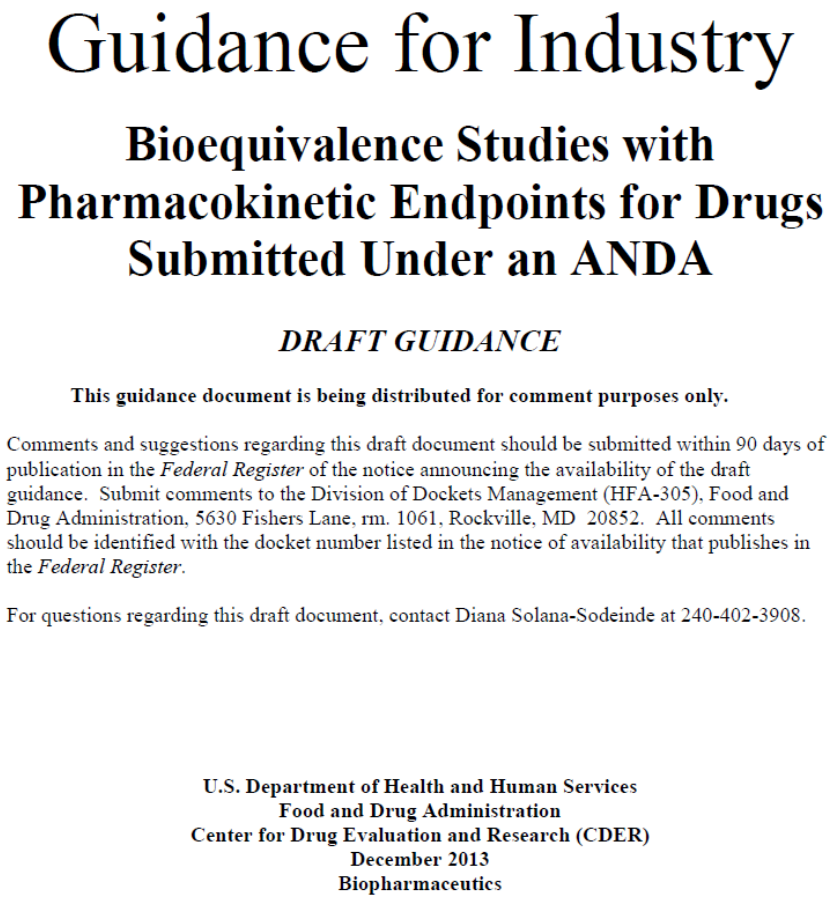
e.g., oral dosage forms



Pharmacokinetic (PK) Endpoints for Systemic Drug Products

- Intended to be delivered to sites of action in the body via the bloodstream
- BE is most often determined with PK studies by measuring drug or metabolite concentrations in the biological matrix
- PK endpoints are the most accurate, sensitive, and reproducible approach for establishing BE for systemic drug products (21 CFR 320.24)
- Typical biological matrices for BE assessment: blood and plasma
- Blood/plasma concentrations:
  - Are used to determine drug rate and extent of absorption
    - Rate of absorption: maximum concentration (Cmax)
    - Extent of absorption: AUC_{0-t} and $AUC_{0-\infty}$
  - Serve as surrogate measures of drug availability at the site of action
  - Provide a comparison of relative formulation performance between generic and reference products

General Guidance on PK Endpoints for BE



Guidance for Industry

Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact Diana Solana-Sodeinde at 240-402-3908.

