GOBIERNO NACIONAL
CON PASO FIRME

salud
Ministerio de Salud
Panamá

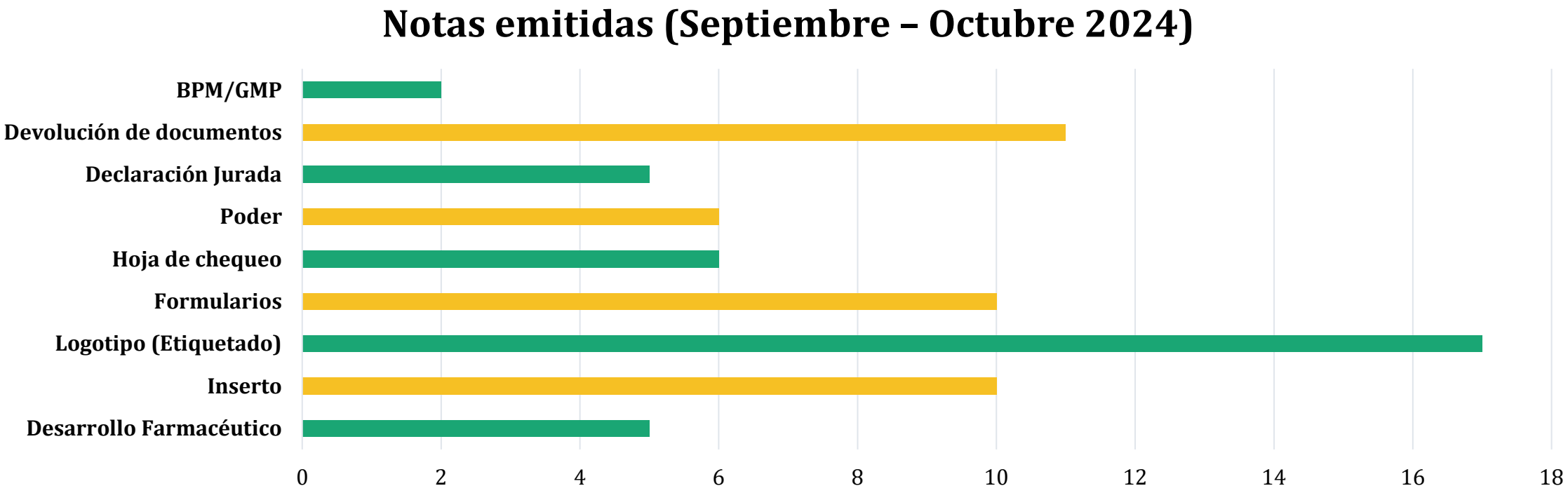
SOLICITUD DE BIOEQUIVALENCIA

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

Lcda. Karina Troya

Panamá, 22 de noviembre de 2024

Documentos Administrativos y de Calidad que reciben observaciones



	Desarrollo Farmacéutico	Inserto	Logotipo (Etiquetado)	Formularios	Hoja de chequeo	Poder	Declaración Jurada	Devolución de documentos	BPM/GMP
# notas	5	10	17	10	6	6	5	11	2

GOBIERNO NACIONAL
CON PASO FIRME

salud
Ministerio de Salud
Panamá

PRESENTACIÓN DE LA SOLICITUD

- Hoja de chequeo
- Formulario de solicitud
(presentado por el profesional responsable “farmacéutico”)
- Requisitos
  - Poder a favor del farmacéutico
  - Declaración Jurada
  - BPM vigentes (para todas las plantas que participen en el proceso de manufactura)
  - Especificaciones y CoA’s de la materia prima (activos y excipientes)
  - Desarrollo Farmacéutico
  - Evidencia (estudios clínicos, estudios de bioequivalencia)

GOBIERNO NACIONAL
CON PASO FIRME

salud
Ministerio de Salud
Panamá

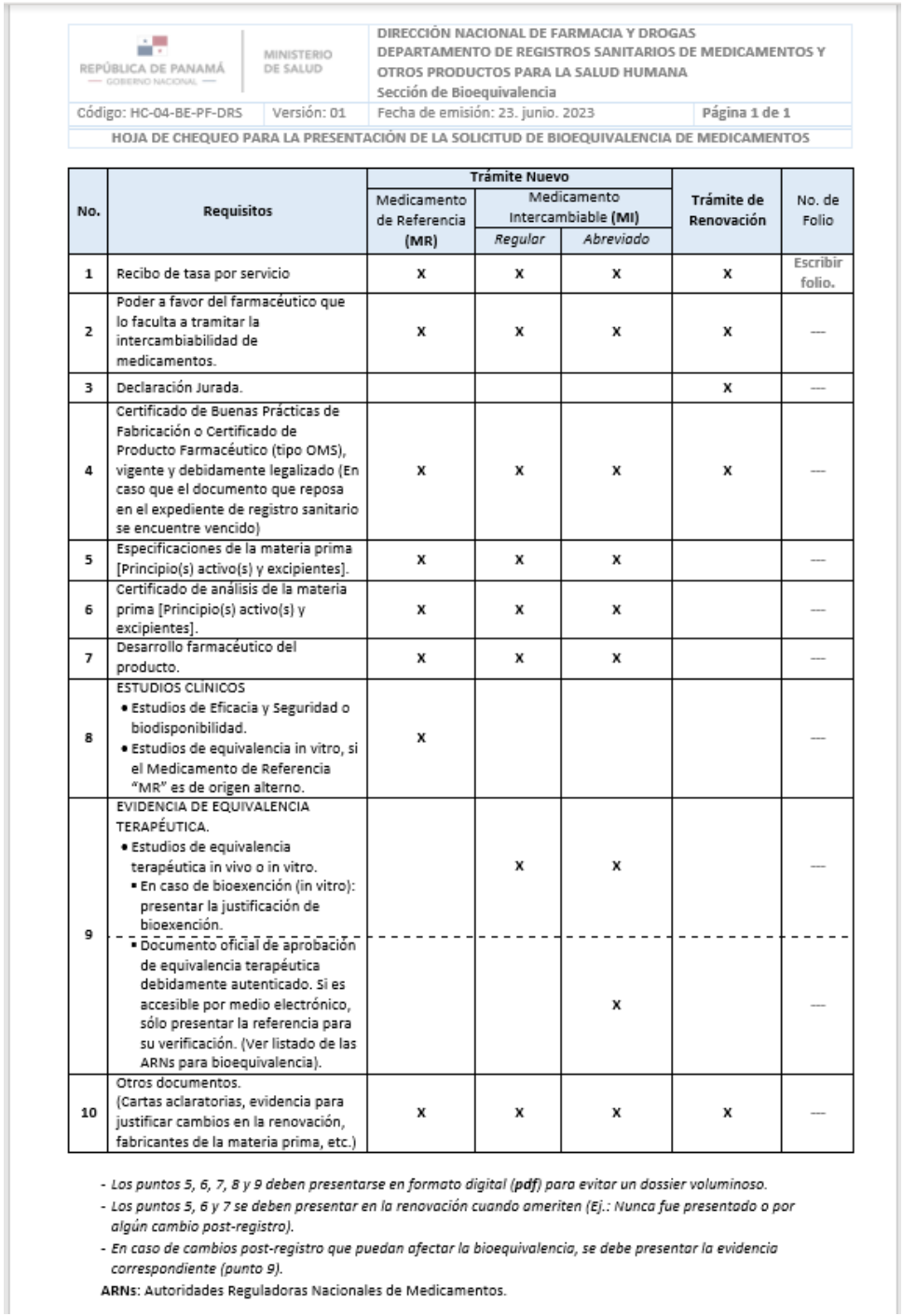
IMPORTANTE

- Cuando VENTANILLA apruebe la solicitud debe proceder a pagar la tasa de servicio *haciendo uso del número de solicitud*, **no se usa el número de registro.**
- **No** presenten copias simples de documentos como: poderes, certificados de BPM o de productos farmacéutico "CPF".

