Aspectos técnicos y legales de la Bioequivalencia en Colombia

Normativa de Bioequivalencia en Europa

Bogotá, 11 de agosto de 2016

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AVISO

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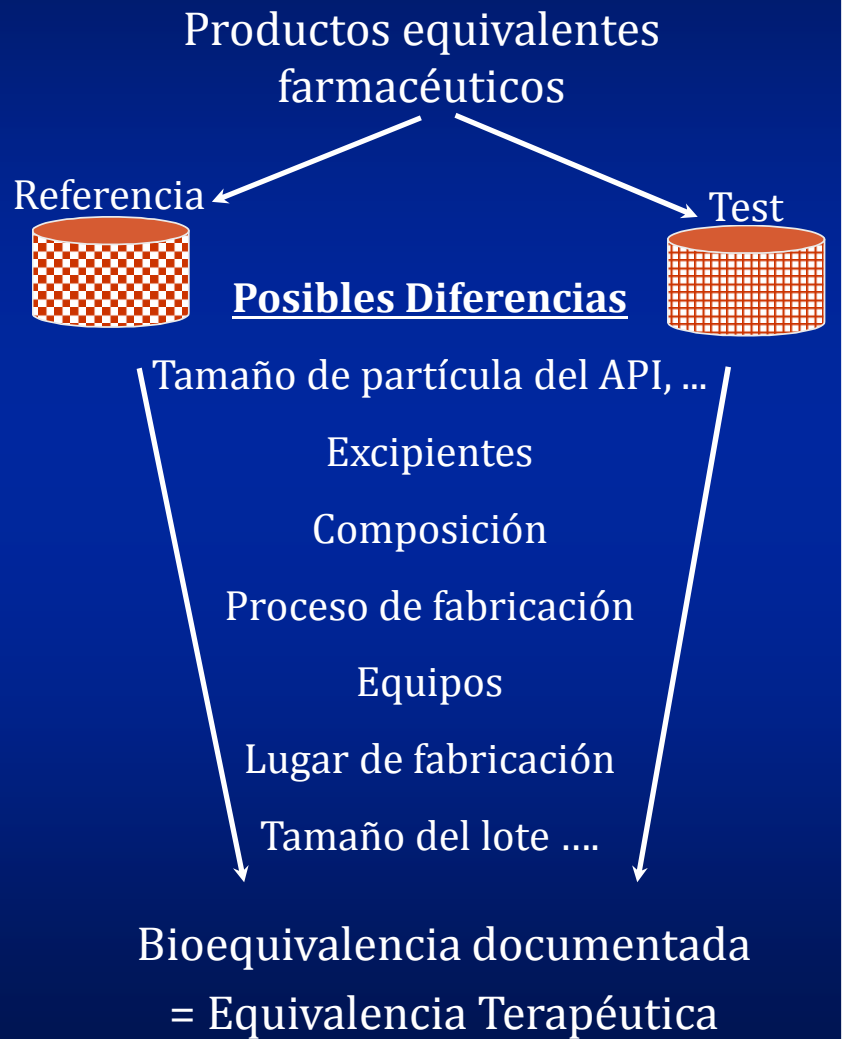
Generalmente, BE no se puede asumir por los datos "in vitro"

- La equivalencia farmacéutica no implica necesariamente la equivalencia terapéutica
- La diferencias en:
  - Materias primas
    - Fármaco (p. e. Tamaño de partícula, polimorfismo, etc.)
    - Excipientes (p. e. grado)
  - Formulación / composición
    - Q1 y Q2 (efecto sobre la disolución in vivo y la absorción)
  - Proceso de fabricación (p. e. granulación por vía seca vs. húmeda)
  - Equipos
  - Lugar de fabricación
  - Tamaño del lote
- Pueden afectar la biodisponibilidad de los equivalentes farmacéuticos o las alternativas farmacéuticas
- Por tanto, la bioequivalencia debe demostrarse.



