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Elementos para el Análisis Crítico de Antibiótcios Innovadores vs. Genéricos

Ubier Gómez M.D.
Toxicólogo Clínico
Profesor de Farmacología y Toxicología
Universidad de Antioquia
Hospital Universitario San Vicente Fundación

William Whitering médico inglés 1741-1799

"Es mucho más fácil escribir sobre una enfermedad que sobre un medicamento. La primera está en manos de la naturaleza; el segundo estará siempre a merced de los antojos, el descuido y los desatinos de la humanidad"

Reflexión inicial

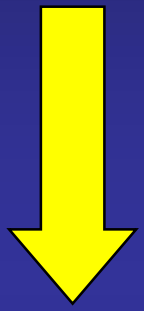
- Las necesidades en salud deben equilibrarse con los recursos disponibles.
- No estamos aquí para descalificar a los medicamentos genéricos.
- Muchos son de excelente calidad y pueden sustituir el medicamento innovador.

Reflexión inicial

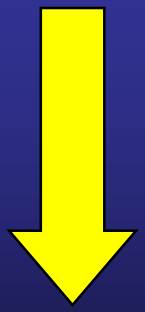
- Cualquier ahorro derivado del empleo de un medicamento genérico se justifica solo si ese medicamento tienen la misma eficacia, seguridad y comodidad que el medicamento original.

Problema Médico

PACIENTE



MEDICAMENTO



RESPUESTA

Medicamentos de Calidad

- Es de buena fe asumir:
  - Veracidad de la información del medicamento
  - Que el medicamento contiene:
    - El ingrediente activo correcto
    - La dosis correcta

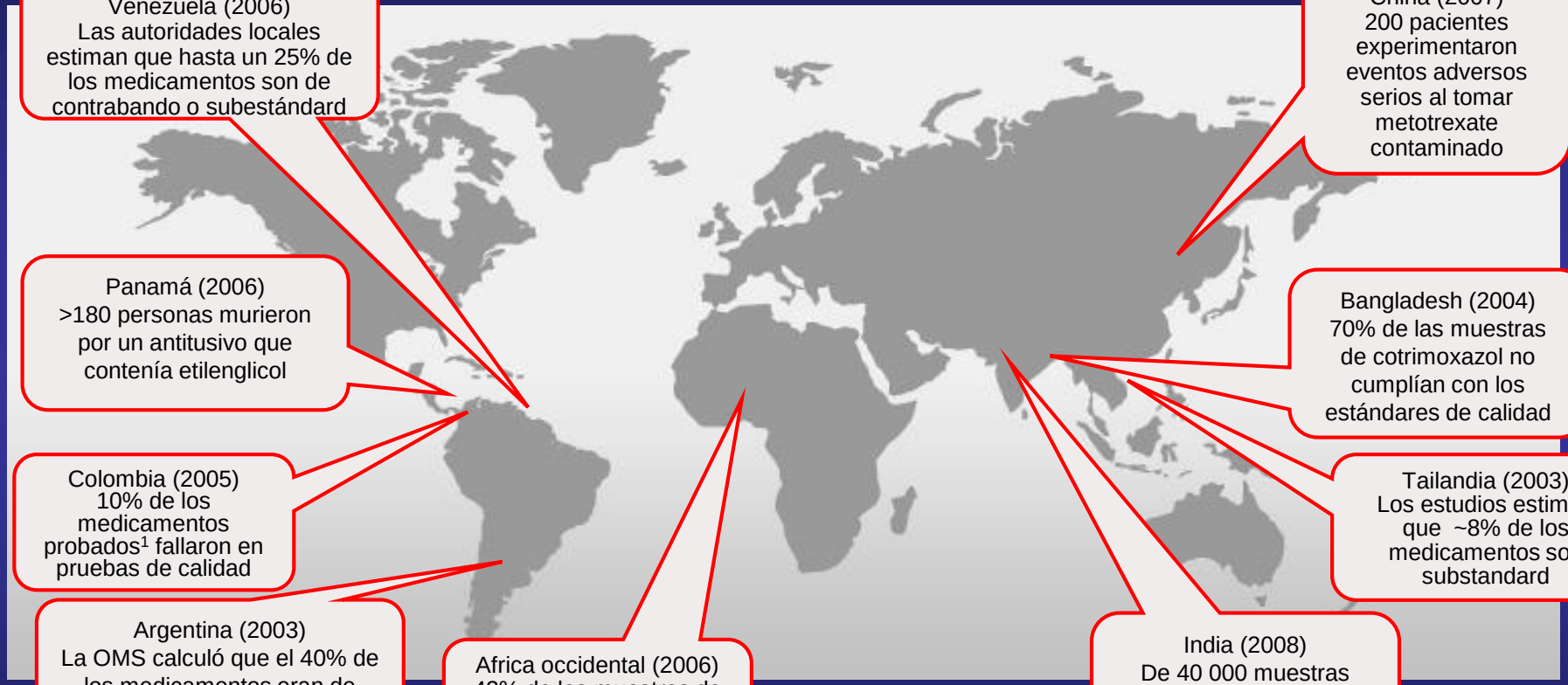
- Que no contiene:
  - Altos niveles de impurezas
  - Impurezas desconocidas o no caracterizadas