GOBIERNO NACIONAL
★ CON PASO FIRME ★

Hoja de Chequeo

- No están presentado la hoja de chequeo al ingresar.
- No colocan el folio correspondiente a cada requisito solicitado según tipo de trámite.



REPÚBLICA DE PANAMÁ — GOBIERNO NACIONAL | MINISTERIO DE SALUD

DIRECCIÓN NACIONAL DE FARMACIA Y DROGAS
DEPARTAMENTO DE REGISTROS SANITARIOS DE MEDICAMENTOS Y OTROS PRODUCTOS PARA LA SALUD HUMANA
Sección de Bioequivalencia

Código: HC-04-BE-PF-DRS	Versión: 01	Fecha de emisión: 23. junio. 2023	Página 1 de 1

HOJA DE CHEQUEO PARA LA PRESENTACIÓN DE LA SOLICITUD DE BIOEQUIVALENCIA DE MEDICAMENTOS

No.	Requisitos	Trámite Nuevo			Trámite de Renovación	No. de Folio
		Medicamento de Referencia (MR)	Medicamento Intercambiable (MI)			
			Regular	*Abreviado*		
1	Recibo de tasa por servicio	X	X	X	X	Escribir folio.
2	Poder a favor del farmacéutico que lo faculta a tramitar la intercambiabilidad de medicamentos.	X	X	X	X	—
3	Declaración Jurada.				X	—
4	Certificado de Buenas Prácticas de Fabricación o Certificado de Producto Farmacéutico (tipo OMS), vigente y debidamente legalizado (En caso que el documento que reposa en el expediente de registro sanitario se encuentre vencido)	X	X	X	X	—
5	Especificaciones de la materia prima [Principio(s) activo(s) y excipientes].	X	X	X		—
6	Certificado de análisis de la materia prima [Principio(s) activo(s) y excipientes].	X	X	X		—
7	Desarrollo farmacéutico del producto.	X	X	X		—
8	ESTUDIOS CLÍNICOS • Estudios de Eficacia y Seguridad o biodisponibilidad. • Estudios de equivalencia in vitro, si el Medicamento de Referencia "MR" es de origen alterno.	X				—
9	EVIDENCIA DE EQUIVALENCIA TERAPÉUTICA. • Estudios de equivalencia terapéutica in vivo o in vitro. ▪ En caso de bioexención (in vitro): presentar la justificación de bioexención.		X	X		—
	▪ Documento oficial de aprobación de equivalencia terapéutica debidamente autenticado. Si es accesible por medio electrónico, sólo presentar la referencia para su verificación. (Ver listado de las ARNs para bioequivalencia).			X		—
10	Otros documentos. (Cartas aclaratorias, evidencia para justificar cambios en la renovación, fabricantes de la materia prima, etc.)	X	X	X	X	—

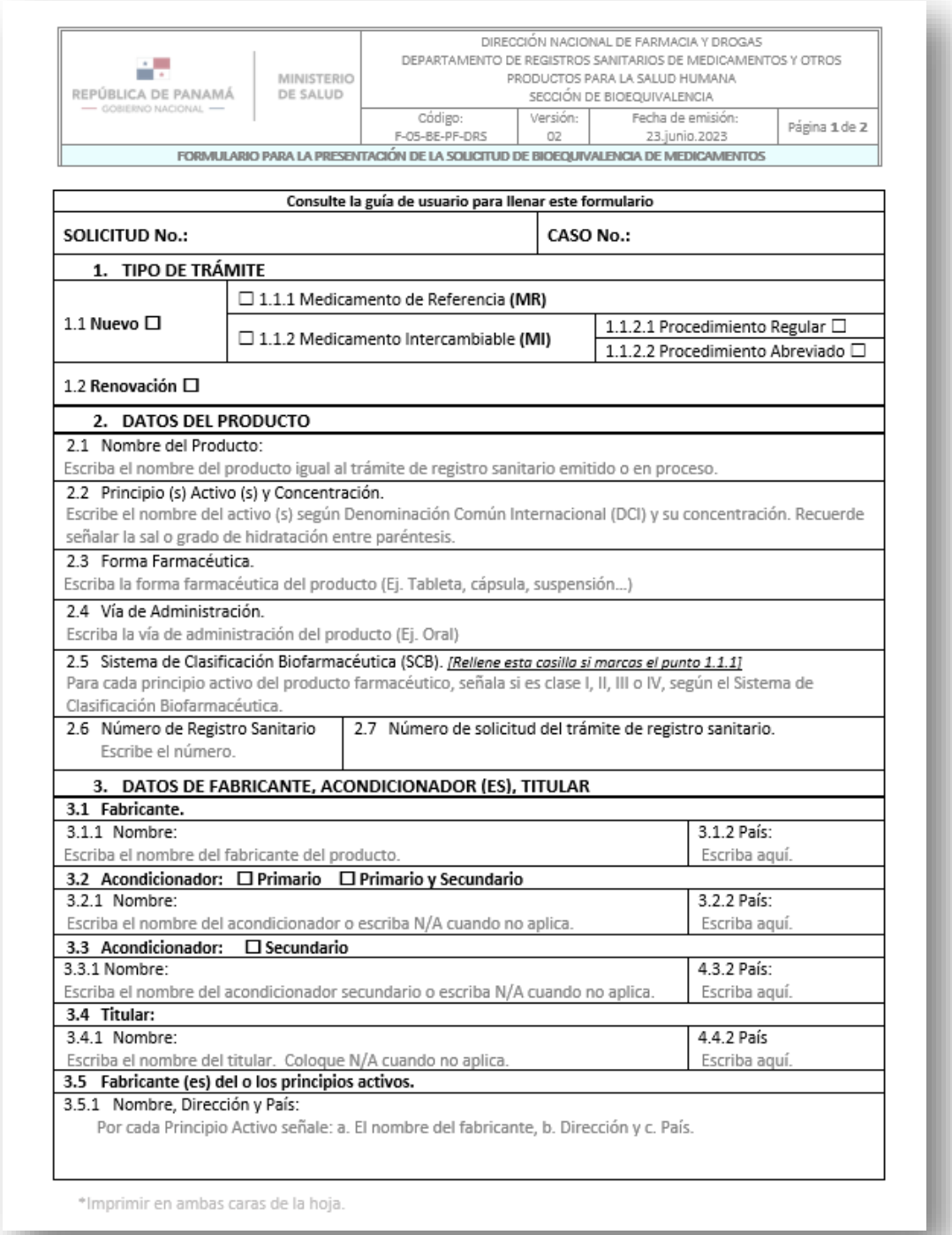
- *Los puntos 5, 6, 7, 8 y 9 deben presentarse en formato digital (**pdf**) para evitar un dossier voluminoso.*
- *Los puntos 5, 6 y 7 se deben presentar en la renovación cuando ameriten (Ej.: Nunca fue presentado o por algún cambio post-registro).*
- *En caso de cambios post-registro que puedan afectar la bioequivalencia, se debe presentar la evidencia correspondiente (punto 9).*

ARNs: Autoridades Reguladoras Nacionales de Medicamentos.