For systemically acting drugs

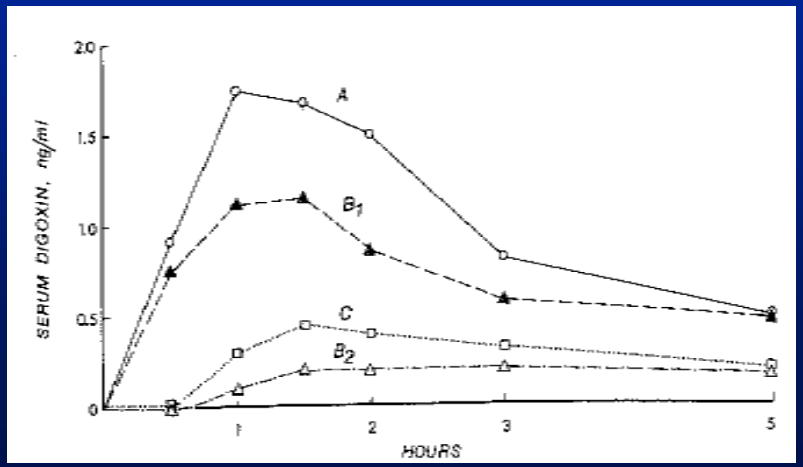
- Bioequivalence studies (for systemically acting drugs) verify that the active ingredient of the test drug product will be absorbed into the body to the same extent and at the same rate as the corresponding reference drug product

Therapeutically equivalent

- When two products are bioequivalent, these product are judged to be therapeutically equivalent.
- Same efficacy and safety when administered under the conditions of use (labelling) of the comparator product

History of bioequivalence

- Patients that took digoxin had variable and poor responses in the early 1970s
- FDA performed systematic testing in April 1970
  - Vitti TG et al. (1971). Bioavailability of digoxin. *N Eng J Med* 285(25):1433-4
  - Assay: 72-158.2% in one of the products



History of bioequivalence

- The bioavailability of different digoxin products in the US market was compared
- One product exhibited 7-fold higher peak serum levels than the others
- Even within manufacturers there was a significant between-lot variability
  - Lindenbaum J et al. (1971) Variation in biologic availability of digoxin from four preparations *NEJM* 285(25): 1344-7
- Confirmed even for tablets that met the acceptance criteria for potency and disintegration by
  - Wagner JG et al. (1973) Equivalence lack of digoxine plasma levels. *JAMA* 224(2): 199-204: AUC was 59% and Cmax was 55%
- Possible reasons: particle size, disintegration, dissolution, effect of excipients

Similar bioavailability problems detected for other products

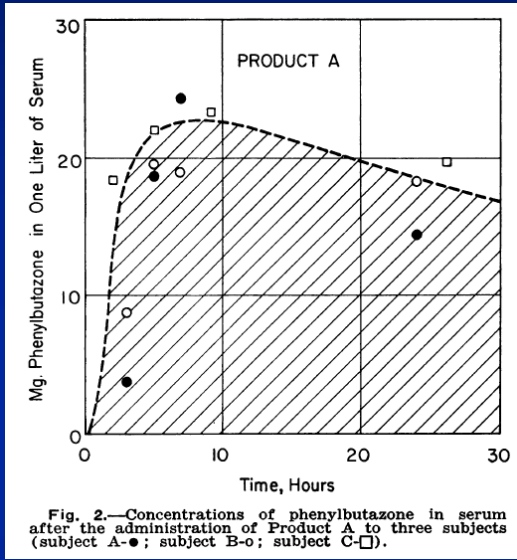


Fig. 2.—Concentrations of phenylbutazone in serum after the administration of Product A to three subjects (subject A-●; subject B-o; subject C-□).

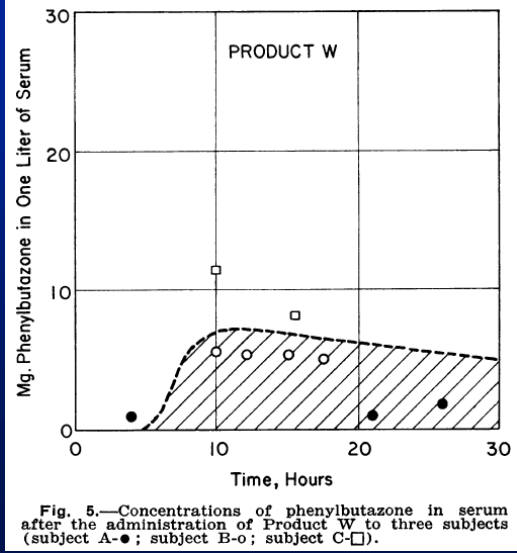
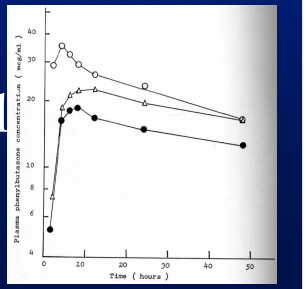