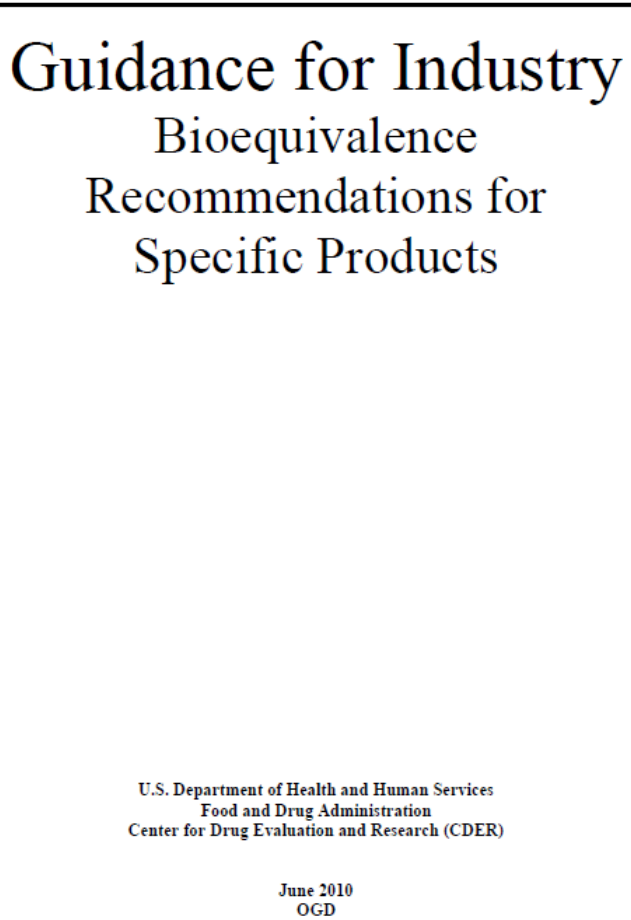
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
December 2013
Biopharmaceutics

- Draft guidance issued December 2013
- Scope: applies to oral and non-oral (e.g., transdermal) drug products in which reliance on systemic exposure measures is suitable for documenting BE
- Covers aspects of BE study design, study population, and specific recommendations for specific dosage forms including cases in which BE testing may be waived

Key Guidance Points: E.g., Modified Release (MR) Products

- MR includes ER and delayed release (DR)
- Recommended PK studies:
  - A single-dose, fasting study
  - A single-dose, fed study
  - (A single-dose, fasting sprinkle study if RLD label states that the product can be administered in soft foods)
  - Studies are typically of two-period, two-sequence, two-treatment, single-dose, crossover design or a replicate study design comparing the highest strength of the test product with the reference product in healthy volunteers
- With acceptable BE studies with the highest strength, additional strengths of MR products may be demonstrated to be BE under 21 CFR 320.24(b)(6) if:
  - Strengths are proportionally similar in their active and inactive ingredients
  - Strengths have the same drug release mechanism
  - Dissolution testing of all strengths is acceptable

Product-Specific Guidances (PSG)


Guidance for Industry

Bioequivalence Recommendations for Specific Products

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

June 2010
OGD

- Provide drug-specific recommendations for demonstrating BE between test and reference drug products: study design, strengths, study population, analytes to measure, dissolution method, and other special considerations
- Enhance transparency between the FDA and generic industry
- Reduce industry inquiries on BE
- Improve quality of submitted ANDAs (i.e., faster approval times)
- Promote FDA's generic drug approval process

Finding PSGs

https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm

- E.g., methylphenidate PSGs

Product-Specific Guidances for Specific Products Arranged by Active Ingredient

A B C D E F G H I J K L M N O P Q R S T U V W X Y Z

Search by Active Ingredient or by RLD or RS Number

methylphenidate Search Reset

13 record(s) found for 'methylphenidate'.

Excel CSV PDF

Show 10 entries Filter:

Active Ingredient	Type	Route	Dosage Form	RLD or RS Number	Date Recommended
Methylphenidate	Draft	Transdermal	Film, Extended Release	021514	10/2018
Methylphenidate	Draft	Oral	Tablets, Extended Release, Orally Disintegrating	205489	07/2018
Methylphenidate Hydrochloride	Draft	Oral	Tablet, Extended Release	021121	07/2018
Methylphenidate Hydrochloride	Draft	Oral	Tablets, Extended Release	018029	10/2017
Methylphenidate Hydrochloride	Draft	Oral	Tablet, Chewable	207960	10/2016
Methylphenidate Hydrochloride	Draft	Oral	Capsule, Extended Release	021259	01/2016
Methylphenidate Hydrochloride	Draft	Oral	Capsule, Extended Release	205831	01/2016
Dexmethylphenidate Hydrochloride	Draft	Oral	Capsule, Extended Release	021802	03/2015
Methylphenidate Hydrochloride	Draft	Oral	Capsules, Extended Release	021284	03/2015
Methylphenidate Hydrochloride	Draft	Oral	Suspension, Extended Release	202100	12/2014

Showing 1 to 10 of 13 entries Previous 1 2 Next

Example PSG

Methylphenidate orally disintegrating ER tablets (NDA 205489, Cotempla XR-ODT®)