GOBIERNO NACIONAL
★ CON PASO FIRME ★

FORMULARIO DE SOLICITUD

- No siguen secuencia numérica.
- Sólo hay 2 tipos de trámites (nuevo y renovación)
- Los productos o medicamentos multiorigen (genéricos) son los que aplican a procedimiento Regular y Abreviado.
- Marcan la casilla 1.2 Renovación y a la vez marcan casillas que corresponden al punto 1.1
- No colocan secuencia correcta de las plantas que participan en el proceso de manufactura (fabricante a granel, acondicionadores y titular)
- **No** imprimen en **ambas caras** en hoja 81/2" x 11" (ver pie de página)
- Revisar formularios detalladamente cuando se trate de medicamentos que posean varias concentraciones; o aquellos donde se vayan a registrar con un nuevo número de registro por cambios de plantas de manufactura, por ejemplo.



REPÚBLICA DE PANAMÁ — GOBIERNO NACIONAL — | MINISTERIO DE SALUD

DIRECCIÓN NACIONAL DE FARMACIA Y DROGAS
DEPARTAMENTO DE REGISTROS SANITARIOS DE MEDICAMENTOS Y OTROS PRODUCTOS PARA LA SALUD HUMANA
SECCIÓN DE BIOEQUIVALENCIA

Código:	Versión:	Fecha de emisión:	Página 1 de 2
F-05-BE-PF-DRS	02	23.junio.2023	

FORMULARIO PARA LA PRESENTACIÓN DE LA SOLICITUD DE BIOEQUIVALENCIA DE MEDICAMENTOS

Consulte la guía de usuario para llenar este formulario

SOLICITUD No.: | **CASO No.:**

1. TIPO DE TRÁMITE

1.1 **Nuevo** ☐
- ☐ 1.1.1 Medicamento de Referencia **(MR)**
- ☐ 1.1.2 Medicamento Intercambiable **(MI)**
  - 1.1.2.1 Procedimiento Regular ☐
  - 1.1.2.2 Procedimiento Abreviado ☐

1.2 **Renovación** ☐

2. DATOS DEL PRODUCTO

2.1 Nombre del Producto:
Escriba el nombre del producto igual al trámite de registro sanitario emitido o en proceso.

2.2 Principio (s) Activo (s) y Concentración.
Escribe el nombre del activo (s) según Denominación Común Internacional (DCI) y su concentración. Recuerde señalar la sal o grado de hidratación entre paréntesis.

2.3 Forma Farmacéutica.
Escriba la forma farmacéutica del producto (Ej. Tableta, cápsula, suspensión…)

2.4 Vía de Administración.
Escriba la vía de administración del producto (Ej. Oral)

2.5 Sistema de Clasificación Biofarmacéutica (SCB). *[Rellene esta casilla si marcas el punto 1.1.1]*
Para cada principio activo del producto farmacéutico, señala si es clase I, II, III o IV, según el Sistema de Clasificación Biofarmacéutica.

2.6 Número de Registro Sanitario Escribe el número.	2.7 Número de solicitud del trámite de registro sanitario.

3. DATOS DE FABRICANTE, ACONDICIONADOR (ES), TITULAR

3.1 Fabricante.

3.1.1 Nombre: Escriba el nombre del fabricante del producto.	3.1.2 País: Escriba aquí.

3.2 Acondicionador: ☐ **Primario** ☐ **Primario y Secundario**

3.2.1 Nombre: Escriba el nombre del acondicionador o escriba N/A cuando no aplica.	3.2.2 País: Escriba aquí.

3.3 Acondicionador: ☐ **Secundario**

3.3.1 Nombre: Escriba el nombre del acondicionador secundario o escriba N/A cuando no aplica.	4.3.2 País: Escriba aquí.

3.4 Titular:

3.4.1 Nombre: Escriba el nombre del titular. Coloque N/A cuando no aplica.	4.4.2 País Escriba aquí.

3.5 Fabricante (es) del o los principios activos.

3.5.1 Nombre, Dirección y País:
Por cada Principio Activo señale: a. El nombre del fabricante, b. Dirección y c. País.

*Imprimir en ambas caras de la hoja.

GOBIERNO NACIONAL
CON PASO FIRME

salud
Ministerio de Salud
Panamá

PODERES

- El farmacéutico es el responsable del trámite de registro sanitario ante la autoridad reguladora.
- Debe haber secuencia en la emisión de poderes.
- Ejemplo: En caso tal se detalle sólo la razón social de la empresa en un poder, ventanilla generalmente solicita se adjunte la personería jurídica en la solicitud de registro sanitario; donde si se declara el nombre de la persona que lo representa.

DECLARACIÓN JURADA

- Se presenta un documento con contenido errado.
  - Declaran que no hay cambios, cuando realmente se dan.
  - Utilizan la redacción que no corresponde a la solicitud de bioequivalencia (Renovación).

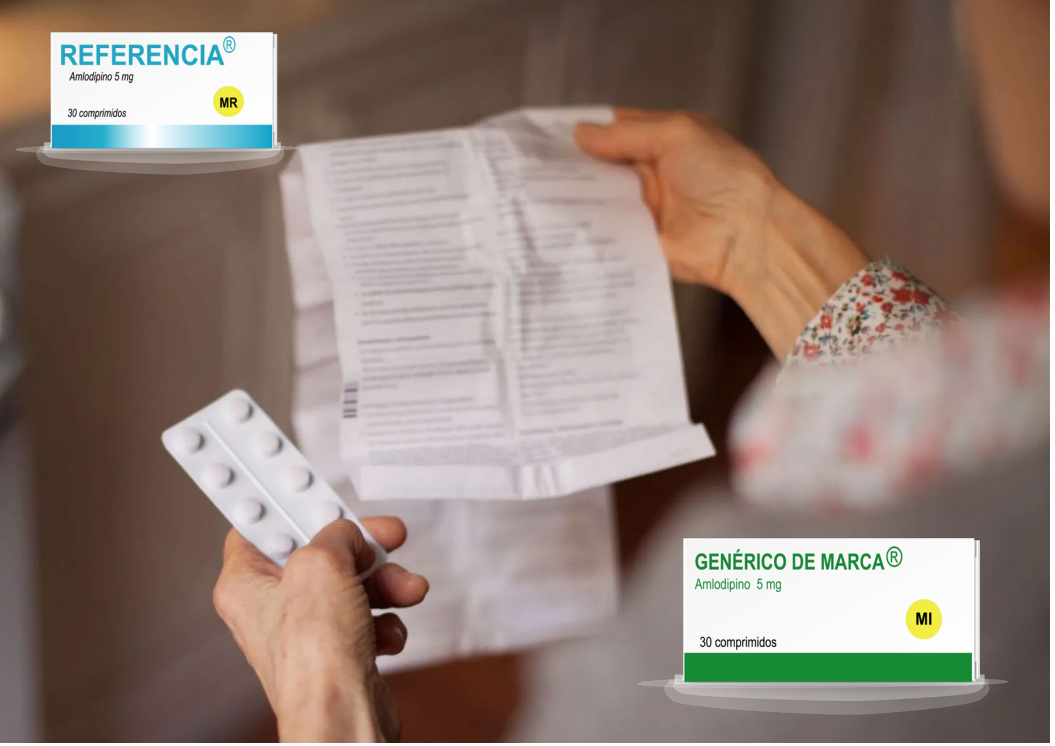
Ver Artículo 80 del Decreto Ejecutivo 27 de 10 de mayo de 2024.

