Regulatory challenges with pharmacokinetic (PK) bioequivalence (BE) studies for drugs containing endogenous compounds

SAAMnow Workshop: Challenges and Strategies for Relative Bioavailability Studies on Drug Products Involving Endogenous Substances

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Disclaimer

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

Outline

- Overview of relevant regulatory guidance
- Summary of product-specific guidance (PSG) recommendations
- Challenges with providing baseline-correction (BLC) recommendations
- Internal research efforts and correspondence with FDA

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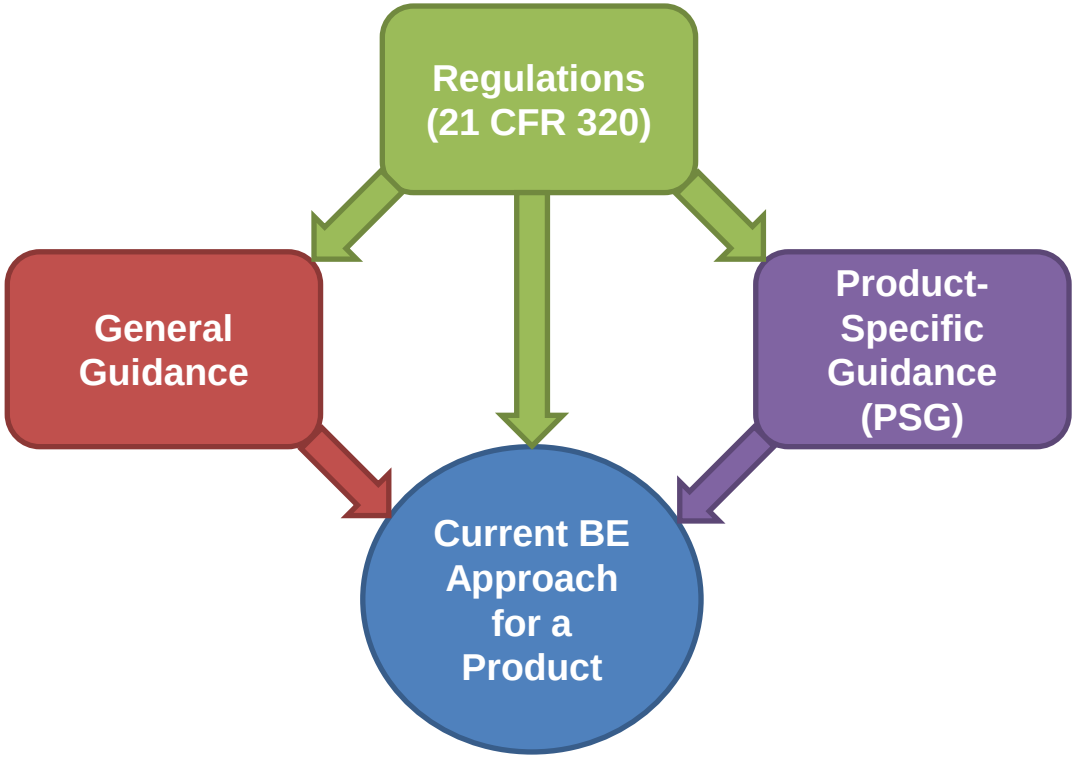
Regulation and Guidance for BE



Guidance for BA/BE Studies

- BA Studies for INDs and NDAs **(not covered in this presentation)**
  - FDA recommends that applicants for INDs, NDAs, and NDA supplements consult the draft guidance for industry ***Bioavailability Studies Submitted in NDAs or INDs —General Considerations*** (February 2019)[1]

- BE Studies for ANDAs
  - FDA recommends that ANDA applicants refer to the draft guidance for industry ***Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*** (August 2021)[2]
    - Generally applicable to dosage forms intended for oral administration and to non-orally administered drug products for which **reliance on systemic exposure measures (PK endpoints) is suitable for establishing BE**, i.e., transdermal delivery systems and certain rectal and nasal drug products

PK BE Guidance for ANDAs

- General BE Principles:

*"The **rate and extent of absorption of the drug do not show a significant difference** from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses."*

- Both in vivo and/or in vitro methods can be used to establish BE
  - **Comparative PK**
  - In vitro tests predictive of human in vivo BA (in vitro-in vivo correlation (IVIVC))
  - Comparative pharmacodynamic (PD)
  - Comparative clinical endpoint
  - In vitro studies

Section 505(j)(8)(B)(i) of the FD&C Act. See also section 505(j)(8)(B)(ii) and (C) of the FD&C Act; 21 CFR 314.3(b);21 CFR 320.23(b); 21 CFR 320.24(b)

Rationale for BLC in PK BE Studies

- In BE studies with PK endpoints, **BLC** is generally recommended for drug products containing an active ingredient that is an *endogenous compound*[2]
- Because these compounds are identical to the drug that is being administered, determining the amount of drug released from the dosage form and absorbed by each subject is challenging
- If unaccounted for, the presence of the endogenous compound **biases towards equivalence** in BE studies of these drugs[3]
- Thus, FDA recommends that ANDA applicants **use BLC methods** to estimate more accurately those differences in PK that result from the two product formulations

PK BE Guidance for ANDAs: Endogenous Compounds

Draft guidance for industry ***Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*** (August 2021)[2]

Section V.E. Endogenous Compounds

"Endogenous compounds are already present in the body either because the body produces them or because they are present in a normal diet. Because these compounds are identical to the drug that is being administered, determining the amount of drug released from the dosage form and absorbed by each subject can be difficult. We recommend that applicants measure and approximate the baseline endogenous concentrations in blood (plasma) or urine and subtract these concentrations from the total concentrations measured from each subject after the drug product is administered to achieve an estimate of the actual drug availability from the drug product. Depending on whether the endogenous compound is naturally produced by the body or is present in the diet, the recommended approaches for determining BE differ as follows:

- When the body produces the compound, we recommend that applicants measure multiple baseline concentrations from each individual subject in the time period before administration of the study drug and subtract the time-averaged baseline or time-matched baseline from post-dose concentrations for those subjects in an appropriate manner consistent with the PK properties of the drug.
- When there is a dietary intake of the compound, we recommend that applicants strictly control the intake both before and during the study. Subjects should be housed at a clinic before the study and served standardized meals containing an amount of the compound similar to that in the meals to be served on the PK sampling day.
- For both approaches above, we recommend that applicants determine baseline concentrations for each dosing period and perform baseline corrections that are period specific. If a baseline correction results in a negative plasma concentration value, the value should be set equal to 0 before calculating the baseline-corrected AUC. PK and statistical analyses should be performed on both uncorrected and corrected data. Determination of BE should be based on the baseline-corrected data."

PK BE Guidance for ANDAs: Endogenous Compounds[2]

- **Subtract baseline endogenous concentrations from the total concentrations** measured from each subject after the drug product is administered to achieve an estimate of the actual drug availability from the drug product

- **When the body produces the compound**, measure multiple pre-dose baseline concentrations and **subtract *the time-averaged* baseline or *time-matched* baseline** from post-dose concentrations
  - Baseline concentrations should be measured for **each subject and dosing period**
  - Baseline corrections should be **subject and period specific**

- **When there is a dietary intake** of the compound, strictly **control the intake** both before and during the study

PK BE Guidance for ANDAs: Endogenous Compounds[2]

- Following baseline-correction, any **negative concentration values should be set to 0** before calculation of PK parameters
- **PK and statistical analyses** should be performed on both **uncorrected and corrected data**
- Determination of **BE** should be based on the **BLC data**

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Product-Specific Guidance (PSG)

- PSGs reflect the FDA's **current thinking and expectations** on how to develop a generic drug product **therapeutically equivalent to a *specific* reference listed drug (RLD)**[4]

- FDA recommends ANDA applicants **consult routinely published PSGs** when considering the appropriate BE study and/or other studies for a proposed drug product

- Refer to Product-Specific Guidances for Generic Drug Development web page at https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development for the most recent version of a PSG