Contains Nonbinding Recommendations

Draft Guidance on Methylphenidate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Methylphenidate

Dosage Form; Route: Extended release tablet; orally disintegrating

Recommended Studies: Two studies

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 25.9 mg
   Subjects: Males and non-pregnant, non-lactating females, general population

   Additional comments:
   The fasting bioequivalence study may be conducted in a single dose, two-treatment, two-sequence, four-period, replicated design. The 90% confidence intervals of the geometric mean test/reference (T/R) ratios for the metrics (C_{max}, AUC_{0-3}, AUC_{3-7}, AUC_{7-12}, $AUC_{0-\infty}$) should fall within the limits of 80.00-125.00%.

2. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 25.9 mg
   Subjects: Males and non-pregnant, non-lactating females, general population

   Additional comments:
   The fed bioequivalence study may be conducted in a single dose, two-treatment, two-sequence, four-period, replicated design. The 90% confidence intervals of the geometric mean T/R ratios for the metrics (C_{max}, AUC_{0-4}, AUC_{4-8}, AUC_{8-12}, $AUC_{0-\infty}$) should fall within the limits of 80.00-125.00%.

Analytes to measure (in appropriate biological fluid): Methylphenidate in plasma

Bioequivalence based on (90% CI): Methylphenidate

Refer to Additional Comments above for more guidance regarding bioequivalence.

Recommended Jul 2018

Waiver request of in vivo testing: 8.6 mg and 17.3 mg based on (i) acceptable bioequivalence studies on the 25.9 mg strength, (ii) acceptable in-vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all strengths.

Dissolution test method and sampling times:

The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods web site, available to the public at the following location: http://www.accessdata.fda.gov/scripts/cder/dissolution/. Conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).

In addition to the method above, for modified release products, dissolution profiles on 12 dosage units each of test and reference products generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be changed if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation. Specifications will be determined upon review of the data submitted in the application.

Due to a concern of dose dumping of drug from this drug product when taken with alcohol, the Agency currently requests that additional dissolution testing be conducted using various concentrations of ethanol in the dissolution medium, as follows:

Testing Conditions: 900 mL, 0.1 N HCl, USP Apparatus II (paddle) @50 rpm, with or without alcohol;

Test 1: 12 units tested according to the proposed method (with 0.1N HCl), with data collected every 15 minutes for a total of 2 hours

Test 2: 12 units analyzed by substituting 5% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Test 3: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Test 4: 12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Both test and RLD products must be tested accordingly and data must be provided on individual unit, means, range, and %CV on all strengths.

Current Recommendations for MPH-based ER Products

RLD #	RLD Brand Name	API	Dosage Form	Route	Version Date (Mo-Yr)	Recommended pAUCs
205831	APTENSIO XR	MPH HCl	Capsules, ER	Oral	01-16	Fasting: AUC0-3, AUC3-7, AUC7-12 Fed: AUC0-4, AUC4-8, AUC8-12
021121	CONCERTA	MPH HCl	Tablets, ER	Oral	07-18	Fasting: AUC0-3, AUC3-7, AUC7-12 Fed: AUC0-4, AUC4-8, AUC8-12
205489	COTEMPLA XR-ODT	MPH	Tablets, ER, Orally Disintegrating	Oral	07-18	Fasting: AUC0-3, AUC3-7, AUC7-12 Fed: AUC0-4, AUC4-8, AUC8-12
021514	DAYTRANA	MPH	Film, ER	Transdermal	10-18	AUC2-9
021802	FOCALIN XR	d-MPH HCl	Capsules, ER	Oral	03-15	Fasting: AUC0-3, AUC3-7, AUC7-12 Fed: AUC0-4, AUC4-8, AUC8-12
021259	METADATE CD	MPH HCl	Capsules, ER	Oral	01-16	Fasting: AUC0-3, AUC3-7, AUC7-t Fed: AUC0-4, AUC4-8, AUC8-t
207960	QUILLICHEW ER	MPH HCl	Tablets, ER, Chewable	Oral	10-16	Fasting: AUC0-3, AUC3-7, AUC7-t Fed: AUC0-4, AUC4-8, AUC8-t
202100	QUILLIVANT XR	MPH HCl	Suspension, ER	Oral	12-14	Fasting: AUC0-3, AUC3-7, AUC7-12 Fed: AUC0-4, AUC4-8, AUC8-12
021284	RITALIN LA	MPH HCl	Capsules, ER	Oral	03-15	Fasting: AUC0-3, AUC3-7, AUC7-12 Fed: AUC0-4, AUC4-8, AUC8-12
018029	RITALIN SR	MPH HCl	Tablets, ER	Oral	10-17	Fasting: AUC0-3, AUC3-7, AUC7-t Fed: AUC0-4, AUC4-8, AUC8-t