GOBIERNO NACIONAL
CON PASO FIRME

salud
Ministerio de Salud
Panamá

BUENAS PRÁCTICAS DE MANUFACTURA

- Presentar documento vigente para todas la plantas que participen en el proceso de manufactura.
- Evite presentar documentos próximos a vencer.
- Si el BPM o GMP, es igual al de la solicitud digital de registro, no es necesario presentarlo.
    - ***Recuerde señalar el número de solicitud y correlativo en el formulario de solicitud.***



INSERTO O PROSPECTO ETIQUETADO

- **INSERTO / PROSPECTO**
  - Obligatorio
- **LOGOTIPO**
  - Presentan etiquetas **<u>sin logotipo</u>** durante las renovaciones o cuando llevan el trámite en paralelo con registro.

MI MR Diámetro 1 cm
Fuente Arial, negrita, tamaño 12

MI MR Diámetro 1.5 cm
Fuente Arial, negrita, tamaño 13

MI MR Diámetro 2 cm
Fuente Arial, negrita, tamaño 14

PANTONE 101 C

Diámetro: 1 - 2 cm
Tipografía o Fuente: Arial - negrita
Tamaño de fuente: entre 12 y 14

- *<u>Recomendación</u>*: detallar los parámetros utilizados para el logotipo en el etiquetado. Esto permite tener más información específica, en el caso que se presente una denuncia de falsificación.
- Tipografía: **Arial negrita** o **Arial bold**
- La circunferencia preferiblemente **sin contorno**

GOBIERNO NACIONAL
★ CON PASO FIRME ★

¿Cuándo ingresa el nuevo requisito?

salud
Ministerio de Salud
Panamá

Decreto Ejecutivo N° 40
13-febrero-2019
Gaceta Oficial 28715
15-feb-2019

2005-06-ET-XXXX

2019-01-ET-XXXX

16-feb-2019

2020

2021

2022

2023

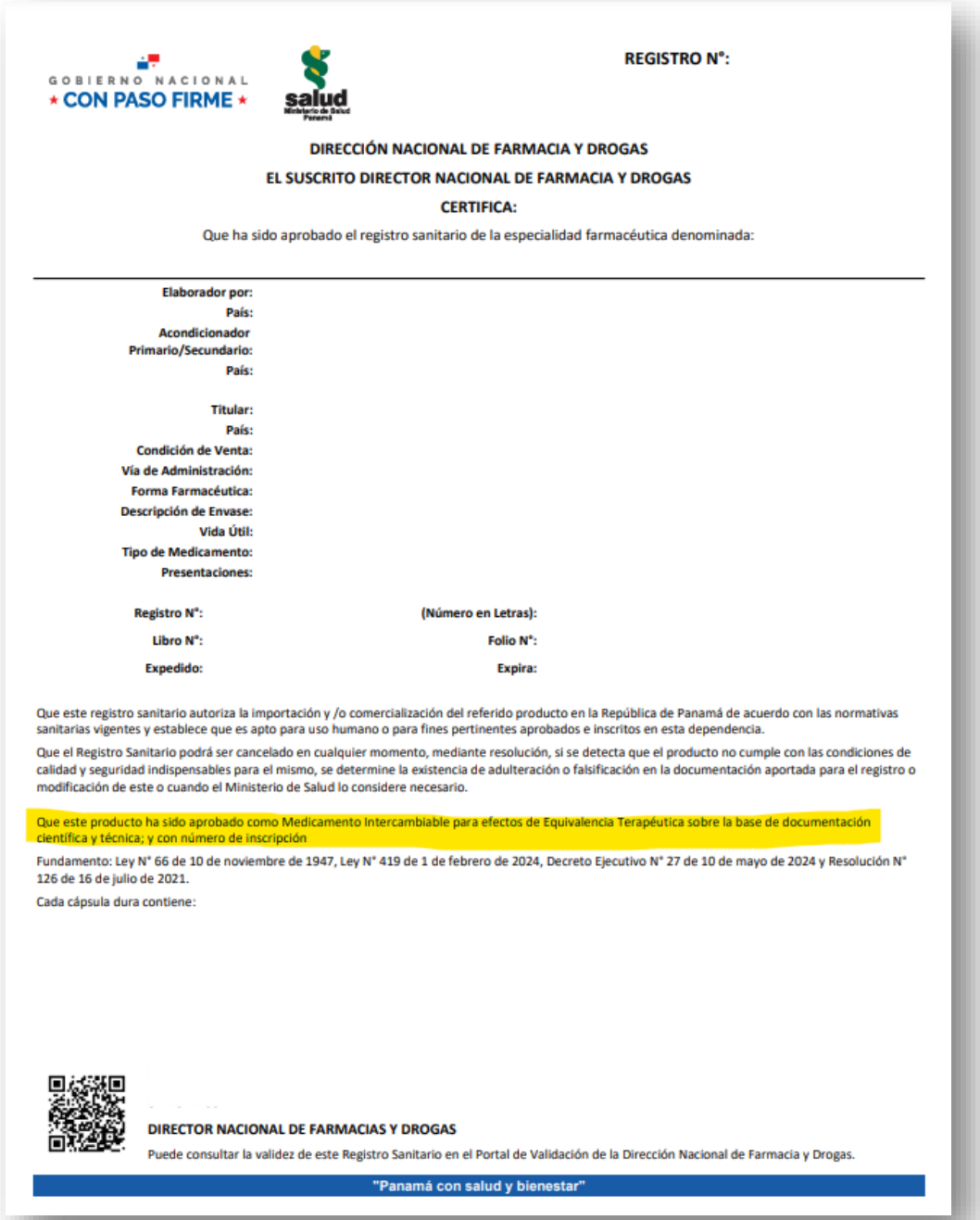
2024

Decreto Ejecutivo N° 6
21-febrero-2005
Gaceta Oficial 25243
23-febrero-2005

Decreto Ejecutivo N° 13
10-mayo-2024
Gaceta Oficial 30028-C
10-mayo-2024

DESARROLLO FARMACÉUTICO

Cápsula 6 ¿Por qué mi solicitud no cumple?
Annex 5, WHO Technical Report Series, No. 929, 2005 (Appendix 3).
Annex 3, WHO Technical Report Series, No. 970, 2012
Annex 5, WHO Technical Report Series, No. 970, 2012



GOBIERNO NACIONAL
CON PASO FIRME

salud
Ministerio de Salud
Panamá

REGISTRO N°:

DIRECCIÓN NACIONAL DE FARMACIA Y DROGAS

EL SUSCRITO DIRECTOR NACIONAL DE FARMACIA Y DROGAS

CERTIFICA:

Que ha sido aprobado el registro sanitario de la especialidad farmacéutica denominada:

Elaborador por:
País:
Acondicionador Primario/Secundario:
País:

Titular:
País:
Condición de Venta:
Vía de Administración:
Forma Farmacéutica:
Descripción de Envase:
Vida Útil:
Tipo de Medicamento:
Presentaciones:

Registro N°: **(Número en Letras):**
Libro N°: **Folio N°:**
Expedido: **Expira:**

Que este registro sanitario autoriza la importación y /o comercialización del referido producto en la República de Panamá de acuerdo con las normativas sanitarias vigentes y establece que es apto para uso humano o para fines pertinentes aprobados e inscritos en esta dependencia.

