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SOLICITUD DE BIOEQUIVALENCIA

Dirección Nacional de Farmacia y Drogas
Departamento de Registro Sanitario
Sección de Bioequivalencia

Nelson Rodríguez MSc

Panamá, 9 de octubre de 2025

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Guías Utilizadas en las Evaluaciones de las Solicitudes de Bioequivalencia

GUÍAS TÉCNICAS

Situación Actual

Panamá adopta como guías técnicas de referencias las guías de FDA, EMA, ICH y OMS*

Guías

- U.S. FOOD & DRUG ADMINISTRATION
- EUROPEAN MEDICINES AGENCY
  SCIENCE MEDICINES HEALTH
- ICH harmonisation for better health
- Organización Mundial de la Salud

*Decreto Ejecutivo N° 27 de 10 de mayo de 2024. G.O. 30028-C

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Data Integrity for In Vivo Bioavailability and Bioequivalence Studies	PDF (339.61 KB)	04/03/2024
Handling and Retention of Bioavailability BA and Bioequivalence BE Testing Samples: Draft Guidance for Industry	PDF (309.45 KB)	03/27/2024
Topical Dermatologic Corticosteroids: In Vivo Bioequivalence	PDF (526.26 KB)	10/24/2023

Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs: Draft Guidance for Industry	PDF (409.31 KB)	04/13/2023
Assessing Adhesion With Transdermal and Topical Delivery Systems for ANDAs Draft Guidance for Industry	PDF (370.85 KB)	04/12/2023
Statistical Approaches to Establishing Bioequivalence	PDF (592.56 KB)	12/02/2022
Evaluation of Therapeutic Equivalence	PDF (353.44 KB)	07/21/2022

In Vitro Permeation Test Studies for Topical Drug Products Submitted in ANDAs	PDF (689.03 KB)	10/21/2022
In Vitro Release Test Studies for Topical Drug Products Submitted in ANDAs	PDF (252.01 KB)	10/21/2022
Physicochemical and Structural (Q3) Characterization of Topical Drug Products Submitted in ANDAs	PDF (469.4 KB)	10/21/2022
Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application	PDF (388.32 KB)	08/20/2021

Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action	PDF (727.41 KB)	04/03/2003	Food-Effect Bioavailability and Fed Bioequivalence Studies: Guidance for Industry	PDF (216.55 KB)	12/01/2002
M9 Biopharmaceutics Classification System-Based Biowaivers	PDF (288.16 KB)	05/11/2021	Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations	PDF (170.47 KB)	09/01/1997
Bioanalytical Method Validation Guidance for Industry	PDF (385.62 KB)	05/22/2018	Dissolution Testing of Immediate Release Solid Oral Dosage Forms	PDF (129.83 KB)	08/25/1997

Clinical pharmacology and pharmacokinetics

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

The European Medicines Agency's scientific guidelines on clinical pharmacology and pharmacokinetics help medicine developers prepare marketing authorisation applications for human medicines.

For a complete list of scientific guidelines currently open for consultation, see: Public consultations.

Finalised guidelines

- Bioanalytical method validation
- Clinical investigation of the pharmacokinetics of therapeutic proteins
- Equivalence studies for the demonstration of therapeutic equivalence for locally applied, locally acting products ir the gastrointestinal tract - Scientific guideline
- Evaluation of the pharmacokinetics of medicinal products in patients with impaired hepatic function
- Evaluation of the pharmacokinetics of medicinal products in patients with decreased renal function
- Investigation of bioequivalence
- Appendix IV of the guideline on the investigation on bioequivalence: presentation of biopharmaceutical and bioanalytical data in module 2.7.1 - Scientific guideline
- Investigation of drug interactions
- Pharmacokinetic and clinical evaluation of modified-release dosage forms
- Pharmacokinetic studies in man
- Reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation
- Reporting the results of population pharmacokinetic analyses
- Role of pharmacokinetics in the development of medicinal products in the paediatric population
- Strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products - Scientific guideline
- Use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products

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M9 Biopharmaceutics Classification System-based Biowaivers

M9 Biopharmaceutics Classification System-based Biowaivers

This topic was endorsed by the ICH Assembly in October 2016.

This new multidisciplinary Guideline addresses Biopharmaceutics Classification System (BCS)-based biowaivers. BCS-based biowaivers may be applicable to BCS Class I and III drugs, however BCS-based biowaivers for these two classes are not recognised worldwide. This means that pharmaceutical companies have to follow different approaches in the different regions.

This Guideline provides recommendations to support the biopharmaceutics classification of medicinal products and to support the waiver of bioequivalence studies.

This will result in the harmonisation of current regional guidance and support streamlined global drug development.

Date of *Step 4*: 20 November 2019

Guideline

M9 Guideline

Endorsed Documents

M9 Concept Paper

M9 Business Plan

WG Presentations / Trainings

M9 Step 4 Presentation

M9 Q&As Q&As on Biopharmaceutics Classification System-based Biowaivers

The ICH M9 Q&As provide clarity to support the implementation of the ICH M9 Guideline on Biopharmaceutics Classification System (BCS)-based biowaivers in ICH Regulatory Member countries/regions.

Date of *Step 4*: 20 November 2019

Q&As

M9 Q&As

M13 Bioequivalence for Immediate-Release Solid Oral Dosage Forms

M13A EWG Bioequivalence for Immediate-Release Solid Oral Dosage Forms

This topic was endorsed by the ICH Assembly in November 2019.

Part of the foreseen ICH M13 Guideline series (M13A-C), the ICH M13A Guideline is intended to provide recommendations on conducting bioequivalence (BE) studies during both development and post approval phases for orally administered immediate-release (IR) solid oral dosage forms designed to deliver drugs to the systemic circulation, such as tablets, capsules, and granules/powders for oral suspension. The ICH M13A Guideline is the first Guideline in the foreseen series to describe the scientific and technical aspects of study design and data analysis to support BE assessment for orally administered IR solid oral dosage forms. How regulatory decisions may be made based on BE assessment is out of the scope of this guideline.

Further information can be found in the M13 Concept Paper and Business Plan.

Date of *Step 4*: 23 July 2024

Guideline
M13A Guideline

Endorsed Documents
M13 Concept Paper

WG Presentations / Trainings
M13A Step 4 Presentation

M13A Q&As Question and Answers: Bioequivalence for Immediate-Release Solid Oral Dosage Forms

ICH M13A Questions and Answers (Q&As) have been developed to provide clarity on concepts related to the evaluation of bioequivalence for immediate-release solid oral dosage forms as covered in the Guideline. This Q&A document is intended to offer additional clarification and improve harmonization.
The scope and organization of this Q&A document align with those of ICH M13A.