PSGs recommending BLC of PK Parameters

Query identified **75 PSGs** recommending BLC of PK parameters; **45 unique active ingredients** or combinations

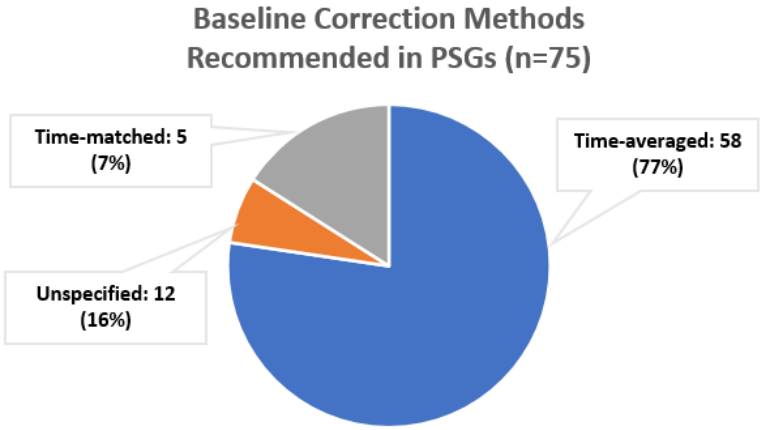
Active Ingredient	Route	Dosage Form	Application No. (RLD/RS)	PSG Date
Alendronate Sodium; Cholecalciferol	Oral	Tablet	N021762	Apr 2009; Oct 2011
Calcifediol	Oral	Capsule	N208010	Mar 2021
Calcitriol	Oral	Capsule	N018044	Jul 2008; Sep 2010
Chenodiol	Oral	Tablet	N018513	Sep 2019
Cholic Acid	Oral	Capsule	N205750	Oct 2016
Cyanocobalamin	Nasal	Spray	N021642	Jul 2017
Dienogest; Estradiol Valerate	Oral	Tablet	N022252	Dec 2010
Doxercalciferol	Oral	Capsule	N020862	Aug 2017
Doxylamine Succinate; Pyridoxine HCl	Oral	DR tablet	N021876	Jul 2014
	Oral	ER tablet	N209661	Feb 2019
Drospirenone; Estradiol	Oral	Tablet	N021355	May 2008; Jun 2013; Jan 2016
Drospirenone; Ethinyl Estradiol; Levomefolate Calcium	Oral	Tablet	N022532, N022574	Mar 2021
Epinephrine	Aerosol, metered	Inhalation	N205920	Nov 2020
Ergocalciferol	Oral	Capsule	N003444	Nov 2010; Jul 2014
Estradiol	Oral	Tablet	A084500, A084499, A081295	Dec 2010
	Transdermal	ER Film	N019081	Nov 2010; Oct 2016; Oct 2018; Nov 2019
	Transdermal	ER Film	N020375, N021674	Nov 2010; Oct 2016; Oct 2018; Nov 2019
	Transdermal	ER Film	N020538	Nov 2010; Oct 2016; Oct 2018; Nov 2019
	Transdermal	ER Film	N203752	Apr 2014; Sep 2015; Oct 2016; Oct 2018; Nov 2019
	Transdermal	Gel	N022038	Nov 2018, Nov 2019
	Gel, metered	Transdermal	N021813	Feb 2022
	Spray	Transdermal	N022014	Feb 2022
	Vaginal	Cream	A086069	Aug 2009; Sep 2014
	Vaginal	Insert ER	N020472	Jun 2020
	Vaginal	Tablet	N020908	Aug 2009; Mar 2011
Estradiol; Levonorgestrel	Transdermal	ER Film	N021258	May 2019; Nov 2019
Estradiol; Norethindrone Acetate	Oral	Tablet	N020907	Mar 2009
	Transdermal	ER Film	N020870	Oct 2018; Nov 2019
Estrogens; Conjugated	Oral	Tablet	N004782	Dec 2014
Estrogens; Conjugated Synthetic A	Oral	Tablet	N020992	Apr 2010
Estrogens; Esterified	Oral	Tablet	A084948, A084949, A084950, A084951	Feb 2008; Sep 2012
Fish Oil Triglycerides	IV	Emulsion	N210589	Jun 2020
Fish Oil; Medium Chain Triglycerides; Olive Oil; Soybean Oil	IV	Emulsion	N207648	Feb 2019
Hydrocortisone Acetate	Rectal	Metered Aerosol	N017351	Oct 2017; Nov 2020
Icosapent Ethyl	Oral	Capsule	N202057	Apr 2013; Feb 2014, Oct 2016
Isotretinoin	Oral	Capsule	A076135, N018662	Sep 2008; Jun 2013; Mar 2015; Nov 2020
	Oral	Capsule	N021951	Mar 2015; Jul 2015; Nov 2020
Leucovorin Calcium	Oral	Tablet	N018342	Jul 2008; Jul 2018