Que el Registro Sanitario podrá ser cancelado en cualquier momento, mediante resolución, si se detecta que el producto no cumple con las condiciones de calidad y seguridad indispensables para el mismo, se determine la existencia de adulteración o falsificación en la documentación aportada para el registro o modificación de este o cuando el Ministerio de Salud lo considere necesario.

Que este producto ha sido aprobado como Medicamento Intercambiable para efectos de Equivalencia Terapéutica sobre la base de documentación científica y técnica; y con número de inscripción

Fundamento: Ley N° 66 de 10 de noviembre de 1947, Ley N° 419 de 1 de febrero de 2024, Decreto Ejecutivo N° 27 de 10 de mayo de 2024 y Resolución N° 126 de 16 de julio de 2021.

Cada cápsula dura contiene:

DIRECTOR NACIONAL DE FARMACIAS Y DROGAS

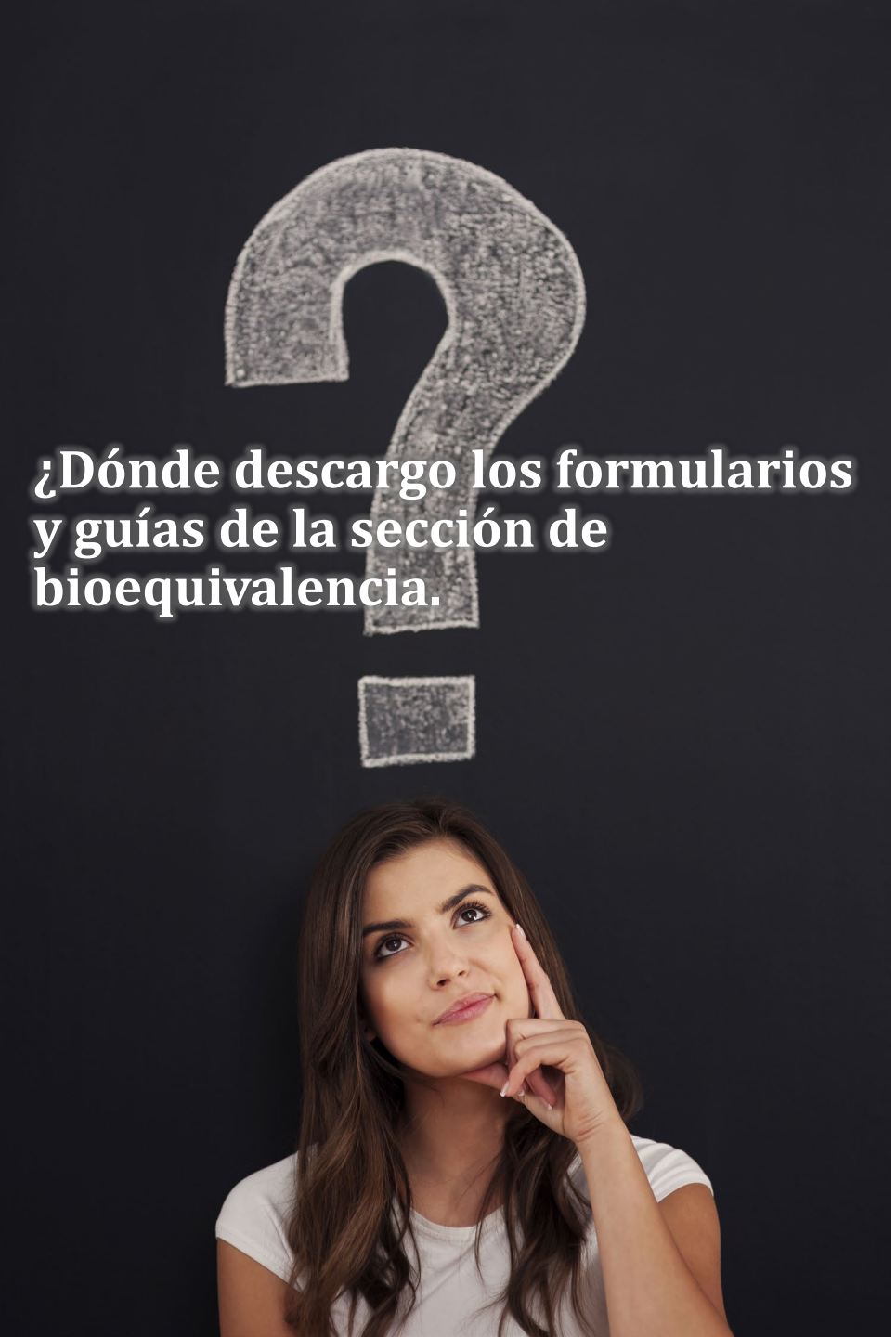
Puede consultar la validez de este Registro Sanitario en el Portal de Validación de la Dirección Nacional de Farmacia y Drogas.

"Panamá con salud y bienestar"

Actualización del formato del Certificado de Registro Sanitario

- Comunicado N° 51/DNFD de 7 de mayo de 2024.

  - Digitalización del trámite de registro sanitario
  - El certificado de Registro Sanitario llevará un acápite indicando si el producto ha sido aprobado como Medicamento de Referencia/ Medicamento Intercambiable, y el número de inscripción.
  - Se dejaron de emitir resoluciones.



salud
Ministerio de Salud
Panamá

ESCANEA

Departamento de Registro Sanitario

GOBIERNO NACIONAL
CON PASO FIRME

salud
Ministerio de Salud
Panamá

SOLICITUD DE BIOEQUIVALENCIA

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

Mgter. Nelson Rodríguez

Panamá, 22 de noviembre de 2024

GOBIERNO NACIONAL
CON PASO FIRME

salud
Ministerio de Salud
Panamá

Guías Utilizadas en las Evaluaciones de las Solicitudes de Bioequivalencia

GOBIERNO NACIONAL
CON PASO FIRME

salud
Ministerio de Salud
Panamá

GUÍAS TÉCNICAS

Situación Actual

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

Guías

- FDA 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

Search for FDA Guidance Documents

The table below provides a convenient way to search for FDA guidance documents from a single location. You can search for documents using key words, and you can narrow or filter your results by product, date issued, FDA organizational unit, type of document, subject, draft or final status, and comment period start and end dates. If you are looking for recently issued guidances, this table by default is sorted by 'issue date'.In addition to the search features within the table, you can also browse collections of guidance documents by topic below.

To be alerted to newly issued guidance, you can subscribe to our e-mail updates on recently issued guidances using the 'subscribe to email updates' button above.