Jarabe para la Tos Mata a 180 Personas

Panamá – dietilen glicol, en vez de glicerol, importado de China en jarabes antitusivos y antialérgicos

http://news.bbc.co.uk/2/hi/americas/6711497.stm, accessed January 24, 2009

Importancia en el Mundo
Medicamentos con problemas de calidad



Venezuela (2006)
Las autoridades locales estiman que hasta un 25% de los medicamentos son de contrabando o subestándard

China (2007)
200 pacientes experimentaron eventos adversos serios al tomar metotrexate contaminado

Panamá (2006)
>180 personas murieron por un antitusivo que contenía etilenglicol

Bangladesh (2004)
70% de las muestras de cotrimoxazol no cumplían con los estándares de calidad

Colombia (2005)
10% de los medicamentos probados[1] fallaron en pruebas de calidad

Tailandia (2003)
Los estudios estiman que ~8% de los medicamentos son substandard

Argentina (2003)
La OMS calculó que el 40% de los medicamentos eran de contrabando o subestándard

Africa occidental (2006)
42% de las muestras de farmacos anti-malaricos estudiadas eran de pobre calidad

India (2008)
De 40 000 muestras estudiadas por las autoridades locales 10% eran substandard

1 fluoxetina, cefalexina, hidroclorotiazida, glibenclamida, lovastatina, verapamilo, diclofenaco, tamoxifeno, ketoconazol, ibuprofeno. vecuronio

Importancia en el Mundo

Alianza Europea para el Acceso a Medicamentos Seguros (EAASM):

- 62% de los medicamentos que se venden a través de la Red son falsos.
- 95,6% de las farmacias virtuales operan de forma ilegal.
- 90% de las páginas web vende sin receta fármacos que requieren prescripción médica

Importancia en Colombia

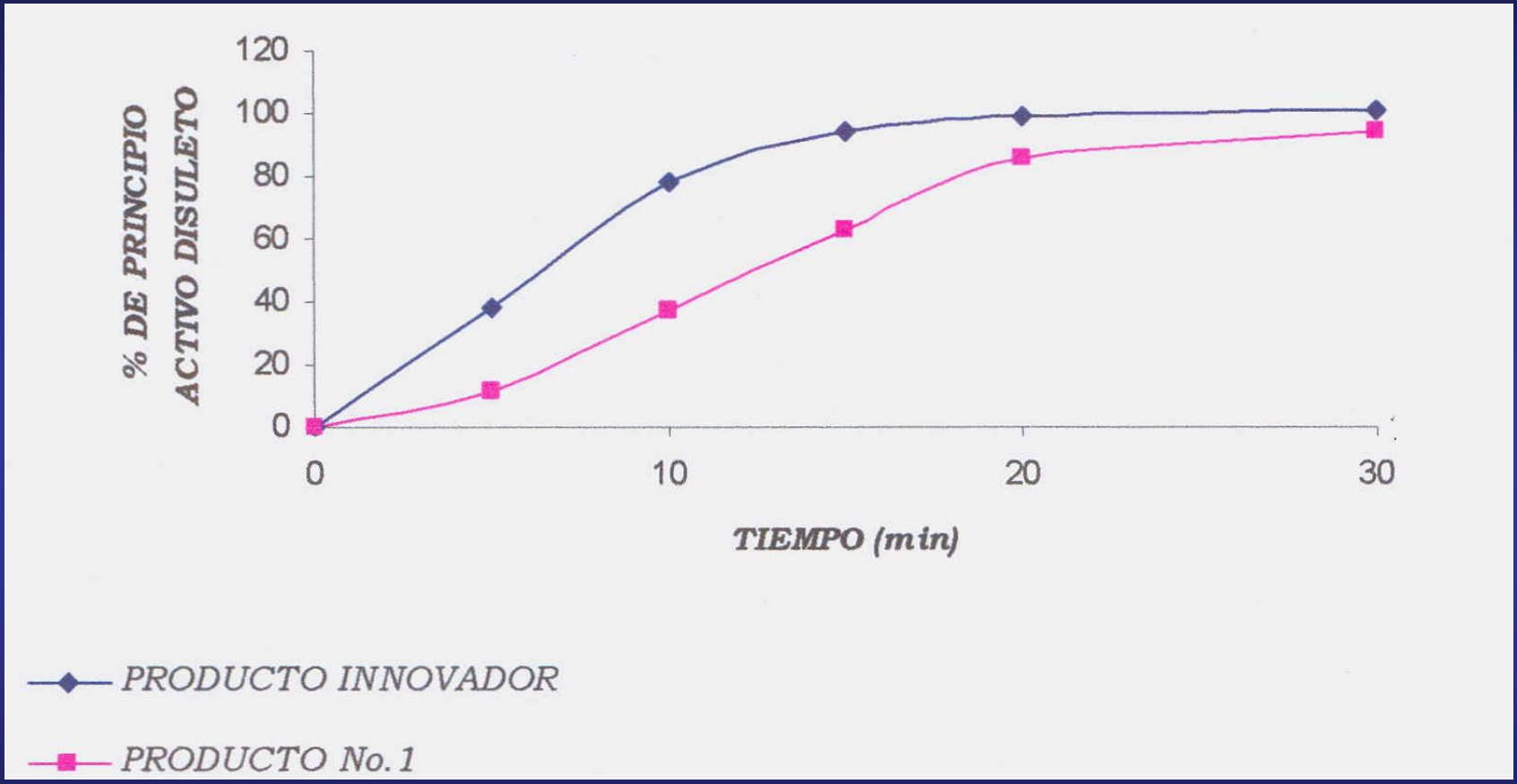
- Medicamentos Subéstandar
  - Adulterados
  - Fraudulento
- Biodisponibilidad deficiente
- Problemas con medicamentos de contrabando
- Problemas con almacenamiento y transporte
- Medicamentos falsificados
- Problemas con medicamentos vencidos

Pruebas de Disolución Para Formas Orales

Cuando el medicamento se disuelve más del 85% en 15 minutos no hay barrera para la absorción del producto.