API = active pharmaceutical ingredient; MPH = methylphenidate; d-MPH = dexmethylphenidate; HCl = hydrochloride

Partial AUC and Regulatory History

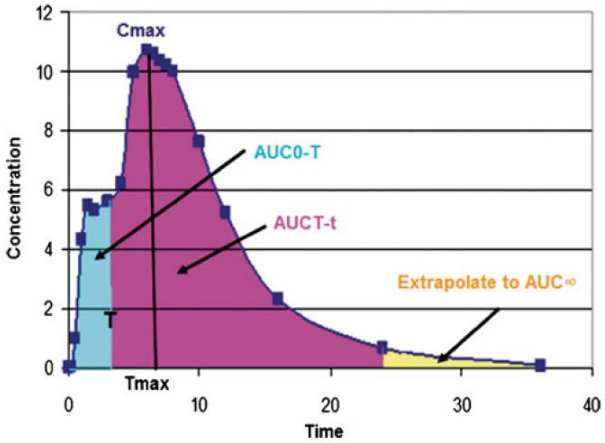
- For some drug products the traditional metrics of AUC and C_{max} may not be sufficient to ensure BE
- An additional PK metric, such as a pAUC to assess exposure during particular time interval, may be necessary to quantify potential differences in therapeutic equivalence
- 2010 Pharmaceutical Science and Clinical Pharmacology (PSCP) Advisory Committee (AC) meeting
  - MR products: multiphasic drug release (IR+ER)
- 2013 draft guidance *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*
  - "We recommend the use of partial AUC as an early exposure measure under certain circumstances. The time to truncate the partial area should be related to a clinically relevant pharmacodynamic (PD) measure."

CDER Efforts Regarding pAUC

- CDER offices discuss and address questions related to use and determination of appropriate pAUC metric for BE assessment to ensure efficacy and safety of new and generic products
- Provide harmonized and consistent recommendations applicable to both new and generic drugs
- Develop a consistent regulatory approach to determining pAUCs

Early pAUCs for MPH ER Products

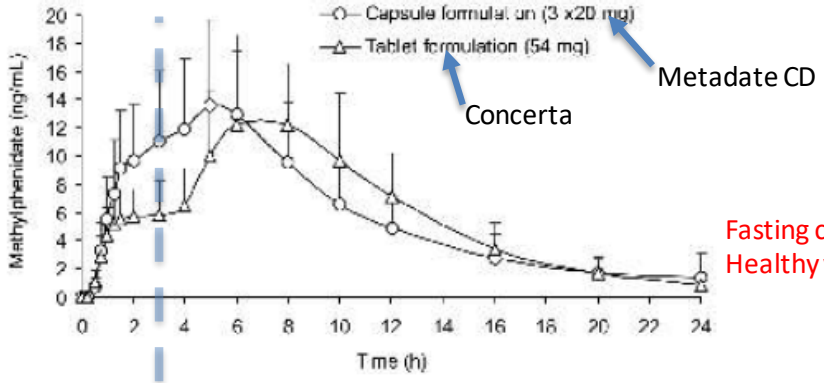
- Currently, the PSGs for all MPH-based oral ER drug products recommend an BE evaluation of AUC_{0-3} and AUC_{0-4} in the fasting and fed state, respectively
- This pAUC was discussed extensively in the 2010 PSCP AC meeting (Appendix C of Briefing Information)
- Formal recommendation laid out FDA's response to citizen petitions FDA-2004-P-0151 and FDA-2004-P-0290 on July 19, 2012
  - Multiphasic drug release due to immediate release (IR) and ER components; IR component intended to give similar onset of effects as an approved IR product
  - Strong relationship between PK and PD – PK/PD model comparing the time course of clinical response (SKAMP ratings) to plasma MPH concentrations
  - Traditional PK metrics including T_{max} (time to C_{max}) would not identify differences in early onset
  - Selection of 3 and 4 hours based upon distribution of T_{max} observed in IR PK studies in fasting and fed, respectively (food prolonged T_{max} by 1 hour); confirmed by modeling and simulation



Stier, Ethan M., et al. "Use of partial area under the curve metrics to assess bioequivalence of methylphenidate multiphasic modified release formulations." *The AAPS journal* 14.4 (2012): 925-926.