Content current as of:
11/18/2024

Go to Guidance Document Search

Browse Guidance Documents By Topic

Guidance Documents By Product Area

Go to Class II Special Controls Documents

Guidance Document Search

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

Share

Human | Regulatory and procedural guidance | Scientific guidelines

Page contents

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 in 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

GOBIERNO NACIONAL
★ CON PASO FIRME ★

salud
Ministerio de Salud
Panamá

Multidisciplinary Guidelines

Those are the cross-cutting topics which do not fit uniquely into one of the Quality, Safety and Efficacy categories. It includes the ICH medical terminology (MedDRA), the Common Technical Document (CTD) and the development of Electronic Standards for the Transfer of Regulatory Information (ESTRI).

- M1 MedDRA Terminology
- M2 Electronic Standards
- M3 Nonclinical Safety Studies
- M4 Common Technical Document
- M5 Data Elements and Standards for Drug Dictionaries
- M6 Gene Therapy
- M7 Mutagenic Impurities
- M8 Electronic Common Technical Document (eCTD)
- M9 Biopharmaceutics Classification System-based Biowaivers
- M10 Bioanalytical Method Validation and Study Sample Analysis
- M11 Clinical electronic Structured Harmonised Protocol (CeSHarP)
- M12 Drug Interaction Studies
- M13 Bioequivalence for Immediate-Release Solid Oral Dosage Forms
- M14 Use of real-world data for safety assessment of medicines
- M15 General Principles for Model-Informed Drug Development

M9 Biopharmaceutics Classification System-based Biowaivers

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

M10 Bioanalytical Method Validation and Study Sample Analysis

M10	Bioanalytical Method Validation and Study Sample Analysis
M10 Q&As	Questions and Answers: Bioanalytical Method Validation and Study Sample Analysis

M11 Clinical electronic Structured Harmonised Protocol (CeSHarP)

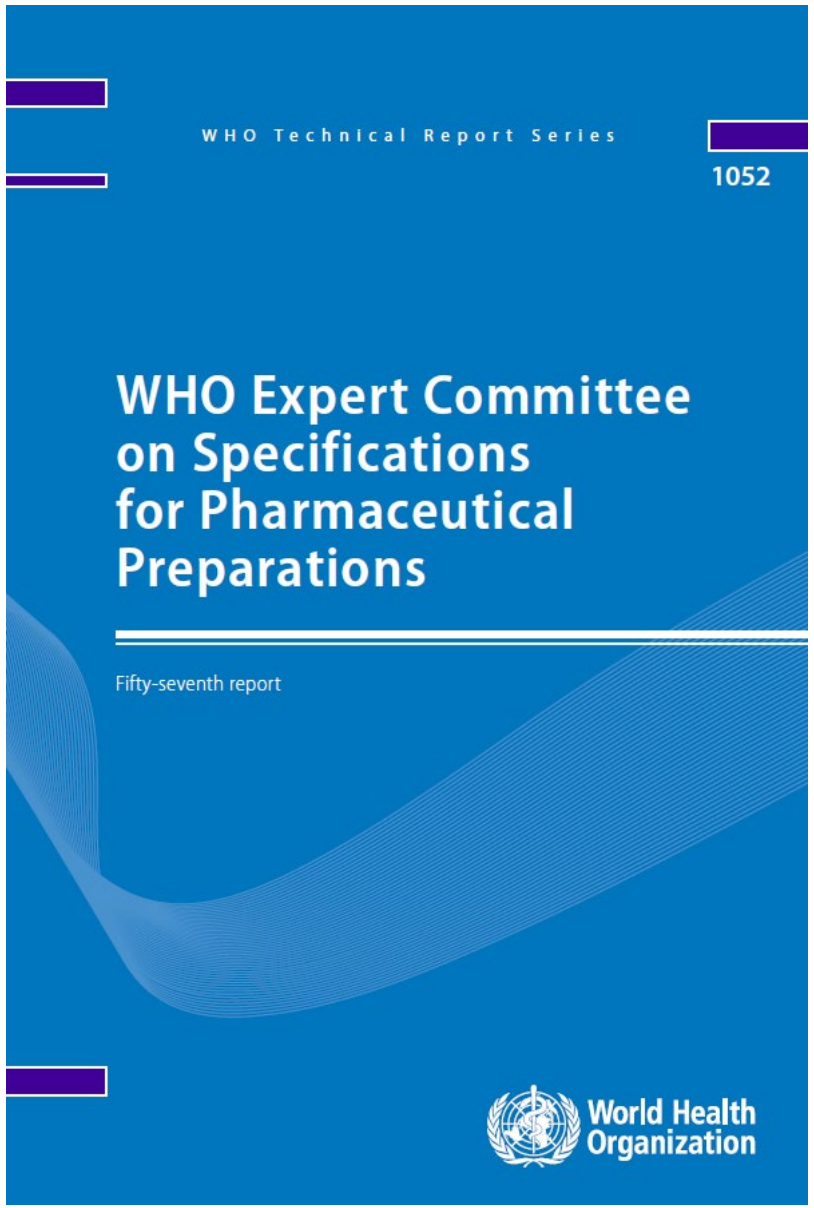
M12 Drug Interaction Studies

M13 Bioequivalence for Immediate-Release Solid Oral Dosage Forms

M13A EWG	Bioequivalence for Immediate-Release Solid Oral Dosage Forms
M13A Q&As	Question and Answers: Bioequivalence for Immediate-Release Solid Oral Dosage Forms
M13B EWG	Bioequivalence for Immediate-Release Solid Oral Dosage Forms