Date of *Step 4*: 23 July 2024

Files
M13A Q&As

M13B EWG Bioequivalence for Immediate-Release Solid Oral Dosage Forms

Part of the foreseen ICH M13 Guideline series (M13A-C), the ICH M13B Guideline is intended to provide recommendations on obtaining waivers of bioequivalence (BE) studies for one or more additional strengths of a drug product in an application where in vivo BE has been demonstrated for at least one of the strengths. This guideline is applicable to both development and post approval phases for orally administered immediate-release (IR) solid oral dosage forms designed to deliver drugs to the systemic circulation, such as tablets, capsules, and granules/powders for oral suspension. The ICH M13B Guideline is the second Guideline in the foreseen series to describe the scientific and technical aspects of demonstrating BE for additional strengths of a drug product, i.e., obtaining waiver(s) for one or more strengths in an application with multiple strengths when BE has been demonstrated for at least one of the strengths following ICH M13A. How regulatory decisions may be made based on BE assessment is out of the scope of this guideline.

Further information can be found in the M13 Concept Paper and Business Plan.

Rapporteur: Dr. Lei Zhang (FDA, United States)

Regulatory Chair: Dr. Jan Welink (EC, Europe)

Date of *Step 2b*: 13 March 2025

Status: *Step 3*

Guideline
M13B Draft Guideline

Endorsed Documents
M13 Concept Paper
M13 Work Plan

Supplemental Documents
M13B Concept Paper Supplement

WG Presentation / Trainings
M13B Step 2 Presentation

WG list

M13C EWG Bioequivalence for Immediate-Release Solid Oral Dosage Forms

Part of the foreseen ICH M13 Guideline series (M13A-C), the ICH M13C Guideline is intended to provide recommendations on data analysis and BE assessment for 1) highly variable drugs, 2) drugs with narrow therapeutic index, and 3) complex BE study design and data analysis considerations, e.g., adaptive BE study design for orally administered immediate-release (IR) solid oral dosage forms designed to deliver drugs to the systemic circulation, such as tablets, capsules, and granules/powders for oral suspension. The ICH M13C Guideline is the third Guideline in the foreseen series to describe the scientific and technical aspects of study design and data analysis to support BE assessment for orally administered IR solid oral dosage forms. How regulatory decisions may be made based on BE assessment is out of the scope of this guideline.

Further information can be found in the M13 Concept Paper and Business Plan.

Endorsed Document
M13 Concept Paper
M13 Work Plan

Supplemental Documents
M13C Concept Paper Supplement

WG list

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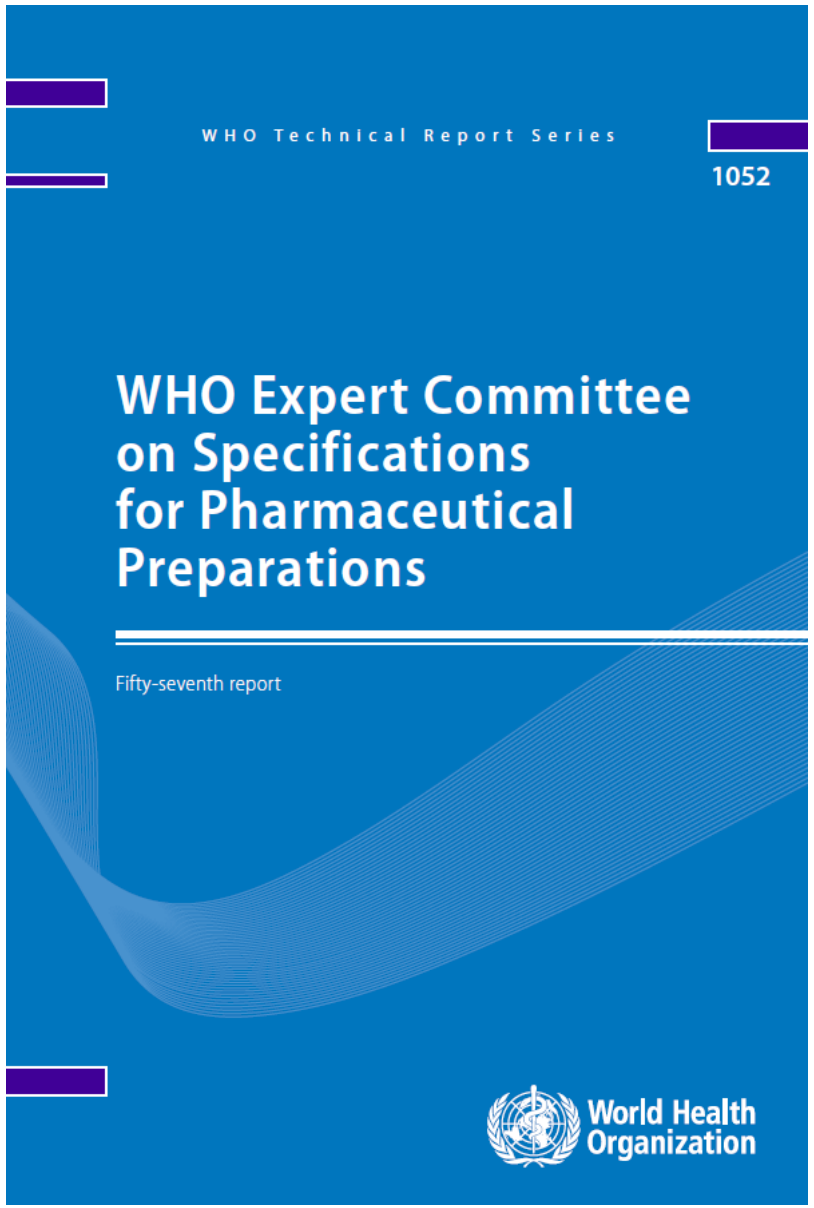

Annex 6

WHO Biowaiver List: proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms

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Annex 7

WHO guideline on Biopharmaceutics Classification System-based biowaivers

Background

A recommendation was made to the World Health Organization (WHO) Norms and Standards for Pharmaceuticals Team by the group of experts participating at the Joint Meeting on Regulatory Guidance for Multisource Products (1–3 November 2022), as well as by other parties, including the WHO Prequalification Team, to update the WHO Biopharmaceutics Classification System (BCS)-based biowaiver requirements (associated section within the overarching WHO *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability*) (*1*) in order to harmonize those guidelines with those stated in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline M9 on *Biopharmaceutics classification system-based biowaivers*, adopted in November 2019 (*2*).

The *WHO guideline on Biopharmaceutics Classification System-based biowaivers* will supersede the BCS-based biowaiver section of the WHO *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (*1*). The purpose of this document is to provide recommendations to support the biopharmaceutics classification of active pharmaceutical ingredients (APIs) and the BCS-based biowaiver of bioequivalence studies for finished pharmaceutical products (FPPs).