Example of Strong PK/PD Link

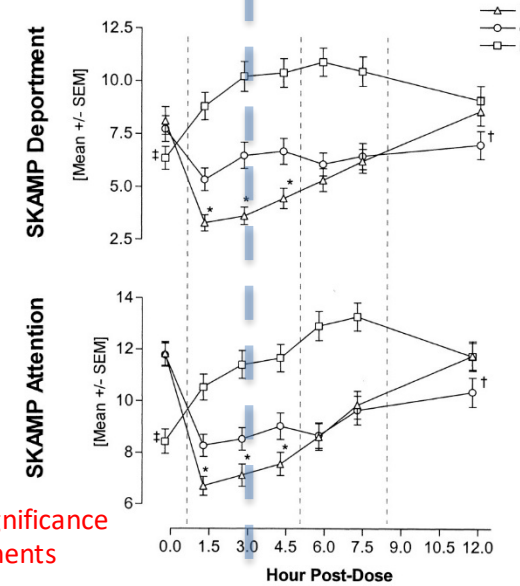
Gonzalez, M. A., et al. "Methylphenidate bioavailability from two extended-release formulations." *International journal of clinical pharmacology and therapeutics* 40.4 (2002): 175-184.



Fasting conditions, Healthy volunteers

MCD = Metadate CD
CON = Concerta
PLA = placebo

Swanson, James M., et al. "A comparison of once-daily extended-release methylphenidate formulations in children with attention-deficit/hyperactivity disorder in the laboratory school (the Comacs Study)." *Pediatrics* 113.3 (2004): e206-e216.



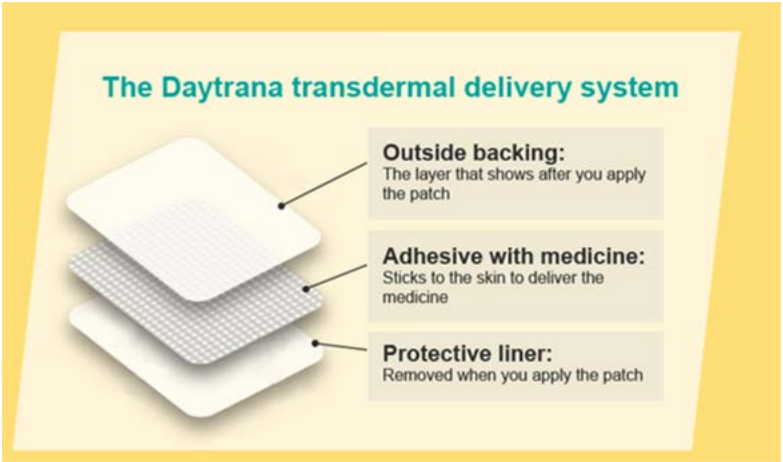
For doses of MPH, differences in PK from 0-3 hours is reflected in the SKAMP ratings

* and †: statistically significance between active treatments

Case Study: Daytrana transdermal ER film

- Approved under NDA 021514 on April 6, 2006
- 4 strengths: 10MG/9HR, 15MG/9HR, 20MG/9HR, and 30MG/9HR
- Indicated for the treatment of ADHD
- "applied to the hip area **2 hours** before an effect is needed and should be removed **9 hours** after application" (Source: drug label)