GOBIERNO NACIONAL
★ CON PASO FIRME ★

salud
Ministerio de Salud
Panamá



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

Contents

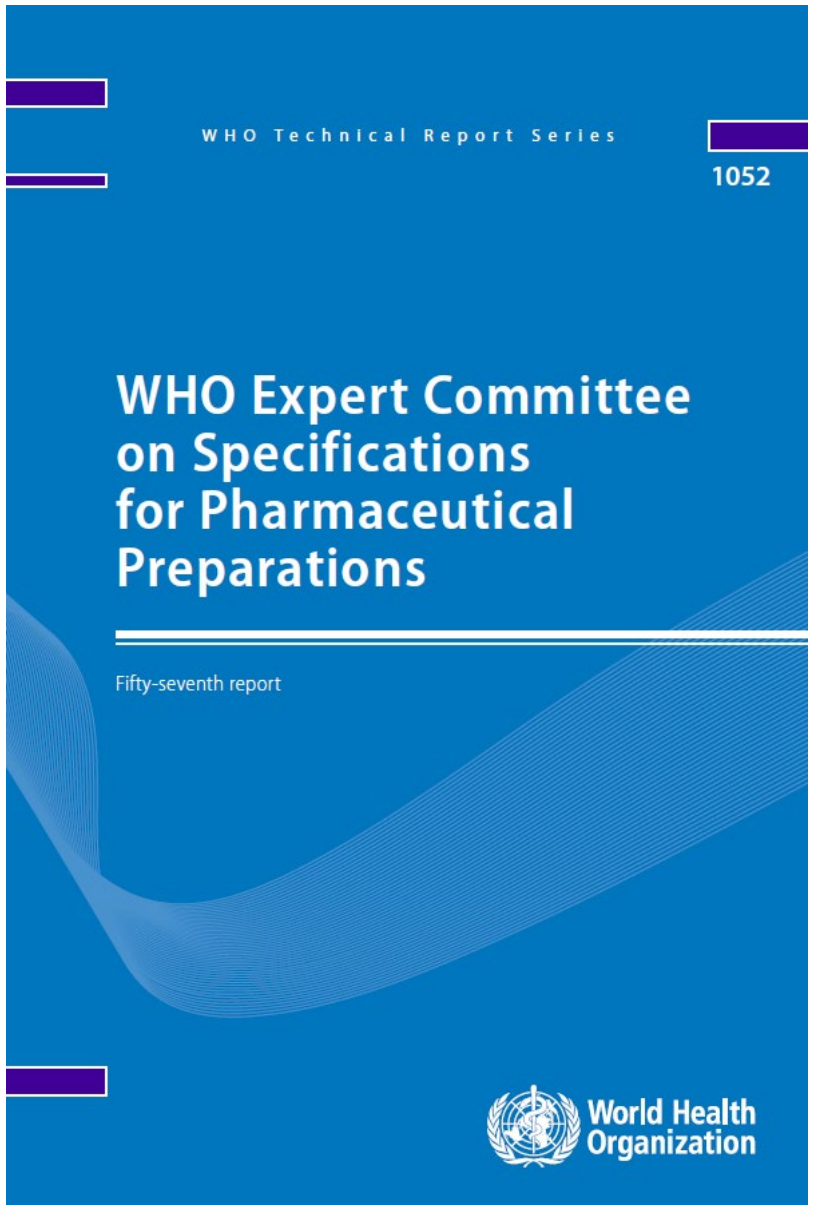
Annex 7

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).



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.*

Contents

GOBIERNO NACIONAL
★ CON PASO FIRME ★

U.S. FOOD & DRUG ADMINISTRATION

salud
Ministerio de Salud
Panamá

FDA REGISTRATION

Product-Specific Guidances for Generic Drug Development

Total number of currently published PSGs: 2252

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

Enter at least 3 characters Search

- Newly Added Guidances since November 19, 2024
- Newly Revised Guidances since November 19, 2024

GOBIERNO NACIONAL
★ CON PASO FIRME ★

salud
Ministerio de Salud
Panamá

U.S. FOOD & DRUG ADMINISTRATION

FDA REGISTRATION

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

Levothyroxine Search Reset

2 record(s) found for 'Levothyroxine'.

Excel CSV PDF

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

Showing 1 to 2 of 2 entries Previous 1 Next

Contains Nonbinding Recommendations

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.

GOBIERNO NACIONAL
★ CON PASO FIRME ★

salud
Ministerio de Salud
Panamá

U.S. FOOD & DRUG ADMINISTRATION

FDA REGISTRATION

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

pregabalin Search Reset

2 record(s) found for 'pregabalin'.

Excel CSV PDF

Show 10 entries Filter:

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

Showing 1 to 2 of 2 entries

Previous 1 Next

Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Pregablin

October 2024

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.

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

About this Database

*Required Field

Search the database

FDA Dissolution Methods

Search for a Dissolution Method*: Pregabalin

Submit Clear

- Printable List of All Drugs in the Database
- Dissolution Methods Disclaimer

FDA/Center for Drug Evaluation and Research
Office of Pharmaceutical Quality/Office of New Drug Products
Division of Biopharmaceutics
Update Frequency: Quarterly
Data Current through: July 28, 2022

Dissolution Methods

About this Database | Back to Search Page

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

Showing 1 to 2 of 2 entries

Previous 1 Next

Contains Nonbinding Recommendations

Draft Guidance on Iron Sucrose

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 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: 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.

---

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)*.

---

[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.

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/.

---

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
- Olaparib product-specific bioequivalence guidance
- 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***

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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

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.

	☒ **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)

Expand section | Collapse section

- 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

Expand section | Collapse section

- 4.1 Bioequivalence studies for generic products containing clopidogrel. June 2009
- 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

Expand section | Collapse section

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

GOBIERNO NACIONAL
CON PASO FIRME

salud
Ministerio de Salud
Panamá

SOLICITUD DE BIOEQUIVALENCIA

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

Rubens Donoso, MSc

Panamá, 22 de noviembre de 2024

GOBIERNO NACIONAL
CON PASO FIRME

salud
Ministerio de Salud
Panamá

¿Puedo optar por Reconocimiento abreviado si el producto está aprobado por Autoridades Reguladoras de Referencia Regional “Nivel 4”?

Organización Panamericana de la Salud

Organización Mundial de la Salud
OFICINA REGIONAL PARA LAS Américas

ANVISA

anmat
Administración Nacional de Medicamentos, Alimentos y Tecnología Médica

CECMED

Cofepris
Comisión Federal para la Protección contra Riesgos Sanitarios

Instituto de Salud Pública
Ministerio de Salud
Gobierno de Chile

GOBIERNO NACIONAL
★ CON PASO FIRME ★

salud
Ministerio de Salud
Panamá

Solo aplican para procedimiento abreviado al momento de solicitar la intercambiabilidad de medicamentos las autoridades descritas en el artículo 75 del Decreto Ejecutivo N°27 de 10 de mayo de 2024.

Artículo 75. El procedimiento abreviado aplica a los medicamentos aprobados como bioequivalentes, equivalentes terapéuticos o intercambiables por las entidades abajo listadas:

1. La Administración de Alimentos y Medicamentos de los Estados Unidos (US Food and Drug Administration, FDA).
2. Health Canada
3. La Agencia Europea de Medicamentos (The European Medicines Agency, EMA).
4. Autoridades Reguladoras de Medicamentos miembro de la Unión Europea.
* 5. Programa OMS de Precalificación de Medicamentos (PQP)/ The WHO Prequalification of Medicines Programme (PQP)
6. La Agencia de Productos Medicamentosos de Suiza (Swissmedic).
7. Agencia de Productos Farmacéuticos y de Dispositivos Médicos (PMDA) de Japón.
8. Administración de Productos Terapéuticos de Australia (TGA).
9. Agencia Regulatoria para Medicamentos y Productos Sanitarios de Reino Unido (MHRA)

* Precalificación de los medicamentos por la OMS.

GOBIERNO NACIONAL
CON PASO FIRME

salud
Ministerio de Salud
Panamá

¿Qué productos deben realizar la solicitud de intercambiabilidad de medicamentos de forma paralela a la solicitud de registro sanitario?

- ❑ Productos que contengan principios activos incluidos en la Resolución N°386 de 9 de junio de 2023.
- ❑ Productos que ya cuenten con la intercambiabilidad de medicamentos.

GOBIERNO NACIONAL
CON PASO FIRME

salud
Ministerio de Salud
Panamá

¿Cuándo debo incluir el logotipo MI en mis artes de etiqueta?

- Para productos en **renovación** o que vayan a obtener el **registro sanitario por primera vez** cuyo principio activo se encuentre en la Resolución N°386 de 9 de junio de 2023, deben solicitarlo durante el trámite ya sea de renovación/obtención del registro sanitario.
- Para productos cuyo principio activo esté listados en la Resolución N°385 de 9 de junio de 2023, deben incluir el logotipo posterior a la aprobación de la intercambiabilidad de medicamentos.