Active Ingredient	Route	Dosage Form	Application No. (RLD/RS)	PSG Date
Levocarnitine	Oral	Tablet	N018948	Sep 2015
Levothyroxine Sodium	Oral	Capsule	N021924	Nov 2018
	Oral	Tablet	N021116, N021210, N021301, N021342, N021402	Dec 2014
Liothyronine Sodium	Oral	Tablet	N010379	Feb 2006; May 2008; Dec 2012; Aug 2021
Olive Oil; Soybean Oil	Injectable	Injection	N204508	Sep 2018
Omega 3 Acid Ethyl Esters	Oral	Capsule	N021654	Sept 2012; Oct 2016, Dec 2016; Aug 2020
Omega3 Acid Ethyl Esters Type A	Oral	Capsule	N204977	Dec 2016
Omega3 Carboxylic Acids	Oral	Capsule	N205060	Jan 2016; Dec 2016
Phytonadione	Oral	Tablet	N010104	Feb 2010, Sep 2012, Jan 2016
	Injectable	Injection	N012223	Oct 2011, Sep 2012
Potassium Chloride	Oral	ER Capsule	N018238	Aug, 2011
	Oral	ER tablet	N018279	Mar, 2015
	Oral	ER tablet	N019123	Oct, 2011
	Oral	ER tablet	N019439	Sep, 2011
Potassium Citrate	Oral	ER tablet	N19071	Aug 2010; Feb 2018
Progesterone	Oral	Capsule	N019781	Apr 2010; Feb 2011
	Vaginal	Gel	N020701	Oct 2015
	Vaginal	Insert	N022057	Sep 2012
	Vaginal	System	N201110	Feb 2022
Sapropterin Dihydrochloride	Oral	Tablet	N022181	Sep 2008; Sep 2012
Sodium Phosphate Dibasic Anhydrous; Sodium Phosphate Monobasic Monohydrate	Oral	Tablet	N021892	Dec 2012
Soybean Oil	Injectable	Injection	N019531	Feb 2018
	Injectable	Injection	N020248, N018449, N017643	Feb 2018
Testosterone	Buccal	ER tablet	N021543	May 2008
	Implantation	Pellet	A080911	Aug 2011
	Transdermal	ER Film	N020489	Dec 2014; Apr 2016; Oct 2016; Oct 2018; Nov 2019
	Transdermal	Gel	N021454	Apr 2013
	Transdermal	Gel	N021015	Apr 2013; Nov 2013
	Transdermal	Gel, Metered 1%	N021015	Apr 2013; Nov 2013
	Transdermal	Gel, Metered	N021463	Apr 2013
	Transdermal	Gel	N022309	Apr 2013; Nov 2013
	Transdermal	Gel, Metered	N022309	Apr 2013; Nov 2013
Testosterone Undecanoate	Oral	Capsule	N206089	Mar 2021
Tretinoin	Oral	Capsule	N020438	Sep 2010
Uridine Triacetate	Oral	Granules	N208159, N208169	Jul 2017
Ursodiol	Oral	Tablet	N020675	Jul 2008; Mar 2021
	Oral	Capsule	N019594	Feb 2010; Mar 2021