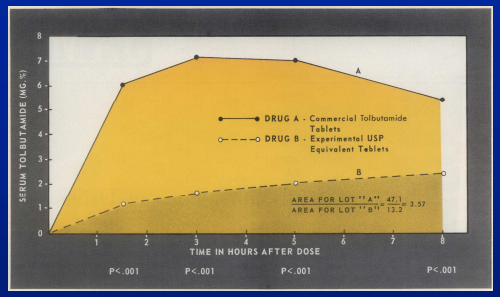
Fig. 5.—Concentrations of phenylbutazone in serum after the administration of Product W to three subjects (subject A-●; subject B-o; subject C-□).

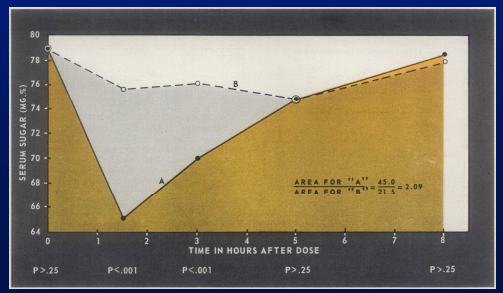
- Phenylbutazone
  - Searl RO and Pernarowski M. (1967) The biopharmaceutical properties of solid dosage forms. I. An evaluation of 23 brands of phenylbutazone tablets. *Canad Med. Ass J.* 96(23):1513-1520
  - Van Petten GR et al. (1971) The physiologic availability of solid dosage forms of phenylbutazone. I. In vivo physiologic availability and pharmacologic considerations. *J Clin Pharmacol New Drugs* 11(3):177-186
  - Chiou WL (1972) Determination of physiologic availability of commercial phenylbutazone preparations. *J Clin Pharmacol New Drugs* 12(7):296-300



Similar bioavailability problems detected for other products

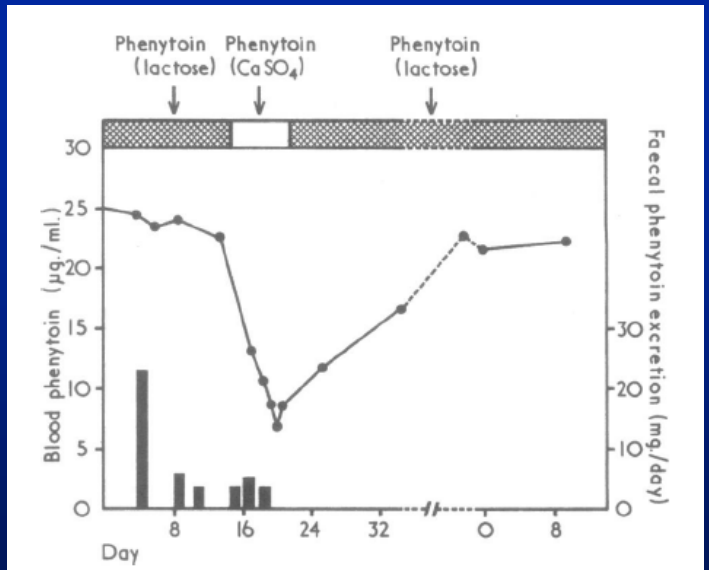
- Chloramphenicol
  - Glazko AJ et al. (1968) An evaluation of the absorption characteristics of different chloramphenicol preparations in normal human subjects. *Clin Pharmacol Ther* 9(4):472-83
- Tolbutamide
  - Varley AB (1968) The generic inequivalence of drugs . *JAMA 206(8)*:1745-8
    - Simply halving the amount of disintegrant (Vee Gum) and continue to comply with USP specifications
- These products exhibited large variations in drug plasma levels exposing patients to potential deadly hazards