Source: https://dailymed.nlm.nih.gov/

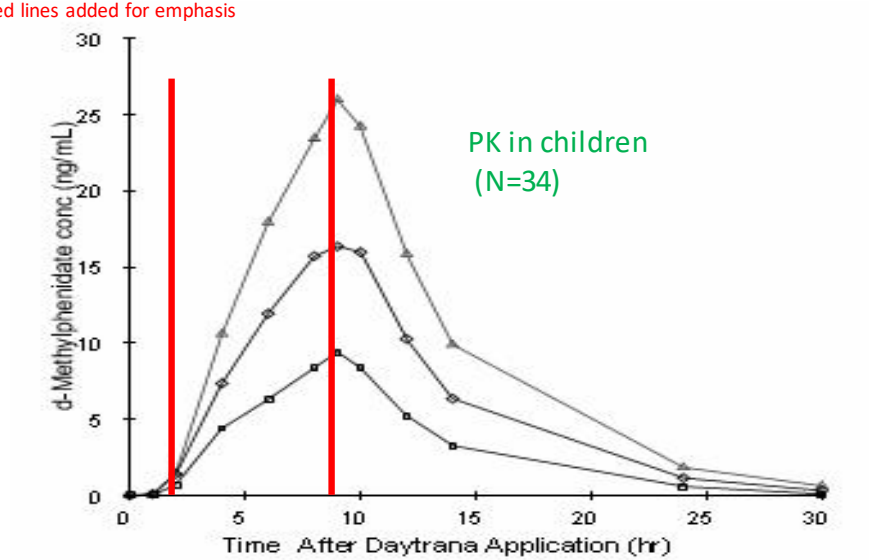


Source: https://www.daytrana.com/

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021514s030lbl.pdf

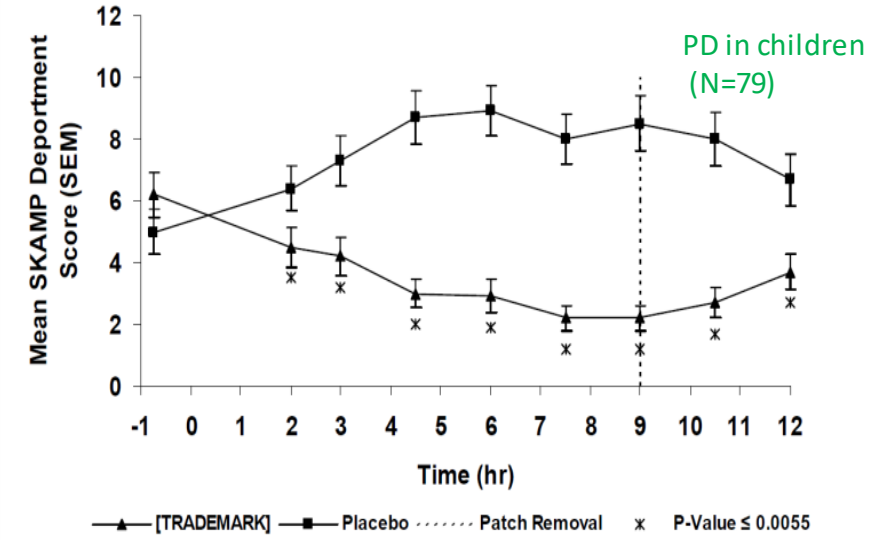
Daytrana PK and PD

Source: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021514s030lbl.pdf
Red lines added for emphasis



- ✓ Serum MPH levels increase over wear time,
- ✓ T_{max}: 8 to 10 h for 9 h wear time
- ✓ Elimination half-life: 3-4 h

Source: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/021514s000_MedR_P1.pdf



- ✓ Effects have significance over placebo from 2 h and remain up to 12 h

Daytrana PK Modeling and Simulation

- Population PK model developed in NONMEM based on individual level data from Daytrana application:
  - Final structural model: one-compartment model with zero-order absorption and first-order elimination
  - Final parameters using nonlinear mixed-effect modeling with a first-order estimation method

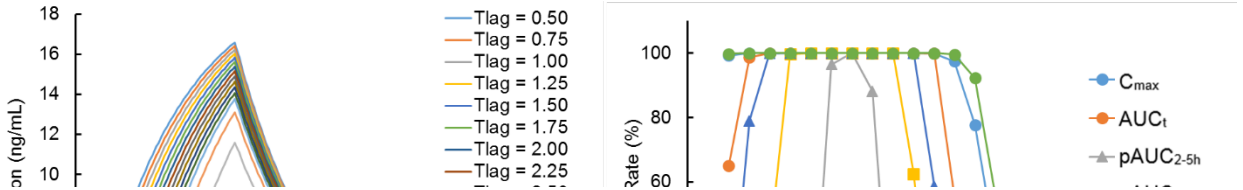
Parameter	Population estimate (% RSE)	Between-subject variability (BSV) % CV (% RSE)
CL, clearance, (L/h)	202 (6)	N.A.
V, volume of distribution, (L)	1030 (9)	29.9 (40)
D, duration of absorption, (h)	7.39 (2)	N.A.
T_{lag}, *absorption lag* time, (h)	2.08 (13)	44.0 (79)
F, relative bioavailability	0.36 (fixed)	61.2 (30)
σ^2_{prop}, *proportional residual error*, (%)	13.8 (16)	N.A.
σ^2_{add}, *additive residual error*, (ng/mL)	0.0676 (34)	N.A.