BLC Methods Recommended in PSGs

Of the 75 PSGs recommending BLC of PK parameters:

- The majority (n=58, 77%) of PSGs recommend the time-averaged BLC method
- A few PSGs (n=5, 7%) recommend the time-matched BLC method
  - Potassium chloride ER tablet and capsule
  - Potassium citrate ER tablet
- BLC method was unspecified in some PSGs (n=12, 16%)
- BLC method was consistent for products with the same active ingredient(s) and different dosage forms

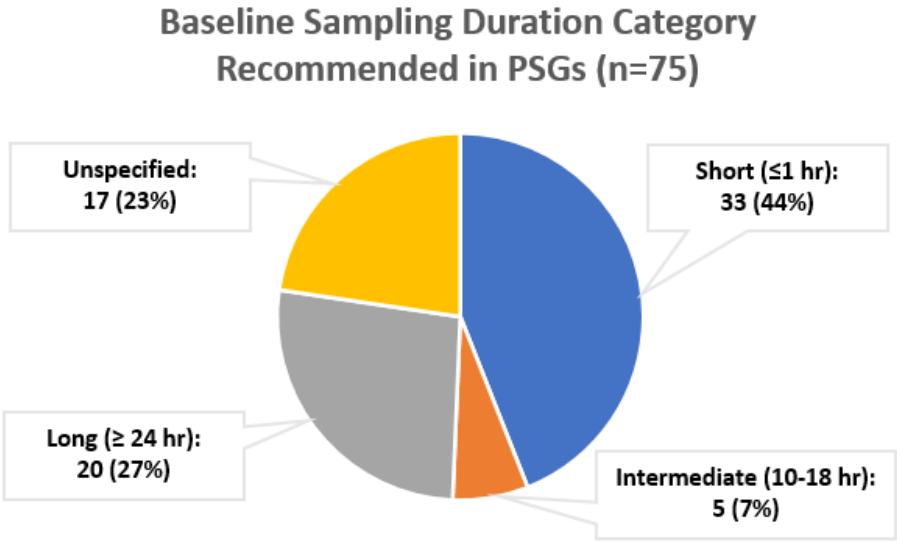


Baseline Sampling Duration

Summary of baseline sampling duration in 75 PSGs recommending BLC of PK parameters

Baseline sampling duration categories:

- **Short**: ≤ 1 hour
- **Intermediate**: 10 to 18 hours
- **Long**: ≥ 24 hours
- **Unspecified**



Baseline Sampling Scheme

Baseline sampling schemes within the designated sampling categories were compared and various baseline sampling schemes are observed