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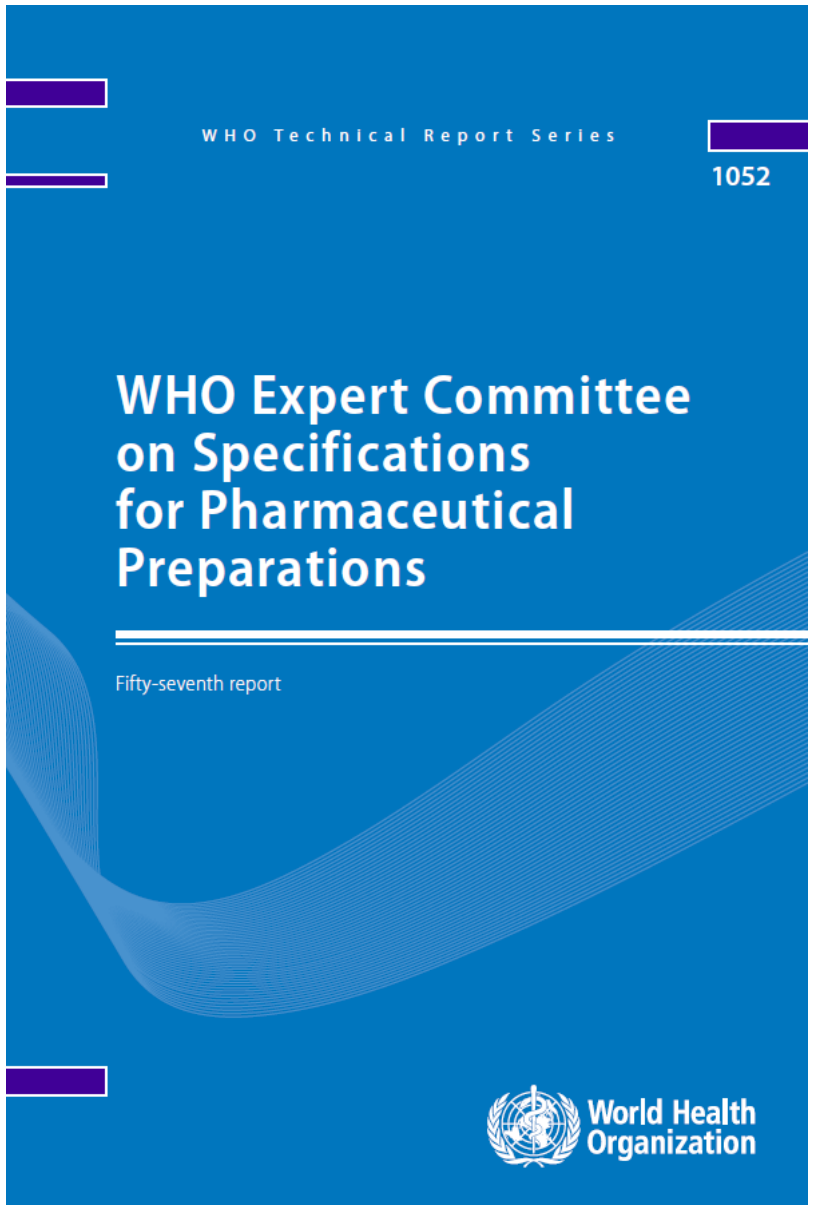

Annex 8

Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability

Republication of *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability*, WHO Technical Report Series No. 1003, Annex 6.

Background

Following the publication of the *WHO guideline on Biopharmaceutics Classification System-based biowaivers*, the relevant sections from this guideline have been removed, including the appendix *Equilibrium solubility experiments for the purpose of classification of active pharmaceutical ingredients according to the Biopharmaceutics Classification System.*

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Product-Specific Guidances for Generic Drug Development

Total number of currently published PSGs: 2252

Product-Specific Guidances for Specific Products Arranged by Active Ingredient

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Product-Specific Guidances for Specific Products Arranged by Active Ingredient

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Levothyroxine Search Reset

2 record(s) found for 'Levothyroxine'.

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Show 10 entries Filter:

Active Ingredient	Type	Route	Dosage Form	RLD or RS Number	Date Recommended
Levothyroxine Sodium	Draft	Oral	Tablet	021116 021210 021301 021342 021402	12/29/2014
Levothyroxine sodium	Draft	Oral	Capsule	021924	11/28/2018

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Draft Guidance on Levothyroxine Sodium

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind the FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Levothyroxine sodium

Dosage Form; Route: Tablet; oral

Recommended Studies: One study

1. Type of study: Fasting
   Design: Single-dose, four-way, fully replicated crossover in vivo
   Strength: 0.3 mg
   Subjects: Healthy males and non-pregnant females, general population
   Additional comments:
   1. Females should not be pregnant or lactating, and should practice abstention or use appropriate forms of contraception during the study.
   2. Levothyroxine has a long elimination half-life, hence adequate washout periods should be ensured between treatments in the crossover study. Measurement of levothyroxine may be truncated to 48 h post-dose.
   3. The dose for R and T administered during the study should be 0.6 mg to ensure adequate measurement of the analyte.
   4. Given the numerous drug-drug interactions for levothyroxine sodium, caution should be exercised in administering concomitant medications during the study.
   5. Post-dose levothyroxine measurements by the baseline levothyroxine value should be corrected in each period for each subject. The baseline value should be obtained from the average of three levothyroxine measurements taken before dosing (i.e., at 0.5 h, 0.25 h, and 0 h pre-dose).
   6. Applicant may consider using the reference-scaled average bioequivalence approach for levothyroxine sodium.

Analytes to measure (in appropriate biological fluid): Levothyroxine in serum

Bioequivalence based on (90% CI): Baseline-corrected levothyroxine

Waiver request of in vivo testing: 0.025 mg, 0.05 mg, 0.075 mg, 0.088 mg, 0.1 mg, 0.112 mg, 0.125 mg, 0.137 mg, 0.15 mg, 0.175 mg, and 0.2 mg based on: (i) an acceptable bioequivalence study on the 0.3 mg strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all strengths.

Regulatory Filing Recommendations: Note that there are five different reference listed drug (RLD) products for levothyroxine sodium tablets. A separate fasting bioequivalence study (and a separate fed study, if appropriate) must be conducted against the highest strength of each RLD product for which a sponsor wishes its product to receive an 'AB' rating. However, it is not necessary to submit a separate abbreviated new drug application (ANDA) for each RLD product being referenced. Instead, a sponsor may seek an 'AB' rating for its product against one of the RLD products in the original submission, and then submit one supplement to the original submission per each of the other RLD products against which it wishes its product to obtain an 'AB' rating.

Dissolution test method and sampling times: The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods website 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).