En caso de un porcentaje inferior se debe recurrir a una segunda valoración, con un modelo de similitud que el cual deberá ser mayor o igual a 50.

Pruebas de Disolución Para Formas Orales



A los 15 minutos el medicamento de referencia alcanzó una disolución superior al 85% (94%) y el producto genérico solo alcanzó un 63%.

Algunos Medicamentos con Problemas de Calidad

PRODUCTOS QUE SE RAJARON EN LAS PRUEBAS DE CALIDAD DEL 2006

Fluoxetina (antidepresivo), cápsulas por 20 mg de los laboratorios: La Santé, lote 506. Angiopharma, lote 605. Lafrancol, lote 24955. American Generics, lotes 31035 y 38155. Memphis Products, lote 19331005. Pragmaten Novamed, lotes 411891 y 510163.

Hidroclorotiazida (diurético antihipertensivo), tabletas por 50 mg de los laboratorios: Industrias Farmacéuticas S.A., lote 15B05. Hidroclorotiazida MK Tecnoquímicas S.A. lotes 5R9834, 4D1630, 5H2306 y 4R9190.

Lovastatina (tratamiento del colesterol), tabletas por 20 mg de los laboratorios: Pentacoop, lotes 60239, 60240, 52019, 52929 y 60238. Novamed, lote 505022. Lovasterol Farmacol, lote 2VT32.

Tamoxifeno (manejo del cáncer), tabletas por 20 mg de los laboratorios: Taxifen Ebewe de Ropsohn Terapeutics, lotes 607379, 503410, 504553, 505299 y 507822.

Diclofenaco sódico (analgésico antiinflamatorio), tabletas por 50 mg de los laboratorios: Anglo Pharma, lote 306. La Santé, lote 614. América, lote 1460606. Best, lote 2005. Lakor Farmacéutica, lote 50805. Diclofenaco sódico, tabletas por 75 mg: Artrites California, lote 21401204.

Ibuprofeno (analgésico antiinflamatorio), tabletas por 200 mg de los laboratorios: Sanofi-Synthelabo, lote 10206.

Tomado del periódico
EL TIEMPO,
página 1-7
Agosto 26 de 2007

www.med-informatica.com/FARMACOVIGILANCIA/Invima_DeMuestralaCalidad2006.pdf

Algunos Productos con Problemas de Calidad en Colombia

TRES DROGUERÍAS Y UNA LITOGRAFÍA FUERON ALLANADAS

Capturados traficantes de medicamentos falsos

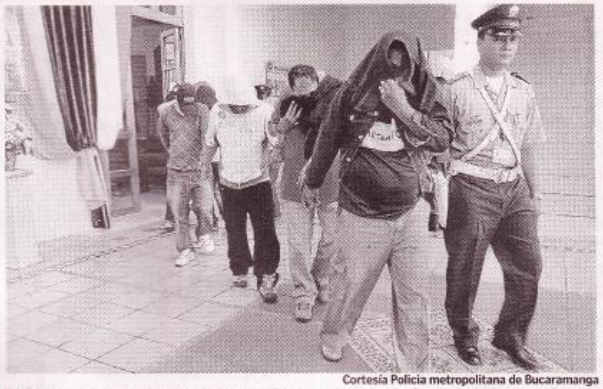
BUCARAMANGA

Seis meses duró la investigación de la Policía Metropolitana de Bucaramanga, en coordinación con la Dijín y la Fiscalía General de la Nación, contra una red de traficantes de medicamentos en Santander.

El comandante de la Policía, general Yesid Vásquez Prada, dijo ayer en rueda de prensa que capturaron a 11 personas, integrantes de una banda que delinquía desde hacía dos años, en 10 allanamientos realizados simultáneamente en Bucaramanga, Girón y Floridablanca.

Los detenidos se dedicaban a comercializar medicamentos vencidos, adulterados y de contrabando, especialmente de alto costo para enfermedades como sida y cáncer.

En el operativo, se decomisaron 35.000 pastillas falsas, que "se vendían en droguerías y estamos investigando si hacen parte de la red. Dentro de los inmuebles allanados, hay tres droguerías y una litografía", explicó el general. Los capturados, entre ellos tres mujeres, están a disposición judicial.



Cortesía Policía metropolitana de Bucaramanga

Seis meses duró la investigación que dio como fruto la captura de once personas en Bucaramanga y sus alrededores.

35.000

medicamentos vencidos y sin registro sanitario eran comercializados en droguerías como nuevos, a precios más económicos.

El oficial agregó que, de acuerdo con las autoridades de salud, estos medicamentos son de uso hospitalario, de nivel institucional y control especial: "eran medicamentos vencidos y sin registro sanitario, mientras otros eran muestras médicas prohibidas para la venta, y otros tenían su fecha caducada".

Tras el operativo, apoyado por el Invima y la Secretaría de Salud, el general aseguró ser "el inicio de otros golpes certeros que vienen en camino para desarticular la banda desde el primer escalón".