RSE - Relative Standard Error; CV – Coefficient of Variation; N.A. - Not Available / Not Estimated

- PK simulations conducted typical subject by changing:
  - T_{lag}: range 0.5-5 hours; no change in rate of absorption
  - T_{lag} and *D* (i.e., absorption) while keeping *F* constant: e.g., larger lag time -> larger absorption rate
  - Simulated 1000 virtual crossover BE studies (against Daytrana)

Shivva, Vittal, et al. "A Model Based Approach for the Evaluation of a Partial Area Under the Curve Metric to Assess the Bioequivalence of Methylphenidate Transdermal Delivery Systems." *In preparation.*

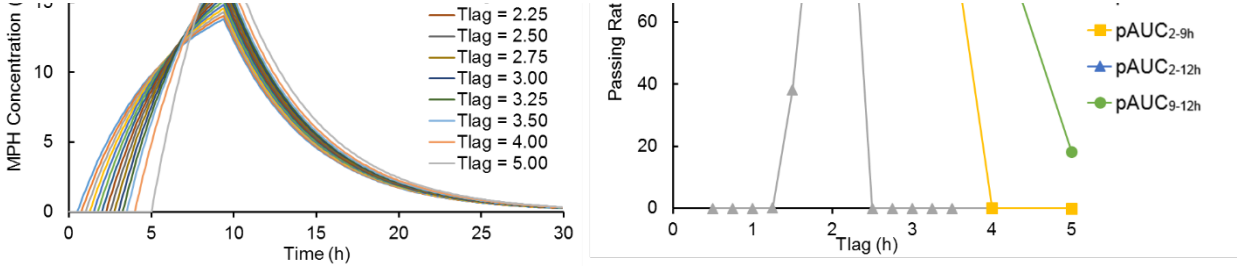
PK Simulation Results



T_{lag}

- $AUC_{2\text{-}5}$: most sensitive to detect deviation in T_{lag} (must be in rage of 1.75-2.25 hrs), although substantial variability may exist such a pAUC
- $AUC_{2\text{-}9}$: next most sensitive (T_{lag} must be in range of 1.25-2.5 hrs)
- AUC_t and C_{max}: relatively insensitive in detecting T_{lag} differences

T_{lag} ar... D, F constant



Shivva, Vittal, et al. "A Model Based Approach for the Evaluation of a Partial Area Under the Curve Metric to Assess the Bioequivalence of Methylphenidate Transdermal Delivery Systems." *In preparation.*

Daytrana PD Modeling and Simulation

- A previous published meta-analytic PKPD model for MPH ER was utilized:

  Kimko, Holly, et al. "Population pharmacodynamic modeling of various extended-release formulations of methylphenidate in children with attention deficit hyperactivity disorder via meta-analysis." Journal of pharmacokinetics and pharmacodynamics 39.2 (2012): 161-176.

  - PD was mean SKAMP-Composite score from pediatric efficacy studies
  - PK was mean PK data in adults
  - PD effect described by E_{max} model with time-dependent tolerance
    - Includes placebo effect and drug-induced effect on SKAMP-Composite score