Explanation: FDA has concluded that levothyroxine sodium is a narrow therapeutic index (NTI) drug based on the following evidence:

- The range between serum levothyroxine therapeutic and toxic concentrations is narrow;
- Some levothyroxine-associated toxicities are serious and/or irreversible;
- Sub-therapeutic levothyroxine concentrations result in inadequate treatment and lead to poor clinical outcomes;
- Levothyroxine sodium requires individual dose titration to achieve a satisfactory balance between maximizing efficacy and minimizing serious dose-related toxicity;
- Therapeutic drug monitoring based on serum TSH and total or free-T_4 levels is routinely employed to facilitate levothyroxine dose titration; and
- Levothyroxine has small-to-medium within-subject variability.

The study design should be a fully replicated crossover approach in order to
- Scale bioequivalence limits to the variability of the referenced product; and
- Compare test and referenced product within-subject variability.

For details about Method for Statistical Analysis Using the Reference-Scaled Average Bioequivalence Approach for narrow therapeutic index drugs, refer to the draft Guidance on Warfarin Sodium.

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pregabalin Search Reset

2 record(s) found for 'pregabalin'.

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Active Ingredient	Type	Route	Dosage Form	RLD or RS Number	Date Recommended
Pregabalin	Draft	Oral	Capsule	021446	10/30/2024
Pregabalin	Draft	Oral	Tablet, Extended Release	209501	09/13/2018

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Draft Guidance on Pregablin

October 2024

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In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredient: Pregabalin

Dosage Form: Capsule

Route: Oral

Strengths: 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, 300 mg

Recommended Studies: Two options: (1) Biopharmaceutics Classification System (BCS)-based biowaiver or (2) one in vivo bioequivalence study with pharmacokinetic endpoints

I. Option 1: BCS Class I-based biowaiver

A waiver request of in vivo testing for all the strengths of this product may be considered provided that the appropriate documentation regarding high solubility, high permeability and rapid dissolution as detailed in the most recent version of the FDA guidance for industry on *M9 Biopharmaceutics Classification System-Based Biowaivers*[a] is submitted in the application. Applicants may use the information contained in the approved labeling of the reference listed drug (RLD). Peer reviewed articles may not contain the necessary details of the testing for the Agency to make a judgment regarding the quality of the studies. A decision regarding the acceptability of the waiver request can only be made upon assessment of the data submitted in the application.

II. Option 2: In vivo bioequivalence study with pharmacokinetic endpoints

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 300 mg
   Subjects: Healthy males and healthy females not of reproductive potential
   Additional comments: Males with female partners of reproductive potential should use condoms during the study and for at least 10 weeks (one complete sperm cycle) after the last dose.

Analyte to measure: Pregabalin in plasma

Bioequivalence based on (90% CI): Pregabalin

Waiver request of in vivo testing: 25, 50, 75, 100, 150, 200, and 225 mg strengths based on (i) acceptable bioequivalence study on the 300 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 in the FDA's Dissolution Methods database, http://www.accessdata.fda.gov/scripts/cder/dissolution/. Conduct comparative dissolution testing on 12 dosage units for each of all strengths of the test product and RLD.[1] Specifications will be determined upon review of the abbreviated new drug application.

Document History: Recommended May 2009; Finalized October 2011; Revised October 2024

Unique Agency Identifier: PSG_021446

[a] For the most recent version of a guidance, check the FDA guidance website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[1] If the RLD is not available, refer to the most recent version of the FDA guidance for industry on *Referencing Approved Drug Products in ANDA Submissions*.

Dissolution Methods

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Dissolution Methods

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Search Results for: "Pregabalin"

CSV Excel

Filter:

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)	Date Updated
Pregabalin	Capsule			Refer to FDA's Dissolution Guidance, 2018			07/02/2020
Pregabalin	Tablet (Extended Release)	II (Paddle)	50	0.06 M HCl	900	1, 2, 4, 6, 8, 10, 12, 16 and 24 hours	02/08/2018

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Draft Guidance on Iron Sucrose

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Active ingredient: Iron Sucrose

Form/Route: Injectable; Intravenous

Recommended studies: 2 studies

1. Type of study: Fasting
   Design: Single-dose, randomized, parallel in vivo study
   Strength: 100mg/5mL (Dose 100 mg)
   Subjects: Healthy males and females, general population
   Additional Comments: The products should be administered undiluted as a slow intravenous injection dose of 100 mg over 5 minutes.

   Analytes to measure (in appropriate biological fluid): Measure each of the following:

   1. [Total Iron] in serum
   2. [Transferrin-bound Iron] in serum

   Bioequivalence based on (90% CI):
   - Maximum value of the difference in concentration between Total Iron and Transferrin-bound Iron over all time points measured; and
   - Difference in AUC between Total Iron and Transferrin-bound Iron*

   *AUC of Total Iron and AUC of Transferrin-bound Iron should be calculated separately to maximize the number of data points used in cases of missing data in the transferrin-bound iron and total iron concentration-time profiles. In addition, there is no need to perform baseline correction of Total Iron and Transferrin-bound Iron.

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2. Type of study: Particle size distribution
   Design: In vitro testing on at least three lots of both test and reference products

   Parameters to measure: D_{10}, D_{50}, D_{90}

   Bioequivalence based on: D50 and SPAN [i.e. $(D_{90}-D_{10})/D_{50}$] or polydispersity index using the population bioequivalence statistical approach.

Waiver request of in vivo testing: 50mg/2.5mL, 65mg/3.25mL, and 200mg/10mL, based on (i) acceptable bioequivalence studies on the 100mg/5mL strength; and (ii) proportional similarity of the formulations across all strengths.

Dissolution test method and sampling times: Not Applicable.

Special Considerations:

1. The proposed parenteral drug product should be qualitatively (Q1) and quantitatively (Q2) the same as the RLD. Equivalence in the stoichiometric ratios of iron, sucrose, and other relevant components need to be established.

2. Sameness in physicochemical properties needs to be established. These in vitro characterizations should be conducted on at least three batches of the ANDA and RLD. Attributes that should be included in the characterization are:
   - Iron core characterizations including but not limited to core size determination, iron oxide crystalline structure and iron environment.
   - Composition of carbohydrate shell and surface properties.
   - Particle morphology.
   - Labile iron determination under physiologically relevant conditions. The tests can be performed with in vitro haemodialysis system [1], the catalytic bleomycin assay of spiked human serum samples [1,2], the spectrophotometric measurement of Fe reduction, or other methods that are validated for accuracy and precision.

3. For additional information regarding statistical analysis of in vitro data, please refer to *Bioequivalence Recommendations for Specific Products: Budesonide Suspension (Draft)*.

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[1] Balakrishnan VS, *et al*. Physicochemical properties of ferumoxytol, a new intravenous iron preparation. *Eur J Clin Invest.* 2009 Jun;39(6):489-96.
[2] Burkitt MJ, *et al*. A simple, highly sensitive and improved method for the measurement of bleomycin-detectable iron: the 'catalytic iron index' and its value in the assessment of iron status in haemochromatosis. *Clin Sci (Lond).* 2001 Mar;100(3):239-47.