Tomado de el periódico EL TIEMPO, página 1-17 Agosto 6 de 2010

Federal Injunction Blocks Ranbaxy from Marketing in U.S.

By John Gever, Senior Editor, MedPage Today
Published: January 25, 2012

WASHINGTON -- The Justice Department filed a consent decree today preventing generic drug giant Ranbaxy from selling drugs made at four of its manufacturing plants until it brings them into compliance with the FDA's quality standards.

As part of the order, Ranbaxy has agreed "to remedy deviations from the current good manufacturing practice (cGMP) requirements and to correct data integrity problems at numerous facilities," according to a statement from the Justice Department.

The order comes after the FDA had imposed an import alert on three manufacturing plants in India and instructed Ranbaxy to fix problems at its Ohm Laboratories factory in Gloversville, N.Y., which has since been closed.

In 2008, the FDA had blocked imports from two of Ranbaxy's Indian plants, citing repeated failures to comply with cGMP standards.

In announcing the new Justice Department filing, the FDA said Ranbaxy had not only failed to take adequate steps to bring the facilities into compliance, it "continued ... to falsify information on drug applications."

In a statement, Ranbaxy CEO Arun Sawhney admitted that the company had made mistakes.

"While we were disappointed by the conduct that led to the FDA's investigation, we are proud of the systematic corrective steps we have taken to upgrade and enhance the quality of our business and manufacturing processes," he said. "We look forward to continuing to work cooperatively with the FDA to strengthen the public trust in our company."

Equivalencia Química

Dos productos son equivalentes químicos cuando contienen las mismas **cantidades** rotuladas del medicamento.

Equivalentes Químicos pero no Farmacéuticos

- Succinato vs tartrato de metoprolol
- Vitamina K1 o Vitamina K3
- Carbonato vs citrato de calcio
- Eritromicina etilsuccinato vs estolato

Equivalencia Farmacéutica

Dos productos son considerados equivalentes farmacéuticos si contienen el mismo principio activo o fármaco, en la misma sal o derivado químico y si son idénticos en presentación, potencia, concentración, dosificación y vía.

Equivalencia Terapéutica

Dos productos son considerados equivalentes terapéuticos si son equivalentes desde el punto de vista farmacéutico y después de la administración a la misma dosis, sus efectos respecto a eficacia y seguridad son esencialmente los mismos, según se determina por estudios adecuados (bio-bio, PD, clínicos, in vitro).

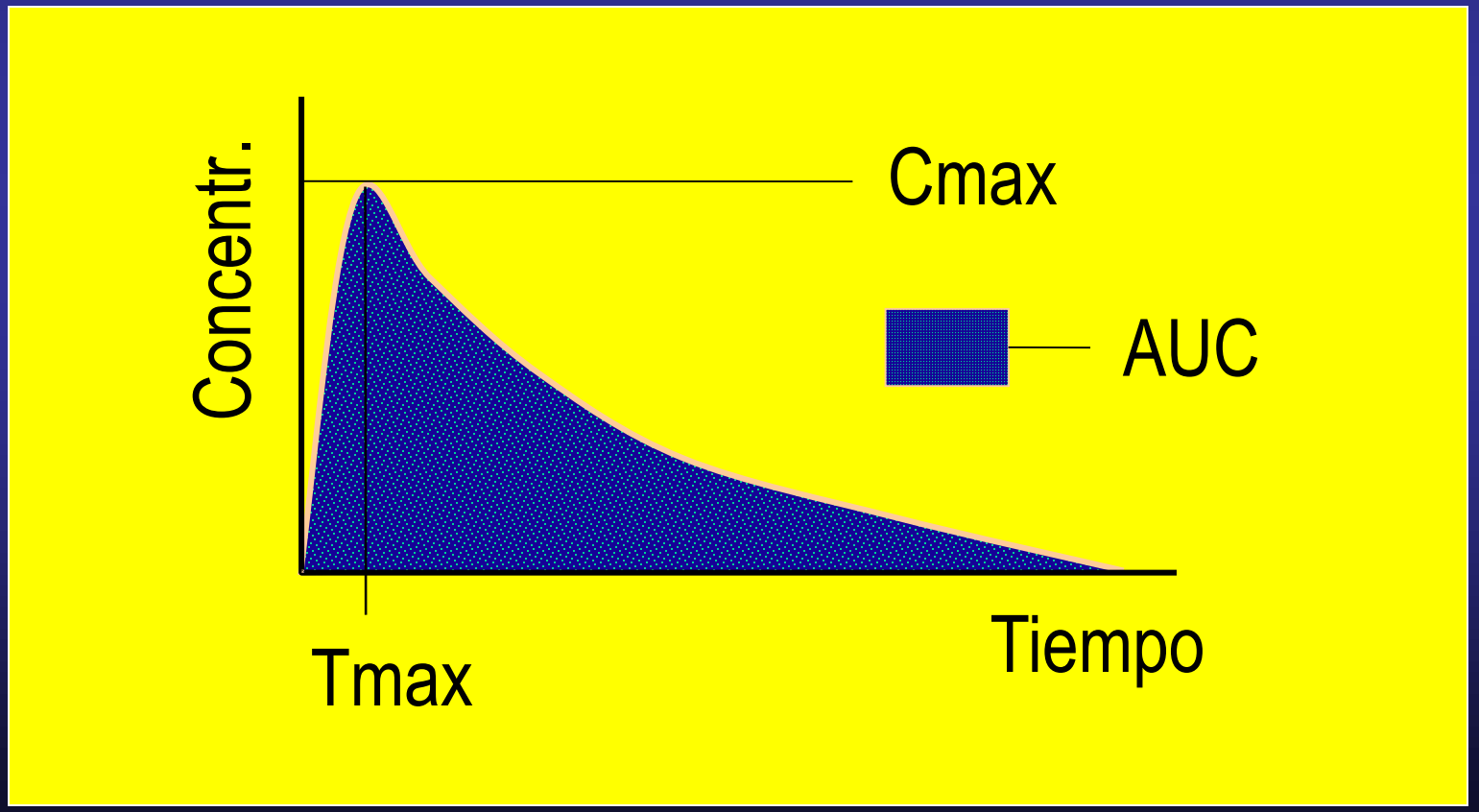
OMS, serie de informes* técnicos, *863:134)