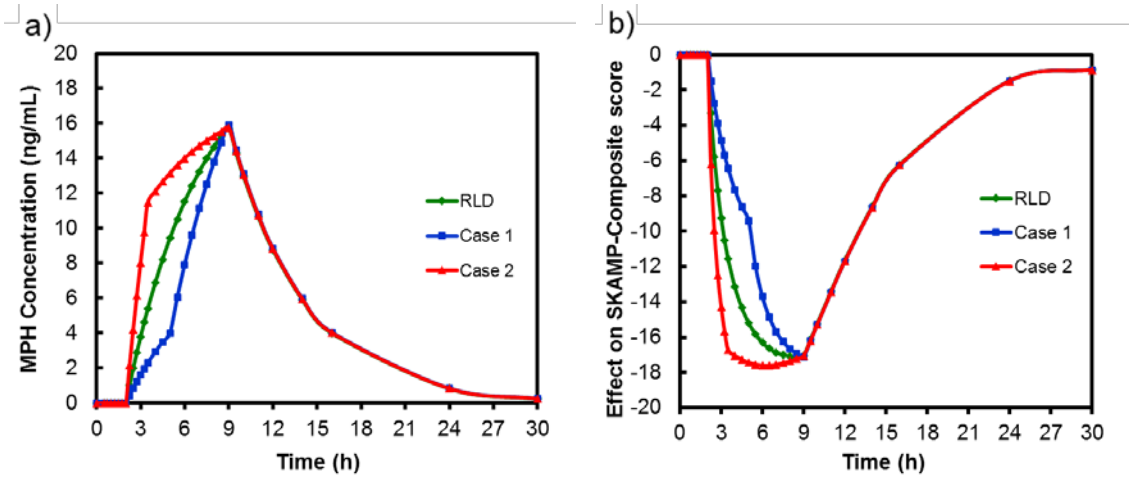
$$\text{Effect} = \delta + E_{max} \times C/(EC_{50} + C)$$

$$EC_{50} = EC_{50,start}\left(1 + t^{\gamma}/\left(t_{50}^{\gamma} + t^{\gamma}\right)\right)$$

- PD simulations in clinically meaning differences in PK resulting in greater than 20% difference in predicted efficacy outcome at clinically relevant time windows

Shivva, Vittal, et al. "A Model Based Approach for the Evaluation of a Partial Area Under the Curve Metric to Assess the Bioequivalence of Methylphenidate Transdermal Delivery Systems." *In preparation.*

PD Simulation Results



- Example case: zero-order release followed by first-order release
- AUC and C_{max} of simulated cases within BE limits against Daytrana; AUC_{2-9} outside of BE limits
- A greater than 20% change in AUC_{2-9} was associated with a greater than 20% change in efficacy between 2-5 hours

Shivva, Vittal, et al. "A Model Based Approach for the Evaluation of a Partial Area Under the Curve Metric to Assess the Bioequivalence of Methylphenidate Transdermal Delivery Systems." *In preparation.*

Daytrana PSG

- $AUC_{2\text{-}9}$ is sensitive to differences in T_{lag}
- $AUC_{2\text{-}9}$ can detect PK changes associated with clinically meaning differences

Analytes to measure (in appropriate biological fluid): Methylphenidate in plasma, using an achiral assay for d- and l-methylphenidate

Bioequivalence based on (90% CI): Methylphenidate

- The confidence intervals of the geometric mean test/reference (T/R) ratios for the metrics (C_{max}, $AUC_{2\text{-}9}$, $AUC_{0\text{-}tlast}$, and $AUC_{0\text{-}\infty}$) should fall within the limits of 80-125%, where $AUC_{2\text{-}9}$ is the area under the plasma concentration vs. time curve from 2 to 9 hours.

- Adequate pharmacokinetic samples are needed, particularly during the first 2-3 hours, to enable the evaluation of drug release into systemic circulation following TDS application.

https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_021514.pdf

Summary

- For systemic drug products such as MPH ER, establishment of BE through PK endpoints ensures that the approved generic is interchangeable with the brand name

- For certain drug products, traditional PK endpoints of rate and total extent of exposure are not sufficient to ensure BE and pAUCs are part of the BE evaluation

- Given the strong relationship between PK and clinical outcomes for methylphenidate and the design of ER formulations containing an IR component for early onset (or in the case of Daytrana, a lack of effect for 2 hours), pAUCs have been applied to methylphenidate ER to ensure equivalent efficacy throughout the day

- FDA has created a CDER-wide framework to increase coordination between offices in the standards applied for new drug and generic drug approval

Acknowledgements

The work presented today is compilation of work spanning decades in the FDA by countless number of individuals. Below represents those that assisted in the preparation of today's materials

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- Ethan Stier
- Bing Li
- Xiaojian Jiang

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- Ramana Uppoor


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