Ministerio de Salud Dirección Nacional de Farmacia y Drogas Departamento de Registros Sanitarios y Otros Productos para la Salud Humana Sección de Bioequivalencia Hoja de Evaluación	Número de solicitud: Página 5 de 7

Se presenta estudios de similitud in vitro con las siguientes pruebas:
1-Microscopia de Transmisión Electrónica
2-Espectroscopia UV-Vis
3-Difracciónde Rayos X
4-Resonancia Electrónica de Spin
5-Espectroscopia Mossbauer
6-Espectroscopia FTIR
7-Mobilidad Electroforética (Potencial Z)
8-Dispersión de Luz Dinámica
9-Microscopia de Fuerza Atómica
10-Espectrometría de Masas de Plasma (ICP-OES)
11-Estudios de Degradación Cinética
12-Resonancia Magnética Nuclear de Protón 1H RMN
13-Resonancia Magnética Nuclear de Carbono 13C RMN
14-Analisis Elemental
15-Análisis Termogravimétrico
16-Espectroscopia RAMAN
17-Contenido de Hierro por Espectrometría de Masas de Plasma Acoplado Inductivamente (ICP-MS)

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De las técnicas numeradas, las que determinan las características solicitadas en la nota son:
Núcleo de Hierro:
• Morfología y Tamaño del Núcleo de Hierro: Microscopia de Transmisión Electrónica; Difracción de Rayos X; Espectroscopia Mossbauer; Microscopia de Fuerza Atómica
• Cristalinidad: Difracción de Rayos X; Espectroscopia Mossbauer; Espectroscopia RAMAN
• Ambiente del Hierro: Espectroscopia UV-Vis; Resonancia Electrónica de Spin; Espectroscopia Mossbauer; Espectroscopia RAMAN
• Contenido de Hiero: Contenido de Hierro por Espectrometría de Masas de Plasma Acoplado Inductivamente (ICP-MS)
Composición del Cubierta de Carbohidratos y Propiedades de Superficie:
• Composición del Carbohidrato e Interacciones del Núcleo de Hierro y Carbohidrato: Espectroscopia FTIR; Análisis Termogravimétrico
• Carga en la Superficie: Prueba Mobilidad Electroforética (Potencial Z)

(Ctrl)

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

rivastigmine Search Reset

2 record(s) found for 'rivastigmine'.

Excel CSV PDF

Show 10 entries Filter:

Active Ingredient	Type	Route	Dosage Form	RLD or RS Number	Date Recommended
Rivastigmine	Draft	Transdermal	Film, Extended Release	022083	11/21/2019
Rivastigmine Tartrate	Draft	Oral	Capsule	020823	10/30/2024

Showing 1 to 2 of 2 entries

Previous 1 Next

Contains Nonbinding Recommendations

Draft Guidance on Rivastigmine

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: Rivastigmine

Dosage Form; Route: Film, extended release; transdermal

Recommended Studies: Three studies

1. Type of study: Bioequivalence study with pharmacokinetic endpoints
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 9.5 mg/24 hr
Subjects: Males and non-pregnant, non-lactating females, general population
Additional comments:
   - In this document, this dosage form is referred to as a transdermal delivery system (TDS) and includes products that may be described elsewhere or known as *patches* or *extended release films*.
   - Unless otherwise justified, the rivastigmine TDS should be applied to the same anatomical site on all subjects, selected from among those recommended for dosing in the approved labeling for the reference product, and worn for 24 hours. Applicants should randomize subjects to receive either the test or reference product in a given study period. When possible, the TDS administered in the second study period should be applied to the same anatomical site as in the first study period, but on the contralateral side of the body.
   - Contact of the TDS with the skin is essential for the in vivo performance of the TDS, and the pharmacokinetics may be altered when a TDS loses its adherence to the skin. Therefore, the adhesion of each TDS should be monitored and recorded throughout the pharmacokinetic study. The applicant should prespecify their inclusion criteria for the statistical analysis of pharmacokinetic endpoints and perform their primary pharmacokinetic analysis on the per protocol population, however, pharmacokinetic samples should be collected and analyzed from all subjects at all sampling times regardless of the adhesion scores of the TDS and regardless of the inclusion criteria for the statistical analysis of pharmacokinetic endpoints. Provisions should be included in the study protocol to ensure that deliberate actions with the intent to re-apply a detached area of the TDS, to apply pressure to the TDS, or to reinforce TDS adhesion with the skin (e.g., overlays) are avoided throughout the study.
   - The applicant should follow FDA's current thinking in the guidance *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA* for the design and conduct of the pharmacokinetic bioequivalence study.

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

Bioequivalence based on (90% CI): Rivastigmine

Waiver request of in vivo testing: The 4.6 mg/24 hr and 13.3 mg/24 hr strengths of the TDS may be considered for a waiver of in vivo bioequivalence testing based on (i) an acceptable bioequivalence study with the 9.5 mg/24 hr strength TDS, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the TDS formulation across all strengths.

NOTE: The proportional similarity of the TDS formulation across all strengths means i) that the amounts of active and inactive ingredients per unit of active surface area are the identical for the different strengths of the test product, and ii) that the ratios of the active surface areas of each strength of the test product compared to the 9.5 mg/24 hr strength of the test product are the same as the corresponding ratios for the active surface areas of each strength of the reference product compared to the 9.5 mg/24 hr strength of the reference product.

The ratios of labeled strength across all strengths of this product are not proportional to the ratios of active surface areas across all strengths, and so the labeled strengths should not be used as the basis for determining the proportionality of the TDS formulations across all strengths.

Dissolution test method and sampling times: Comparative dissolution testing should be conducted on 12 dosage units each, of all strengths of the test and reference products. Information on a dissolution method for this drug product can be found on the FDA Dissolution Methods web site, accessible at: http://www.accessdata.fda.gov/scripts/cder/dissolution/.

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2. Type of study: Adhesion study
Design: Single-dose, two-treatment, two period crossover in vivo
Strength: 9.5 mg/24 hr
Subjects: Males and non-pregnant, non-lactating females, general population
Additional comments:
   - The applicant may elect to evaluate the pharmacokinetic bioequivalence (study 1) and the adhesion (study 2) in a single study with a combined purpose, or in independent studies. In either case, the studies should be adequately powered to evaluate the bioequivalence, and independently, the comparative assessment of adhesion.
   - The applicant should follow FDA's current thinking in the guidance *Assessing Adhesion With Transdermal and Topical Delivery Systems for ANDAs* for the design and conduct of the independent adhesion study or the combined study to evaluate both pharmacokinetic bioequivalence and adhesion.