Denominación Genérica ≠ Medicamento Genérico

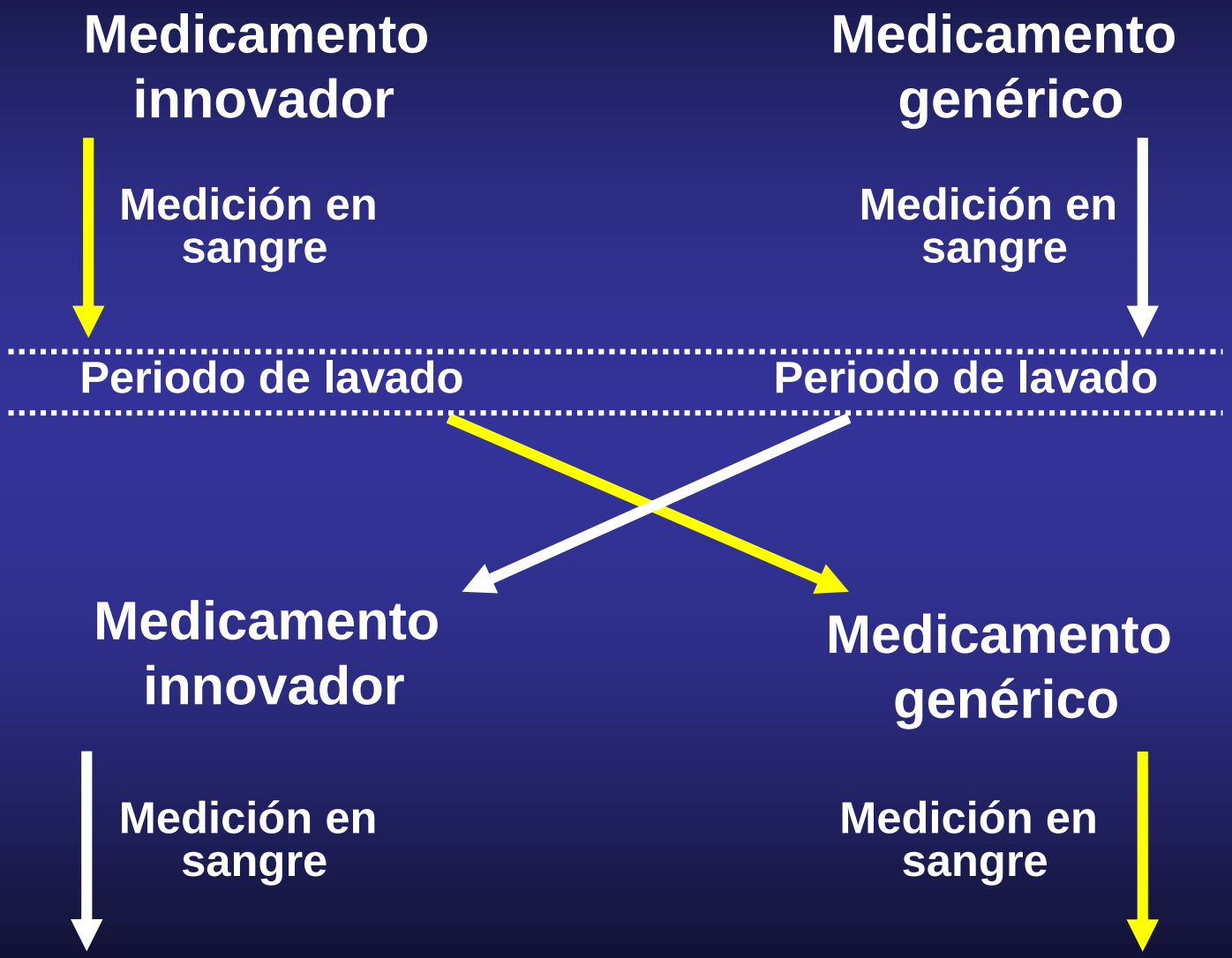
- **Denominación genérica**: Es la denominación común internacional (DCI) con la que se conoce un principio o sustancia activa.
- **Medicamento genérico**: es aquel registrado una vez vencida la patente del innovador y que demostró ser bioequivalente con el medicamento original.