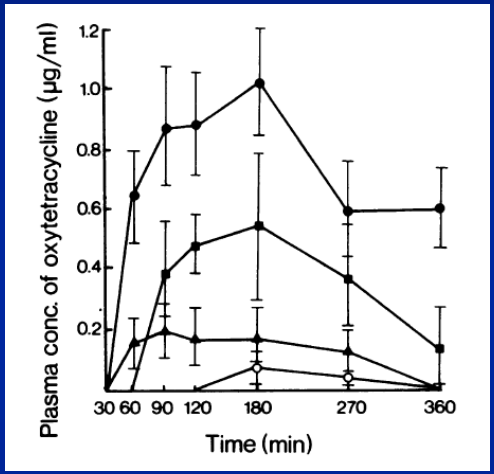
Similar bioavailability problems detected for other products

- Nitrofurantoine
  - Conklin JD and Hailey FJ (1969) Urinary drug excretion in man during oral dosage of different nitrofurantoin formulations. *Clin Pharmacol Ther* 10(4):534-9
- Phenytoin
  - Tyrer JH et al. (1970) Outbreak of anticonvulsivant intoxication in an Australian city. *BMJ* 4:271-3

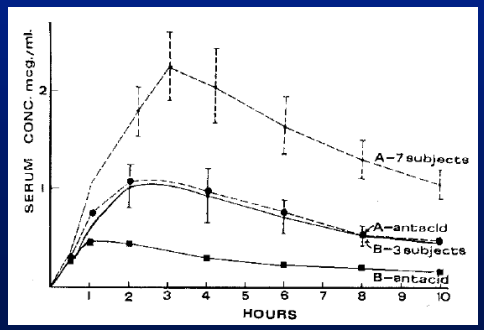


Blood phenytoin concentrations in a patient taking phenytoin (400 mg./day), with excipients respectively as shown (lactose, calcium sulphate, lactose). Vertical columns represent daily faecal excretion of phenytoin when measured.

Similar bioavailability problems detected for other products



- Oxytetracycline
  - Brice GW and Hammer HF. (1969). Therapeutic nonequivalence of oxytetracycline capsules. *JAMA* 208(7):1189-90
  - Barber HE et al. (1974) Biological availability and in vitro dissolution of oxytetracycline dihydrate tablets. *Br J Clin Pharmacol* 1(5):405-408



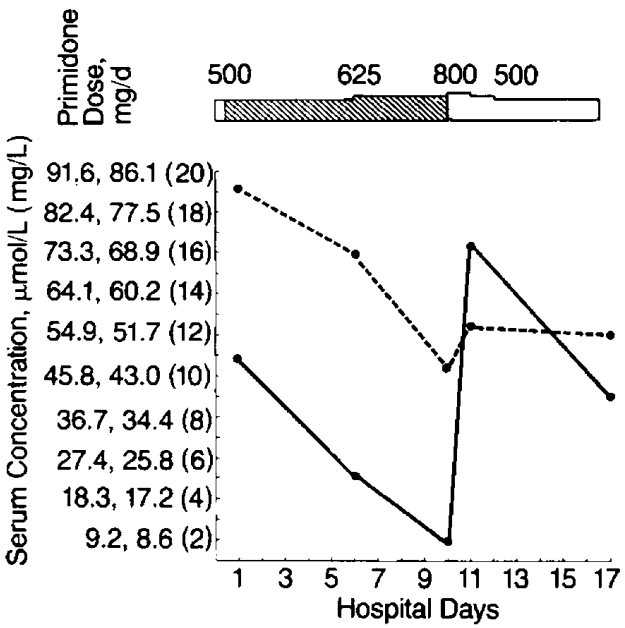
- Tetracycline
  - Barr WH et al. (1972) Assessment of the biologic availability of tetraycline products in man. *Clin Pharmacol Ther* 13:97-108
  - Barnet DB et al. (1974) Bioavailability of commercial tetracycline products. *Br J Clin Pharmacol* 1(4):319-323

Conclusions of the FDA Office of Technology assessment in 1974

- Current standards and regulatory practices do not assure bioequivalence
- Variations in bioavailability are recognised as responsible for a few therapeutic failures
- It is probable that other therapeutic failures (or toxicity) of a similar origin have escaped recognition
- Analytical methodology and experimental procedures for the conduct of bioequivalence studies in man are available