Category	Baseline Sampling Scheme	Active Ingredient	Route	Dosage Form	Application No. (RLD/RS)	PSG Date
Short (≤ 1 hour)	-0.5, -0.25, and 0 hr	Levothyroxine Sodium	Oral	Capsule	N021924	Nov 2018
			Oral	Tablet	N021116, N021210, N021301, N021342, N021402	Dec 2014
		Liothyronine Sodium	Oral	Tablet	N010379	Feb 2006; May 2008; Dec 2012; Aug 2021
	-1, -0.5, and 0 hr	Epinephrine	Aerosol, metered	Inhalation	N205920	Nov 2020
		Progesterone	Oral	Capsule	N019781	Apr 2010; Feb 2011
			Vaginal	Gel	N020701	Oct 2015
			Vaginal	Insert	N022057	Sep 2012
			Vaginal	System	N201110	Feb 2022
		Sapropterin Dihydrochloride	Oral	Tablet	N022181	Sep 2008; Sep 2012
	At least 3 samples (e.g. -1, -0.5, 0 hr)	Leucovorin Calcium	Oral	Tablet	N018342	Jul 2008; Jul 2018
Intermediate (10 to 18 hr)	At least 3 samples (e.g. -10, -2, and 0 hr)	Isotretinoin	Oral	Capsule	A076135, N018662	Sep 2008; Jun 2013; Mar 2015; Nov 2020
			Oral	Capsule	N021951	Mar 2015; Jul 2015; Nov 2020
	-12, -6, and 0 hr	Calcitriol	Oral	Capsule	N018044	Jul 2008; Sep 2010
	-18, -12, -6, and 0 hr	Calcitriol	Oral	Capsule	N018044	Jul 2008; Sep 2010
Long (≥ 24 hr)	-24, -16, -8, and 0 hr	Ergocalciferol	Oral	Capsule	N003444	Nov 2010; Jul 2014
		Doxercalciferol	Oral	Capsule	N020862	Aug 2017
	At least 3 samples between 0 and 24 hr (inclusive)	Icosapent Ethyl	Oral	Capsule	N202057	Apr 2013; Feb 2014, Oct 2016
		Omega 3 Acid Ethyl Esters	Oral	Capsule	N021654	Sept 2012; Oct 2016, Dec 2016; Aug 2020
		Omega3 Acid Ethyl Esters Type A	Oral	Capsule	N204977	Dec 2016
		Omega3 Carboxylic Acids	Oral	Capsule	N205060	Jan 2016; Dec 2016
	At least 4 samples between 0 and 24 hr (inclusive)	Alendronate Sodium; Cholecalciferol	Oral	Tablet	N021762	Apr 2009; Oct 2011
	-48, -24, and 0 hr	Estrogens; Conjugated	Oral	Tablet	N004782	Dec 2014
		Estrogens; Conjugated Synthetic A	Oral	Tablet	N020992	Apr 2010
		Estrogens; Esterified	Oral	Tablet	A084948, A084949, A084950, A084951	Feb 2008; Sep 2012
	-48, -42, -36, -30, -24, -18, -12, -6, and 0 hr	Cholic Acid	Oral	Capsule	N205750	Oct 2016
		Phytonadione	Oral	Tablet	N010104	Feb 2010, Sep 2012, Jan 2016
			Injectable	Injection	N012223	Oct 2011, Sep 2012
		Ursodiol	Oral	Tablet	N020675	Jul 2008; Mar 2021
			Oral	Capsule	N019594	Feb 2010; Mar 2021

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Challenge: Provide consistent BLC recommendations in PSGs

- Determining an appropriate and consistent BLC approach for each drug product may present some challenges due to the **numerous factors considered** in the assessments
  - Limited baseline data available
  - Baseline patterns and variability
  - Baseline contribution to total concentration
  - Number of samples and duration
  - Sample matrix
  - Study population
  - Post-dose response
  - BLC method used in the new drug application (NDA)
  - Recommendations for related drug products

Challenge: Dose Selection

- Post-dose concentrations should be sufficiently elevated above baseline[3,5-7]
  - Minimize the confounding effects of endogenous levels on the BE assessment
    - Reduce the contribution of the baseline levels to the post-dose levels
    - May reduce variability in PK parameters following BLC
    - Improve ability to adequately characterize the terminal elimination phase following BLC
  - Improve sensitivity to detect formulation differences between test and reference products

- In some cases, supratherapeutic doses are recommended for PK BE studies[8,9]
  - Need to assess potential safety concerns in healthy subjects
    - PK BE studies are commonly conducted using a single-dose in **healthy subjects**[2]
    - There may be insufficient safety data available on supratherapeutic doses in healthy subjects

Challenge: Population Selection and Baseline Modulation

- Baseline endogenous levels may be controlled through selection of the study population or pre-treatment with a drug to modulate the baseline[3]
  - PSG for many estradiol drug products recommend that PK BE studies are conducted in healthy, postmenopausal women (PMW)[10,11]
    - Menstrual cycle is absent in PMW resulting in relatively stable plasma estradiol concentrations[12]
    - PMW have lower estradiol plasma concentrations than women of reproductive age[13,14]
  - Some PSGs recommend administration of dexamethasone prior to drug administration as a pre-treatment to lower endogenous hydrocortisone levels[15,16]
- May minimize the impact of endogenous levels on the BE assessment

Challenges: Statistical Methods and BE Assessment

- Inability to adequately characterize the terminal elimination phase following BLC

- Exclusion of subjects with pre-dose concentration >5% of Cmax[2]