Biodisponibilidad

Es la proporción y velocidad con la que un fármaco es absorbido a la circulación sistémica



Estudio de bioequivalencia

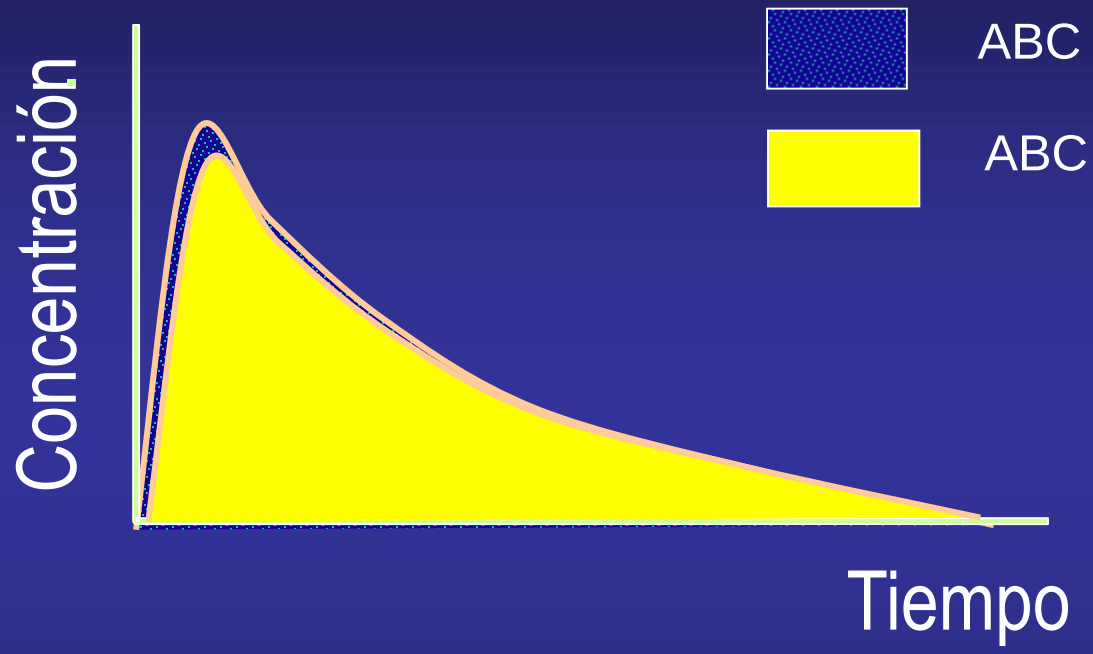


Bioequivalencia

Dos productos son considerados bioequivalentes si sus biodisponibilidades son similares entre sí, administrados a dosis equimolares.

En los productos de administración parenteral se asume que la biodisponibilidad es del 100% (igual a 1).

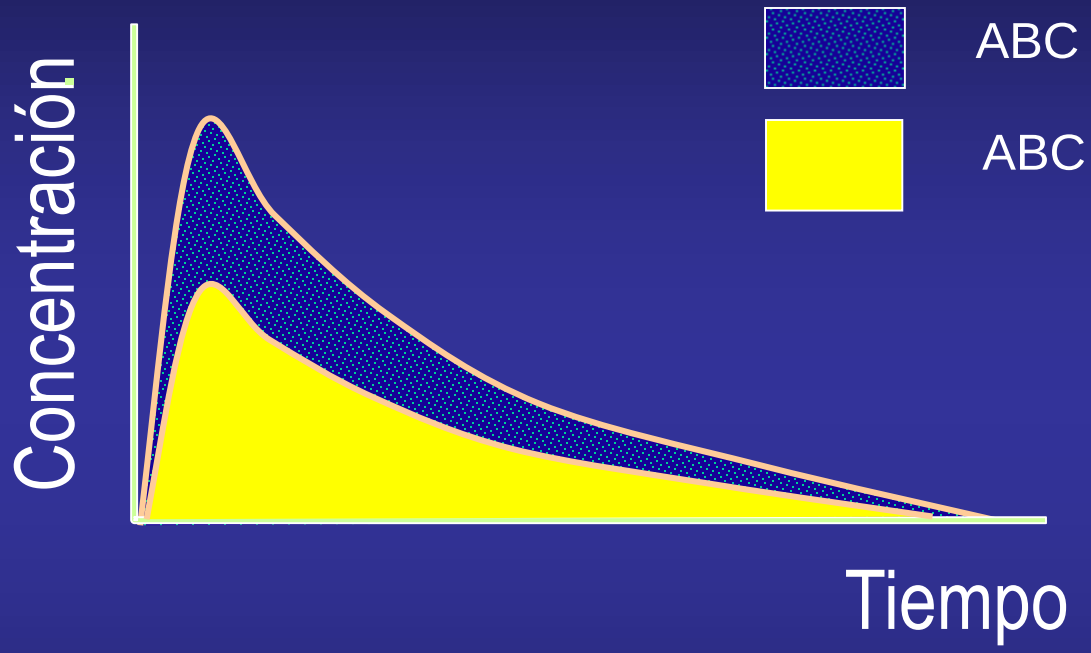
Bioequivalencia



Si la variabilidad de las ABC es menor a un 20% el estudio mostrará biodisponibilidad similar y por tanto bioequivalencia, lo cual hace presumir intercambiabilidad.