Bioavailability problems continued in the 80's

- Primidone
  - Wyllie E et al. (1987) Increased Seizure Frequency with generic primidone. *JAMA* 258(9):1216-7



Serum concentrations of primidone (solid line) and phenobarbital (broken line) decreased when patient was switched from primidone (Mysoline, Ayerst Laboratories, New York, shaded bar at top) to generic primidone (Bolar Pharmaceutical Co, Copiague, NY, crosshatched bar at top). For serum concentrations, first number refers to primidone SI unit value; second number, phenobarbital SI unit value; and third number in parentheses, milligrams per liter.

Bioavailability problems continued in the 90's

- In 1995 a levo-thyroxine product (Levothroid, Hoechst Marion Roussel, now Sanofi-Aventis) changed from micronised to non-micronised active substance in Spain and bioavailability was reduced with serious clinical consequences
  - Mayayo Dehesa E et al. (1997) Asunto: "Levothroid" *An Esp Pediatr* 46:109-10
  - Variation performed without regulatory authorisation

https://www.aeped.es/sites/default/files/anales/46-2-2.pdf. Accessed 22/02/2015

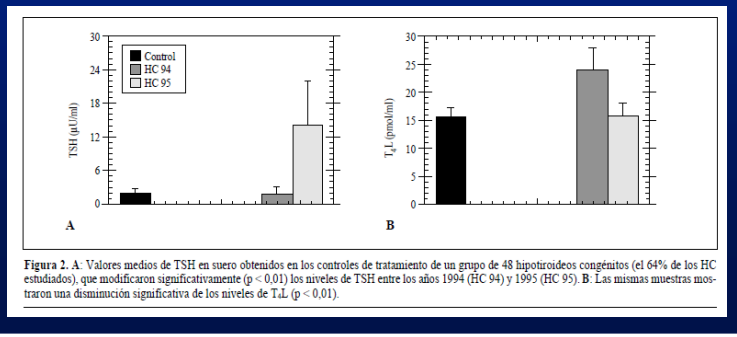
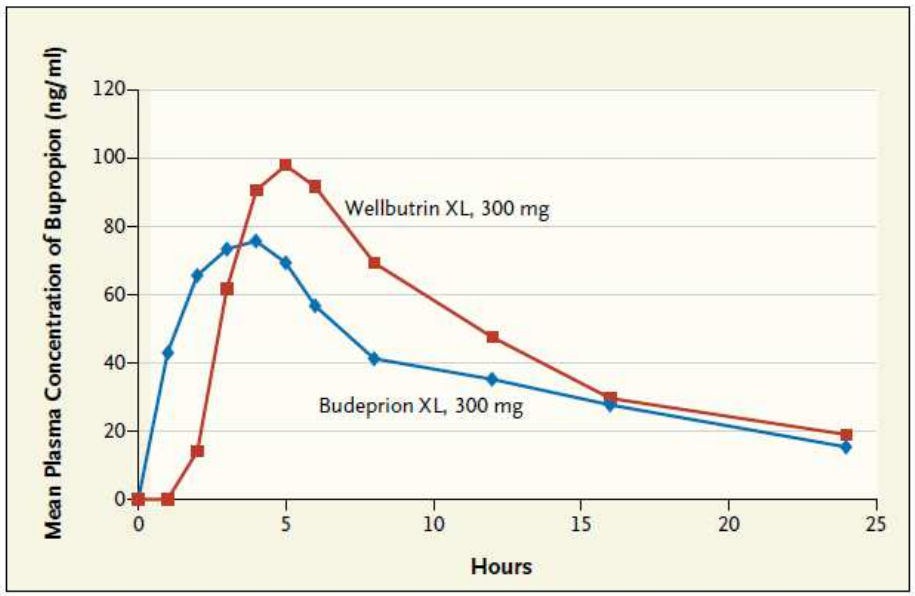


Figura 2. A: Valores medios de TSH en suero obtenidos en los controles de tratamiento de un grupo de 48 hipotiroideos congénitos (el 64% de los HC estudiados), que modificaron significativamente ($p < 0,01$) los niveles de TSH entre los años 1994 (HC 94) y 1995 (HC 95). **B**: Las mismas muestras mostraron una disminución significativa de los niveles de T_4L ($p < 0,01$).