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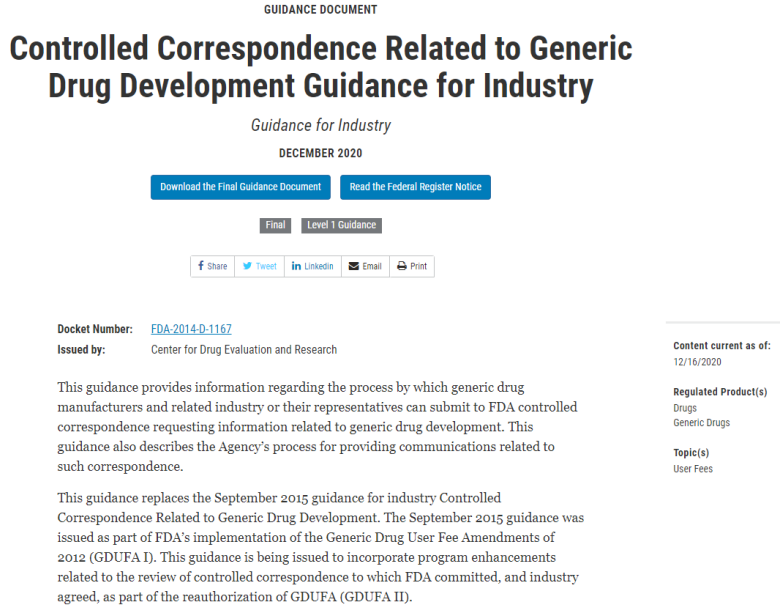
Internal efforts at FDA

Internal efforts and research are currently underway at FDA:

- To **establish a general framework** for developing the most appropriate BLC approach for BE assessment
- To **identify discrepancies and ambiguities** with the recommended BLC methods in published PSGs and **harmonize** the recommendations

Correspondence with FDA

Generic drug applicants may seek correspondence with FDA to clarify BE recommendations in PSGs or to propose alternative BE approaches for drug products



GUIDANCE DOCUMENT

Controlled Correspondence Related to Generic Drug Development Guidance for Industry

Guidance for Industry

DECEMBER 2020

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Final | Level 1 Guidance

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Docket Number: FDA-2014-D-1167
Issued by: Center for Drug Evaluation and Research

This guidance provides information regarding the process by which generic drug manufacturers and related industry or their representatives can submit to FDA controlled correspondence requesting information related to generic drug development. This guidance also describes the Agency's process for providing communications related to such correspondence.

This guidance replaces the September 2015 guidance for industry Controlled Correspondence Related to Generic Drug Development. The September 2015 guidance was issued as part of FDA's implementation of the Generic Drug User Fee Amendments of 2012 (GDUFA I). This guidance is being issued to incorporate program enhancements related to the review of controlled correspondence to which FDA committed, and industry agreed, as part of the reauthorization of GDUFA (GDUFA II).

Content current as of: 12/16/2020

Regulated Product(s)
Drugs
Generic Drugs

Topic(s)
User Fees

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/controlled-correspondence-related-generic-drug-development-guidance-industry

GUIDANCE DOCUMENT

Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA Guidance for Industry

NOVEMBER 2020

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Final

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Docket Number: FDA-2017-D-5739
Issued by: Center for Drug Evaluation and Research

This guidance describes an enhanced pathway for discussions between FDA and a prospective applicant preparing to submit to FDA or an applicant that has submitted to FDA an abbreviated new drug application (ANDA) for a complex product, as defined in this guidance. Specifically, this guidance provides information on requesting and conducting product development meetings, pre-submission meetings, and mid-review-cycle meetings with FDA.