¿Los únicos requisitos para optar por la Bioexención basada en el SCB son la solubilidad y permeabilidad del principio activo y la disolución?

No, depende también de otros factores como:

- ❑ Farmacocinética complicada
- ❑ Estrecho margen terapéutico
- ❑ Presencia de excipientes críticos en la formulación del Medicamento de Referencia o Medicamento de prueba.

GOBIERNO NACIONAL
CON PASO FIRME

salud
Ministerio de Salud
Panamá

¿Qué tiempo demora la evaluación de la solicitud de intercambiabilidad de medicamentos?

El tiempo de respuesta depende de varios factores:

- ❑ Número de solicitudes que ingresan a la Sección de Bioequivalencia para asignación.
- ❑ Calidad del dossier presentado.
- ❑ Complejidad de la evidencia presentada.

Otros aspectos a tomar en cuenta:

- El tiempo empieza a trascurrir desde que se realiza la primera notificación.
- El usuario tiene hasta 3 meses desde la primera notificación para subsanar cualquier error u omisión.

GOBIERNO NACIONAL
CON PASO FIRME

salud
Ministerio de Salud
Panamá

Si durante la obtención o renovación previa presenté las especificaciones y certificados de calidad de la materia prima, y desarrollo farmacéutico, ¿Debo volver a presentarlo para la renovación?

Dichos documentos solo se presentan una vez.

GOBIERNO NACIONAL
CON PASO FIRME

salud
Ministerio de Salud
Panamá

¿Los estudios de bioequivalencia y el desarrollo farmacéutico deben estar traducidos al idioma español?

- El **desarrollo farmacéutico** se acepta en idioma español o en idioma inglés, el resto de los idiomas deben presentar traducción, (traductor público autorizado).
- La **Evidencia de Equivalencia Terapéutica**:
  - Debe venir en idioma español o en idioma inglés, el resto de los idiomas deben presentar traducción, (traductor público autorizado).
  - El resumen del estudio debe venir en idioma español.

GOBIERNO NACIONAL
CON PASO FIRME

salud
Ministerio de Salud
Panamá

Si el producto presenta cambios en el proceso de fabricación y/o en la fórmula cuali-cuantitativa, ¿Cuándo debo notificar a la DNFD?

Cualquier cambio que se presente durante la vigencia del registro sanitario debe ser notificado a la Sección de Modificaciones al Registro Sanitario.

GOBIERNO NACIONAL
CON PASO FIRME

salud
Ministerio de Salud
Panamá

Cuando presento un cambio en el proceso de fabricación, fórmula cuali-cuantitativa o en el fabricante de la materia prima utilizada para producir el medicamento, ¿Qué debe incluir la declaración jurada en la solicitud de renovación?

En la Declaración Jurada presentada como requisito para la renovación de la intercambiabilidad debe indicarse, tal cual se describe en el artículo 80 del Decreto Ejecutivo N°27 de 10 de mayo de 2024 solo las condiciones que se mantienen, e indicar en la misma declaración jurada o en un documento adicional cuál fue el cambio realizado, adjuntando en dicho caso los documentos que soporten que el cambio no impacta en la equivalencia terapéutica.

GOBIERNO NACIONAL
CON PASO FIRME

salud
Ministerio de Salud
Panamá

¿Es requisito durante la obtención/renovación de la intercambiabilidad la aprobación de un inserto?

Sí, se debe presentar para evaluación por parte de la Sección de Evaluación al Registro Sanitario un inserto durante la obtención/renovación del registro sanitario para todos los productos que contengan principios activos que requieran demostrar equivalencia terapéutica.

GOBIERNO NACIONAL
CON PASO FIRME

salud
Ministerio de Salud
Panamá

Referencias para consultar

- **Capacitaciones realizadas por la Dirección Nacional de Farmacia y Drogas.**
- **FDA**
  - Search for FDA Guidance Documents
  - Product-Specific Guidances for Generic Drug Development
  - Dissolution Methods Database (Additional Information)
  - Dissolution Methods
  - Inactive Ingredients in Approved Drug Products Search: Frequently Asked Questions
- **EMA**
  - Clinical pharmacology and pharmacokinetics
  - Product-specific bioequivalence guindace
  - Clinical pharmacology anda pharmacokinetics: questions and answers
- **ICH**
  - Multidisciplinary Guidelines

GOBIERNO NACIONAL
CON PASO FIRME

salud
Ministerio de Salud
Panamá

Referencias para consultar

- **WHO (OMS)**
  - Acerca de la Precalificación de Medicamentos
  - Lista de Medicamentos Precalificados
  - Guía de precalificación de medicamentos de la OMS
  - Norms and Standards for Pharmaceuticals Terminologies

  - Normas y Estándares de Productos Farmacéuticos
    - Guías: Normas y Estándares de Productos Farmacéuticos
      - TRS 1052 - 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
      - TRS 1052 - Annex 7: **WHO guideline on Biopharmaceutics Classification System-based biowaivers**
      - TRS 1052 - Annex 8: Multisource (generic) pharmaceutical products: **guidelines on registration requirements to establish interchangeability**
      - TRS 970 - Annex 3: **Pharmaceutical development** of multisource (generic) finished pharmaceutical products: **points to consider**
      - TRS 970 - Annex 5: **Development of paediatric medicines: points to consider in formulation**
      - TRS 929 - Annex 5: **Guidelines for registration of fixed-dose combination medicinal products** (2005) – Importante leer los Apéndices.
- **Genéricos complejos**
  - USP Standards for Complex Generics
  - Addressing Barriers to the Development of Complex Generics: Understanding Challenges and Opportunities

GOBIERNO NACIONAL
CON PASO FIRME

salud
Ministerio de Salud
Panamá

Referencias para consultar

- **EUROPA** (Comisión Europea **es miembro fundador ICH previo a 23.oct.2015 – La EMA proporciona a la Comisión el apoyo técnico y científico)**
  - Unión Europea (Estados miembros de la Unión Europea (UE) y del Espacio Económico Europeo (EEE)).
  - Lista de **Autoridades Nacionales Competentes** en el Espacio Económico Europeo (EEE)

- **Autoridades Regulatorias Nacionales Regionales (ARNr)**
  - Health Canada (Canadá) **(Observador ICH previo a 23.oct.2015 – Stringent Regulatory Authority [SRA])**
  - FDA (USA) **(Miembro fundador ICH previo a 23.oct.2015 – Stringent Regulatory Authority [SRA])**
  - COFEPRIS (México)
  - CECMED (Cuba)
  - INVIMA (Colombia)
  - ANVISA (Brasil)
  - ISP (Chile)
  - ANMAT (Argentina)

- **Therapeutic Goods Administration (TGA) – Australia** **(Autoridad Reguladora asociada como miembro ICH a través de un acuerdo jurídicamente vinculante, previo a 23.oct.2015 – Stringent Regulatory Authority [SRA])**
  - ARTG Search Visualiton Tool

GOBIERNO NACIONAL
CON PASO FIRME

salud
Ministerio de Salud
Panamá

CORREO ELECTRÓNICO DE EQUIPO

bioequivalenciadnfd@minsa.gob.pa

Recuerda verificar tus trámites en Seguimiento de Trámite con el número de solicitud y caso.