ABC: Área Bajo la Curva

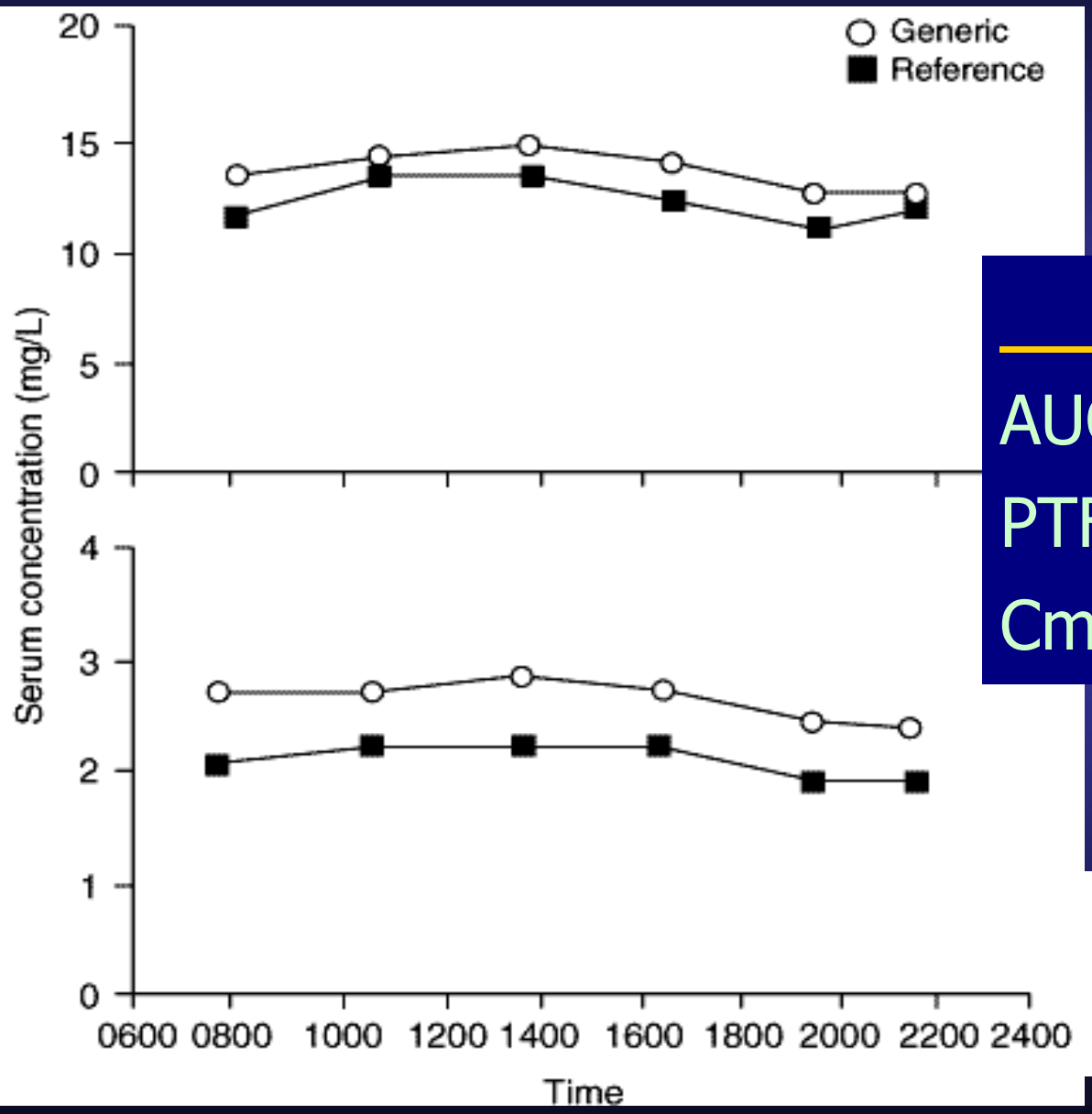
Bioequivalencia



Si la variabilidad de las ABC es mayor a un 20% el estudio mostrará biodisponibilidad pero no bioequivalencia, y por ende no serán intercambiables.

ABC: Área Bajo la Curva

Carbamazepina - SR



14 pacientes

	G/R	90% CI
AUC:	111%	(106-118)
PTF:	91%	(74 - 112)
Cmax:	110%	(100 -117)

Clin Drug Invest 1999; 18(1): 17-26

Carbamazepina de Liberación Lenta

Nuevos E.A.:

8/13 con CMZ-G

Efectos Adversos

Mareo, náusea, ataxia, visión borrosa, nistagmus

1 sujeto se retiró al cambiar a CMZ-G

Clin Drug Invest 1999;18(1): 17-26

¡Los estudios de bioequivalencia

no necesariamente garantizan la

eficacia clínica los medicamentosi

Pautas para analizar estudios de biodisponibilidad y bioequivalencia

- Diseño del estudio:
  - Diseño experimental
  - Estandarización y validación del método analítico
  - Perfiles comparativos de disolución de los medicamentos
  - Tiempos de muestreo
  - Análisis farmacocinético
  - Vida media de eliminación
  - Metodología analítica
  - Presentación de los datos
  - Análisis estadístico
  - Identificación de reacciones adversas

¿Porqué Analizar la Bioequivalencia?

Las diferencias en la formulación y manufactura de un medicamento inciden en la respuesta alcanzada en términos de inicio y duración de acción.

Denominación Genérica ≠ Medicamento Genérico

Denominación genérica: Es la denominación común internacional (DCI) con la que se conoce un principio o sustancia activa.

Medicamento genérico: es aquel registrado una vez vencida la patente del innovador y que demostró ser bioequivalente con el medicamento original.