Content current as of: 11/24/2020

Regulated Product(s)
Drugs
Generic Drugs

Topic(s)
User Fees
Drug Competition Action Plan

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/formal-meetings-between-fda-and-anda-applicants-complex-products-under-gdufa-guidance-industry

Summary

- BE studies with PK endpoints for drug products containing endogenous substances present unique regulatory challenges
- FDA provides general guidance and PSG for PK BE studies on drug products containing endogenous substances
- On-going efforts at FDA are focused on establishing a general framework for recommending the most appropriate BLC method for these drug products and harmonizing BE recommendations in published PSGs
- Generic drug applicants may communicate with FDA to clarify BE recommendations in PSGs or propose alternative BE approaches for drug products containing endogenous substances

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- Keith Gallicano, Keith Gallicano Consulting

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Collaborative Research Opportunities

OGD offers collaborative research opportunities supporting key regulatory science initiatives related to generic drugs

Science & Research

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The Office of Research and Standards, within the FDA's Office of Generic Drugs (OGD), supports the Science and Research program established under the Generic Drug User Fee Amendments (GDUFA). In collaboration with industry and the public, FDA creates an annual list of regulatory science initiatives on generic drugs. The research studies conducted under these initiatives advance public health by contributing to the development of safe and effective generic drugs. The results provide new tools for FDA to evaluate generic drug equivalence and for industry to efficiently develop new generic products.

Content current as of:
03/08/2022

Regulated Product(s)
Drugs
Generic Drugs

Priorities & Projects
Learn more about FDA generic drug research priorities, public workshops, and awarded projects

Research Publications & Resources
Browse FDA generic drug research published in scholarly journal articles, presentations, and posters

Guidances & Reports
View FDA generic drug research publications, including product-specific guidances and annual reports

Collaboration Opportunities
See a listing of available grant and fellowship opportunities

https://www.fda.gov/drugs/generic-drugs/science-research

Generic Drug Research Collaboration Opportunities

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The FDA Office of Generic Drugs implements the GDUFA Regulatory Science Research Program by collaborating within FDA as well as externally through grants or contracts.

Content current as of:
01/21/2022

Regulated Product(s)
Drugs

Contracts

- Broad Agency Announcement (BAA) applications are accepted on a continuous basis (see FDABAA-22-00123)

Grants

- Development of Advanced Analytical Methods for Analyzing Diastereomer Compositions in Oligonucleotides (U01) Clinical Trial Not Allowed (RFA-FD-22-013 Applications Due: 02/07/2022)
- Cutaneous Pharmacokinetics (PK) Based Approaches to Demonstrate Bioequivalence of Topical Products (U01) Clinical Trial Required (RFA-FD-22-017 Applications Due: 03/31/2022)
- PBPK Modeling to Support an Assessment of Bioequivalence for Locally-Acting Drugs in the Gastrointestinal Tract (U01) Clinical Trial Optional (RFA-FD-22-012 Applications Due: 03/31/2022)
- In Vitro Based Approaches to Evaluate the Bioequivalence of Prospective Generic Rectal and Vaginal Products (U01) Clinical Trial Not Allowed (RFA-FD-22-014 Applications Due: 03/31/2022)
- Investigating the In Vivo Behavior and In Vitro Characteristics of a Purportedly Gastro-Retentive Extended Release Formulation to Elucidate Considerations Relevant to Generic Products (U01) Clinical Trials Required (RFA-FD-22-018 Applications Due: 03/31/2022)
- In Vitro Approaches to Evaluate and Compare the Adhesion Performance of Transdermal and Topical Delivery Systems (TDS) (U01) Clinical Trial Required (RFA-FD-22-015 Applications Due: 03/31/2022)
- Physiologically Based Pharmacokinetic Model for Nose-to-Brain Drug Delivery (U01) Clinical Trial Optional (RFA-FD-22-016 Applications Due: 03/31/2022)

https://www.fda.gov/drugs/generic-drugs/generic-drug-research-collaboration-opportunities

Post-dose Response

- **Homeostatic mechanisms** may exist to regulate levels of an endogenous substance within a physiological range

- In some instances, intake or administration of an endogenous analogue may affect production or disposition of the endogenous substance[4]
  - Feedback mechanisms resulting in reduced endogenous production
  - Other homeostatic mechanisms affecting baseline levels or variability
  - Saturable processes and non-linear PK

- The impact of these confounding factors should be considered during PSG development