Bioavailability problems continued in the 2000's

- In 2006 a bupropion prolonged release product that had shown to be bioequivalent at the 150 mg strength was not bioequivalent at the 300 mg strength in the USA.

Woodcock et al. (2012) Withdrawal of generic budeprion for nonbioequivalence. N Engl J Med. 367(26):2463-5



Mean Plasma Concentration of Bupropion (Budeprion XL and Wellbutrin XL) as a Function of Time in 24 Fasting Healthy Volunteers.

AUC = 86% (90% CI: 77 – 96%)
C_{max} = 75% (90% CI: 65 – 87%)

In certain study participants, the Cmax and AUC were less than 40% of the values with Wellbutrin XL.

Adverse events in patients being treated for major depressive disorder

How many BE studies fail?

- Even when the sponsor believes that the generic product is equivalent to the reference as to invest the cost of a BE study, some products are not equivalent
- Ramirez et al. BJCP 70:5 694-702: 22/89 (25%) or 35/124 (28%)
  - 10% due to differences
    - 7% in class I drugs
    - 18% of class II drugs
    - 5% of class III drugs
    - 8% of class IV drugs
  - 15% due to variability
- When BE is not a regulatory requirement the sponsor is less interested in manufacture a BE product, since there is no risk of failure

WHO Technical Report Series, No. 937, 2006. Annex 7

- The national regulatory authorities should ensure that all pharmaceutical products subject to their control conform to acceptable standards of safety, efficacy and quality, and that all premises and practices employed in the manufacture, storage and distribution of these products comply with good manufacturing practice (GMP) standards so as to ensure the continued conformity of the products with these requirements until they are delivered to the end-user.

WHO Technical Report Series, No. 937, 2006. Annex 7

- All pharmaceutical products, including multisource products, should be used in a country only after approval by the national or regional authority
- Regulatory authorities should require the documentation of a multisource pharmaceutical product to meet the following:
  - GMP;
  - quality control specifications; and
  - pharmaceutical product interchangeability.

WHO Technical Report Series, No. 937, 2006. Annex 7

- Multisource pharmaceutical products need to conform to the same appropriate standards of quality, efficacy and safety as those required of the innovator's (comparator) product.
- In addition, reasonable assurance must be provided that the multisource product is therapeutically equivalent and interchangeable with the comparator product

WHO Technical Report Series, No. 937, 2006. Annex 7

- Therapeutic equivalence can be assured when the multisource product is both pharmaceutically equivalent/alternative and bioequivalent.
- Assuming that in the same subject an essentially similar plasma concentration time course will result in essentially similar concentrations at the site(s) of action and thus an essentially similar therapeutic outcome, pharmacokinetic data may be used instead of therapeutic results.

WHO Technical Report Series, No. 937, 2006. Annex 7

- For certain medicines and dosage forms, in vivo documentation of equivalence, through either a pharmacokinetic bioequivalence study, a comparative pharmacodynamic study or a comparative clinical trial, is regarded as especially important.
- In vivo documentation of equivalence is needed when there is a risk that possible differences in bioavailability may result in therapeutic inequivalence.

New WHO recommendations in 2015

- Examples are listed below.

a) Oral immediate-release pharmaceutical products with systemic action, except for BCS biowaivers.

- For all drugs for which a difference in BA may result in therapeutic inequivalence

New WHO recommendations in 2015

Not only for:

- critical use medicines;
- narrow therapeutic range (efficacy/safety margins), steep dose–response curve;
- documented evidence for bioavailability problems or bioinequivalence related to the API or its formulations (unrelated to dissolution problems);
- there is scientific evidence to suggest that polymorphs of API, the excipients and/or the pharmaceutical processes used in manufacturing could affect bioequivalence.

WHO Technical Report Series, No. 937, 2006. Annex 7

b) Non-oral, non-parenteral pharmaceutical products designed to act systemically (such as transdermal patches, suppositories, nicotine chewing gum, testosterone gel and skin-inserted contraceptives).

c) Modified-release pharmaceutical products designed to act systemically.

d) Fixed-combination products with systemic action, where at least one of the APIs requires an in vivo study.