Recommended Feb 2010; Revised Jun 2010, Nov 2010, Nov 2013, Oct 2016, Oct 2018, Nov 2019

3. Type of study: Skin irritation study
Design: Randomized, evaluator-blinded, within-subject repeat in vivo
Strength: 4.6 mg/24 hr (Dose: One-half of 4.6 mg/24 hr TDS)
Subjects: Males and non-pregnant, non-lactating females, general population
Additional comments:

- All test articles (i.e., one-half of the 4.6 mg/24 hr test product[1], one-half of the 4.6 mg/24 hr reference product, one-half of the optional vehicle TDS[2] and optional negative control[3]) should be applied simultaneously to each subject at different positions on an application site recommended for dosing in the approved labeling for the reference product.

- Sequential TDS applications should be made to the same application site every 24 hours, for a total of 21 consecutive days. The TDS applied on Day 21 should be removed on Day 22.

- There is insufficient information to determine whether it is safe to simultaneously apply two whole, active, 4.6 mg/24 hr rivastigmine TDS on the same subject during a 21-day skin irritation and sensitization study. Since the reference product has a matrix design that can be safely cut in half, one half of the reference product can be used for these studies. If the test product also has a design that can be safely cut to a smaller size, it should also be cut in half, and one half of the test product may be applied simultaneously with one half of a reference product (to separate skin sites). It would not be acceptable to manufacture a separate batch of the test product in order to use a smaller TDS in this study. If the test product has a design that cannot be safely cut to a smaller size, and/or if a prospective applicant proposes study design different than what is recommended above, the prospective applicant may submit a pre-abbreviated new drug application (pre-ANDA) meeting request to discuss the proposed approach.

- The applicant should follow FDA's current thinking in the guidance *Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs* for the design and conduct of the skin irritation and sensitization study.

Additional comments relating to all studies:

In addition to the recommendations in the general guidances referenced above, and the product specific recommendations related to the individual studies, the following product specific recommendations should be considered.

- Inclusion Criteria (the applicant may add additional criteria):

[1] The test product evaluated should be the actual TDS to be marketed.
[2] The optional vehicle TDS should contain all of the inactive ingredients in the test product and be identical to the test product in every manner except for the absence of the active ingredient.
[3] An example of the optional negative control treatment is an occlusive cover or device with normal saline applied on a polyester pad under the cover or within the device chamber.

a. Subject has a normal screening echocardiogram; non-specific ST-T wave changes are acceptable.

- Exclusion Criteria (the applicant may add additional criteria):
  a. Clinically relevant findings in a screening 12-lead electrocardiogram, such as second- or third-degree atrioventricular block or complete bundle branch block
  b. Medical history of sick sinus syndrome, conduction defects (sino-atrial block, atrio-ventricular block), gastroduodenal ulcerative conditions, asthma or chronic obstructive pulmonary disease, urinary obstruction, extrapyramidal symptoms such as tremor or seizures
  c. Taking metoclopramide or beta-blockers
  d. Within 3 weeks prior to dosing, use of cholinergic compounds

- Provide a listing of the prescription and over-the-counter drug products that are contraindicated during the study, such as:
  a. Other cholinomimetic drugs
  b. Anticholinergic medications
  c. Succinylcholine-type muscle relaxants during anesthesia

- Subjects should be advised that if they need to have surgery during the study, they should inform their doctor that the rivastigmine TDS may exaggerate the effects of some muscle relaxants during anesthesia.

- Subjects should be advised that the rivastigmine TDS may cause dizziness and drowsiness, mainly at the start of treatment or when increasing the dose. Subjects should be advised that if they feel dizzy or drowsy, they should not drive, operate machines or perform any other tasks that require attention.

Product-specific bioequivalence guidance

Share

This section includes the European Medicines Agency's (EMA) product-specific bioequivalence guidance, which summarises in a standardised format the relevant study design principles for demonstration of bioequivalence.

Human | Regulatory and procedural guidance | Research and development | Scientific guidelines

Page contents

Product-specific guidance helps applicants meet the expectations of regulators in the European Union, particularly for generic applications, across all regulatory submission routes, i.e. via the centralised, decentralised, mutual recognition or national procedures. For more information about product-specific guidance, see:

Concept paper on the development of product-specific guidance on demonstration of bioequivalence

Consultation dates: 01/08/2013 to 30/09/2013
Draft: consultation closed
Reference Number: EMA/CHMP/423137/2013

English (EN) (89.2 KB - PDF)
First published: 01/08/2013 **Last updated:** 01/08/2013

View

Finalised guidelines

- Abiraterone acetate product-specific bioequivalence guidance
- Acenocoumarol product-specific bioequivalence guidance
- Agomelatine product-specific bioequivalence guidance
- Alectinib product-specific bioequivalence guidance
- Aliskiren product-specific bioequivalence guidance
- Apixaban product-specific bioequivalence guidance
- Asenapine product-specific bioequivalence guidance
- Cabozantinib product-specific bioequivalence guidance
- Capecitabine product-specific bioequivalence guidance
- Carglumic acid product-specific bioequivalence guidance
- Cholic acid product-specific bioequivalence guidance
- Colchicine product-specific bioequivalence guidance
- Crizotinib product-specific bioequivalence guidance
- Dabigatran etexilate product-specific bioequivalence guidance
- Dasatinib product-specific bioequivalence guidance
- Deferasirox product-specific bioequivalence guidance
- Dimethyl fumarate product-specific bioequivalence guidance
- Dolutegravir product-specific bioequivalence guidance
- Dronedarone product-specific bioequivalence guidance
- Elvitegravir / cobicistat / emtricitabine / tenofovir disoproxil product-specific bioequivalence guidance
- Elvitegravir product-specific bioequivalence guidance
- Entecavir product-specific bioequivalence guidance
- Enzalutamide product-specific bioequivalence guidance
- Erlotinib product-specific bioequivalence guidance
- Etonogestrel and ethinylestradiol vaginal delivery system product-specific bioequivalence
- Everolimus product-specific bioequivalence guidance
- Exenatide product-specific bioequivalence guidance
- Ezetimibe product-specific bioequivalence guidance
- Fingolimod product-specific bioequivalence guidance
- Gefitinib product-specific bioequivalence guidance
- Ibrutinib product-specific bioequivalence guidance
- Ibuprofen product-specific bioequivalence guidance
- Imatinib product-specific bioequivalence guidance
- Lanreotide acetate product-specific bioequivalence guidance
- Lapatinib product-specific bioequivalence guidance
- Ledipasvir/sofosbuvir product-specific bioequivalence guidance
- Lenalidomide product-specific bioequivalence guidance
- Levodopa/carbidopa/entacapone product-specific bioequivalence guidance
- Levothyroxine product-specific bioequivalence guidance
- Liposomal amphotericin B product-specific bioequivalence guidance
- Memantine product-specific bioequivalence guidance
- Miglustat product-specific bioequivalence guidance
- Octreotide acetate product-specific bioequivalence guidance
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- Oseltamivir product-specific bioequivalence guidance
- Palbociclib product-specific bioequivalence guidance
- Paliperidone palmitate product-specific bioequivalence guidance
- Paliperidone product-specific bioequivalence guidance
- Paracetamol product-specific bioequivalence guidance
- Pazopanib product-specific bioequivalence guidance
- Pegylated liposomal doxorubicin hydrochloride product-specific bioequivalence guidance
- Posaconazole product-specific bioequivalence guidance
- Posaconazole product-specific bioequivalence guidance
- Prasugrel product-specific bioequivalence guidance
- Repaglinide product-specific bioequivalence guidance
- Rilpivirine product-specific bioequivalence guidance
- Rivaroxaban product-specific bioequivalence guidance
- Sirolimus product-specific bioequivalence guidance
- Sitagliptin product-specific bioequivalence guidance
- Sorafenib product-specific bioequivalence guidance
- Sunitinib product-specific bioequivalence guidance
- Tacrolimus granules product-specific bioequivalence guidance
- Tadalafil product-specific bioequivalence guidance
- Telithromycin product-specific bioequivalence guidance
- Ticagrelor product-specific bioequivalence guidance
- Ursodeoxycholic acid product-specific bioequivalence guidance
- Vandetanib product-specific bioequivalence guidance
- Vemurafenib product-specific bioequivalence guidance
- Vismodegib product-specific bioequivalence guidance
- Voriconazole product-specific bioequivalence guidance
- Vortioxetine hydrobromide / vortioxetine lactate product-specific bioequivalence guidance
- Zonisamide product-specific bioequivalence guidance