New WHO recommendations in 2015

e) Non-solution pharmaceutical products, which are for non-systemic use (e.g. for oral, nasal, ocular, dermal, rectal or vaginal application) and are intended to act without systemic absorption. In these cases, the equivalence is established through, e.g. comparative clinical or PD, DPK studies, local availability studies and/or in vitro studies.

In certain cases, measurement of the concentration of the API may still be required for safety reasons, i.e. in order to assess unintended systemic absorption.

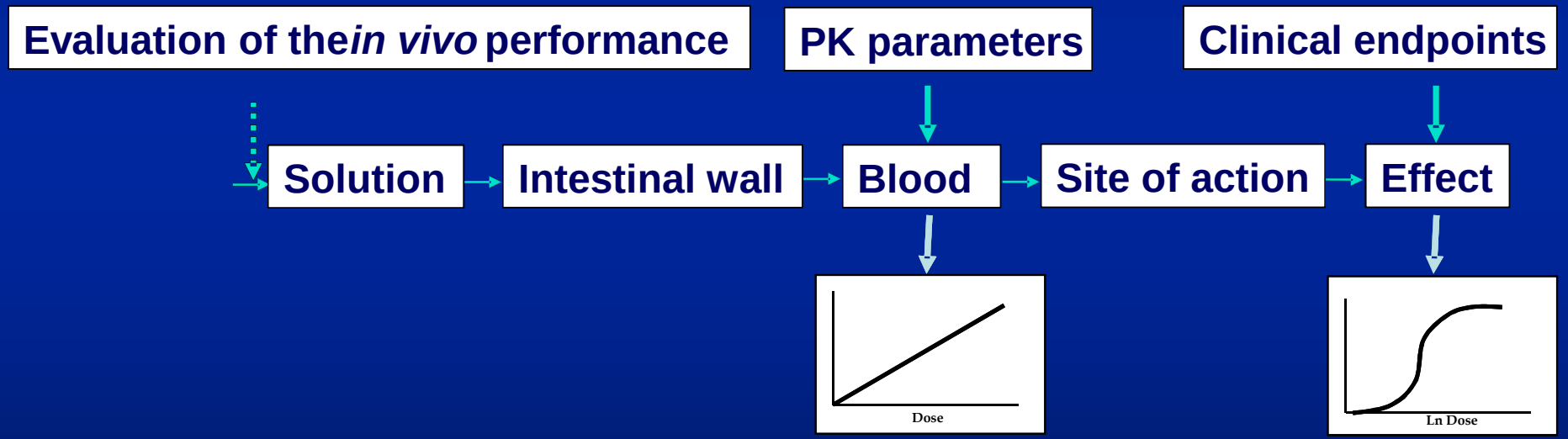
Primero "calidad"

- Antes de exigir bioequivalencia a los medicamentos genéricos es necesario asegurar que se fabrican correctamente.
- El cumplimiento de GMPs es el primer paso para la bioequivalencia.

¿Por qué es necesario exigir bioequivalencia?

- La eficacia y seguridad del medicamento de referencia se deben a su exposición sistémica por ser un producto de acción sistémica.
- Sólo si el medicamento genérico proporciona niveles sistémicos semejantes podremos estar seguros de que su perfil de eficacia y seguridad es equivalente.

¿PK o PD?


Evaluation of the *in vivo* performance
PK parameters
Clinical endpoints
Solution
Intestinal wall
Blood
Site of action
Effect
Dose
Ln Dose

Bioequivalencia como "puente"

- La bioequivalencia es lo único que relaciona el producto genérico con las instrucciones de uso / ficha técnica del medicamento de referencia
- ¿Cómo se debería usar un medicamento genérico que tuviera una exposición sistémica 5 veces mayor que el producto de referencia? ¿Qué instrucciones de uso / ficha técnica darle?

Garantía para los pacientes

- Se trata de garantizar a la población que los medicamentos que toman son de calidad biofarmacéutica
- ya que los estudios in vitro solamente garantizan la calidad biofarmacéutica es casos limitados
  - Fármacos de clase I y III bajo estrictas condiciones de composición y velocidad de disolución que en la mayoría de los casos no se cumplen

Muchas gracias por su atención