10 December 2020
EMA/CHMP/176098/2020
Committee for Medicinal Products for Human Use (CHMP)

Levothyroxine tablets 12.5 mcg, 25 mcg, 50 mcg, 75 mcg, 100 mcg and 200 mcg (and additional strengths within the range) product-specific bioequivalence guidance

Draft Agreed by Pharmacokinetics Working Party (PKWP)*	6 May 2020
Adopted by CHMP for release for consultation	28 May 2020
Start of public consultation	15 June 2020
End of consultation (deadline for comments)	30 September 2020
Agreed by Pharmacokinetics Working Party	19 November 2020
Adopted by CHMP	10 December 2020
Date for coming into effect	1st July 2021

*Experts of the Cardiovascular Working Party (CVSWP) were consulted on specific questions

Keywords	***Bioequivalence, generics, levothyroxine***

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Levothyroxine tablets 12.5 mcg, 25 mcg, 50 mcg, 75 mcg, 100 mcg and 200 mcg (and additional strengths within the range) product-specific bioequivalence guidance

Disclaimer:

This guidance should not be understood as being legally enforceable and is without prejudice to the need to ensure that the data submitted in support of a marketing authorisation application complies with the appropriate scientific, regulatory and legal requirements.

Requirements for bioequivalence demonstration (PKWP)

BCS Classification	**BCS Class:** ☐ **I** ☐ **III** ☒ **Neither of the two** **Background:** Solubility characteristics are atypical with self-association to form aggregates, low intrinsic solubility and intrinsic dissolution rate.
Bioequivalence study design *in case a BCS biowaiver is not feasible or applied*	**single dose** **cross-over**
	healthy volunteers
	☒ **fasting** ☐ **fed** ☐ **both** ☐ **either fasting or fed**
	Number of studies: One study at the highest strength.
	Other design aspects: A single supra-therapeutic dose of 600 mcg of test and reference product should be administered. Given that washout cannot be formally confirmed due to the presence of endogenous hormone, together with a long plasma elimination half-life, a minimum washout period of 35 days between treatment periods is recommended.

Levothyroxine tablets 12.5 mcg, 25 mcg, 50 mcg, 75 mcg, 100 mcg and 200 mcg (and additional strengths within the range) product-specific bioequivalence guidance

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	☒ **parent** ☐ **metabolite** ☐ **both**
Analyte	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
	Recommendations regarding method for baseline adjustment: Plasma/serum levothyroxine values for pharmacokinetic analysis are recommended to be corrected for endogenous thyroxine by subtraction of the mean of three pre-dose plasma thyroxine concentrations (e.g. at 0.5 h, 0.25 h, and 0 h pre-dose) from the values obtained post-dose.
Bioequivalence assessment	**Main pharmacokinetic variables:** AUC_{0-72h} and C_{max} **90% confidence interval:** 90.00 – 111.11% for AUC_{0-72h} and 80.00 – 125.00% for C_{max} **Background:** levothyroxine is a critical dose drug

Related content

- Pharmacokinetics: Q&As
- Methodology Working Party
- Public consultations

Topics

Regulatory and procedural guidance

Research and development

Scientific guidelines

3. Bioequivalence (general)

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- 3.1 Which statistical method for the analysis of a bioequivalence study does the Agency recommend? January 2011
- 3.2 What is the minimum number of subjects that should be included in the second stage of a two-stage bioequivalence study design? February 2013
- 3.3 Regarding the evaluation of orally inhaled medicinal products, to what extent do plasma levels reflect bio-availability in the lung? January 2015
- 3.4 Evaluation of orally inhaled medicinal products: can I scale acceptance limits (for Cmax and perhaps AUC) to allow for variability in reference product for fine particle dose? January 2015
- 3.5 Can I use a 3 period design scheme for the demonstration of within-subject variability for Cmax? June 2015
- 3.6 Would a specific bioequivalence study with administration of crushed/disintegrated tablets be required for a generic application? March 2019
- 3.7 If the test product is an oral solution (or suspension) dosed in single dose sachets and the test product claims the administration with or without water (or makes no claim), how should the test product be administered in the BE study? ... Sept 2017
- 3.8 What are the recommendations for a biowaiver of an additional strength for gastro-resistant preparations (e.g. omeprazole)? July 2010, March 2018 (updated April 2018) and May 2020
- 3.9 Is the Mahalanobis Distance (MD) an adequate measure for use in the assessment of dissolution similarity, in particular in cases where the f2 statistic is not suitable? Can interval estimation be used to inform decision... (superseded/incorporated)
- 3.10 What is the recommendation on what extent of active ingredient that should be released in a comparative local in vivo availability study, in order to allow a conclusion of comparable local exposure for lozenges? March 2020
- 3.11 Expectations for bootstrapping to calculate the 90% confidence interval for the f2 similarity factor - (superseded/incorporated into Q & A 3.13 August 2023)
- 3.12 Clarification on guideline requirements for parenteral oily solutions - December 2022
- 3.13 MWP Q & A on In Vitro Dissolution Profile Comparison for Bioequivalence Inference - New August 2023

4. Product-specific bioequivalence

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- 4.2 Acceptance criteria for bioequivalence studies for losartan. July 2010
- 4.3 What are the requirements for demonstration of bioequivalence for ciclosporine generics? July 2010
- 4.4 Bioequivalence studies for generic application of omega 3 fatty acid ethylesters in a soft gelatine capsule. October 2013
- 4.5 What do I need to consider in a generic application for quetiapine lambda 200, 300, 400 mg prolonged release tablets? October 2013
- 4.6 Requirements for demonstration of bioequivalence for mycophenolate mofetil generics. January 2011
- 4.7 Demonstration of bioequivalence for ebastine. October 2013
- 4.8 CHMP request to PKWP for clarification on demonstrating bioequivalence of low dose acetylsalicylic acid gastro-resistant formulations in fixed dose combinations with substitution indication. December 2016

4.9 Ferric citrate coordination complex 1g film-coated tablets - product specific equivalence guidance December 2018

4.10 PKWP Q & A on pharmacokinetic (PK) characteristics of iron salts for oral use. Acceptable bridging/bioequivalence data. May 2019

4.11 What is the recommendation on the most sensitive analyte and the required studies for establishing therapeutic equivalence by means of pharmacokinetic data for orally inhaled products containing beclomethasone dipropionate? New March 2020

4.12 Clarification on demonstration of bioequivalence for dabigatran etexilate New May 2020

4.13 PKWP Q & A on bioequivalence requirements for pirfenidone tablet formulations. New September 2021

4.14 PKWP Q & A on bioequivalence requirements for tadalafil orodispersible tablet. New September 2021

5. Bioequivalence in special populations

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5.1 Clarifications regarding bioequivalence studies in children. June 2009

5.2 Clarifications on the guideline on the evaluation of the pharmacokinetics of medicinal products in patients with impaired hepatic function. January 2015

6. Biowaivers

Expand section | Collapse section

6.1 What is the effect of sorbitol on the pharmacokinetics of highly permeable drug substances? September 2012

6.2 Is it possible to accept an "additional strengths biowaiver" when bioequivalence to the reference product has been established with a BCS-based biowaiver? October 2013

6.3 Clarification on how to apply the reference made in Appendix II of the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr**), when waiving in vivo studies for oral solutions. December 2016

6.4 How should the conditions regarding fulfilling proportionality in composition of fixed combinations be interpreted in an application with multiple strengths? June 2020

6.5 How large can the deviations from proportionality in composition be in the case of fixed combinations with highly soluble active substances in an application with multiple strengths (see also Q&A 6.4)? New July 2021

8. Modified release products

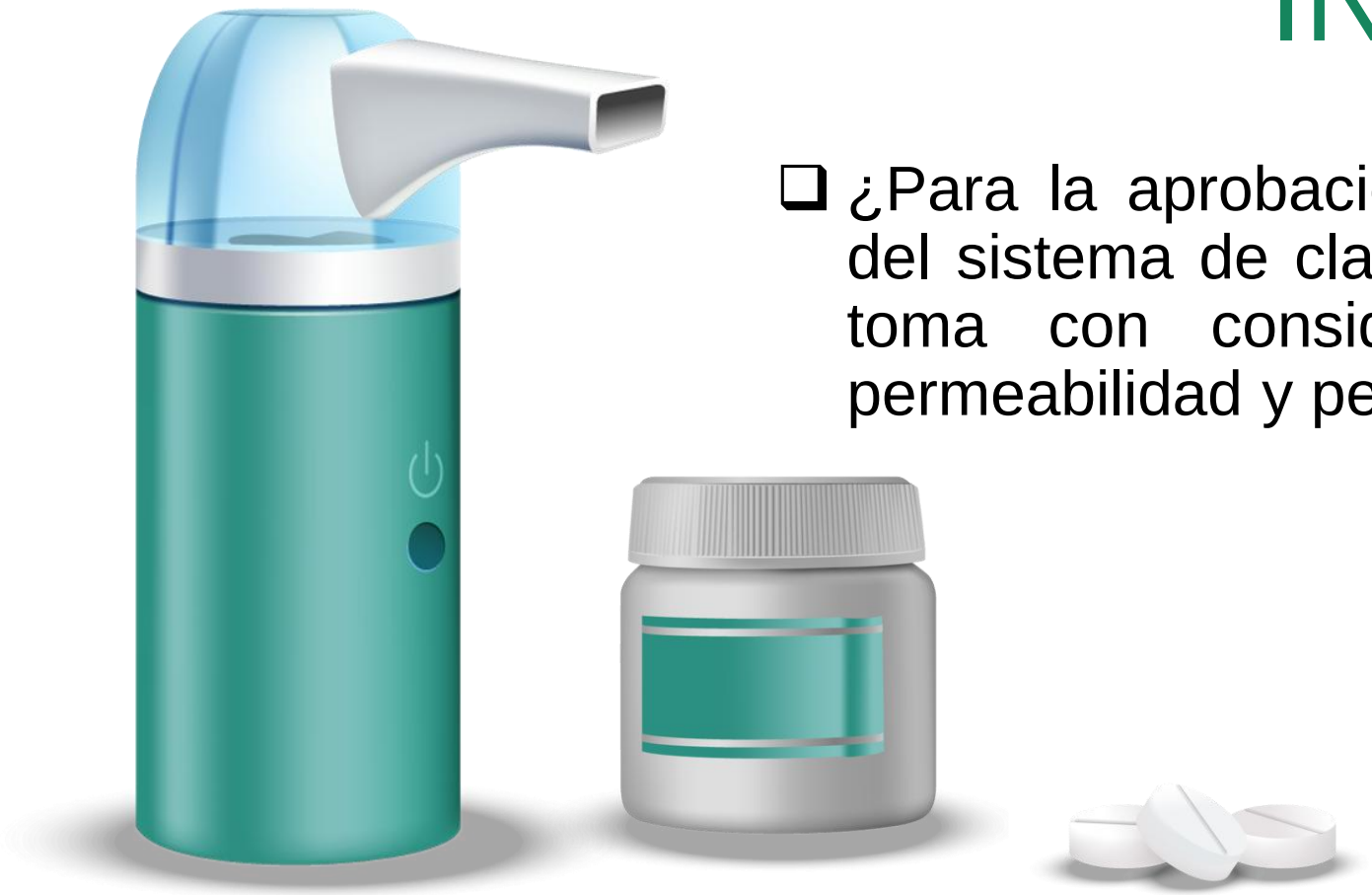
8.1 PKWP is requested to provide clarification on the requirements for sensitisation and irritation tests for transdermal products in Appendix I of the Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms. June 2018

INTERROGANTES

- ¿Los medicamentos aprobados por una autoridad reguladora de Latinoamérica pueden optar por ser evaluado mediante el procedimiento abreviado?

- ¿La documentación en inglés del desarrollo farmacéutico y los estudios de bioequivalencia se traducen al español?

INTERROGANTES



- ¿Para la aprobación de los medicamentos a través del sistema de clasificación biofarmacéutica, solo se toma con consideración su solublidad acuosa, permeabilidad y perfiles de disolución ?