Medicamento Genérico ≠ Medicamento Copia

Medicamento copia: Es aquel que no cuenta con pruebas de bioequivalencia, por lo que aún cuando tenga equivalencia farmacéutica, puede variar su biodisponibilidad, por lo que no debe considerarse intercambiable con el medicamento innovador.

Bioequivalencia

1. Para un medicamentos ser llamado “genérico” debe acreditar estudios de biodisponibilidad y bioequivalencia.
2. El medicamento “copia” no cuenta con estudios de bioequivalencia.

OPEN ACCESS Freely available online

PLoS one

Determination of Therapeutic Equivalence of Generic Products of Gentamicin in the Neutropenic Mouse Thigh Infection Model

Andres F. Zuluaga[1,2], Maria Agudelo[2], John J. Cardeño[2], Carlos A. Rodriguez[1,2], Omar Vesga[1,2,3]*

1 Department of Pharmacology and Toxicology, University of Antioquia Medical School, Medellín, Colombia, 2 Grupo Investigador de Problemas en Enfermedades Infecciosas, University of Antioquia Medical School, Medellín, Colombia, 3 Section of Infectious Diseases, Department of Medicine, Hospital Universitario San Vicente de Paul and University of Antioquia Medical School, Medellín, Colombia

Abstract

Background: Drug regulatory agencies (DRA) support prescription of generic products of intravenous antibiotics assuming therapeutic equivalence from pharmaceutical equivalence. Recent reports of deaths associated with generic heparin and metoprolol have raised concerns about the efficacy and safety of DRA-approved drugs.

Methodology/Principal Findings: To challenge the assumption that pharmaceutical equivalence predicts therapeutic equivalence, we determined in vitro and in vivo the efficacy of the innovator product and 20 pharmaceutically equivalent generics of gentamicin. The data showed that, while only 1 generic product failed in vitro (MIC = 45.3 vs. 0.7 mg/L, P<0.05), 10 products (including gentamicin reference powder) failed in vivo against *E. coli* due to significantly inferior efficacy (E_{max} = 4.81 to 5.32 vs. 5.99 log_{10} CFU/g, P≤0.043). Although the design lacked power to detect differences in survival after thigh infection with *P. aeruginosa*, dissemination to vital organs was significantly higher in animals treated with generic gentamicin despite 4 days of maximally effective treatment.

Conclusion: Pharmaceutical equivalence does not predict therapeutic equivalence of generic gentamicin. Stricter criteria based on solid experimental evidence should be required before approval for human use.

Citation: Zuluaga AF, Agudelo M, Cardeño JJ, Rodriguez CA, Vesga O (2010) Determination of Therapeutic Equivalence of Generic Products of Gentamicin in the Neutropenic Mouse Thigh Infection Model. PLoS ONE 5(5): e10744. doi:10.1371/journal.pone.0010744

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pharmaceutical companies supported the present study.

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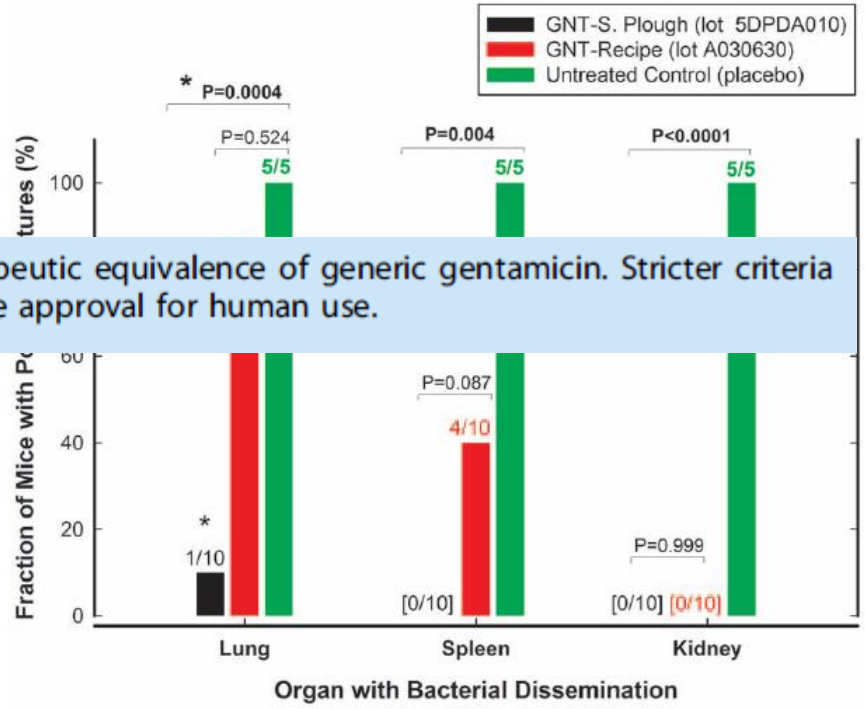
Introduction

There has been a dramatic increase in clinical use of generic medicines since 1980, but there are not systematic evaluations of their therapeutic efficacy compared with innovator products [1,2]. Although essential to reduce health budget costs and to promote pharmaceutical competition and employment, generic drugs remain a topic of intense controversy as a result of the accelerated approval process for human use (which some disagree with), and sporadic reports of failures and deaths associated with their use [3–5]. There is an unsurpassable point in this controversy: forcing the manufacturers of generic drugs to go through the same process required to bring innovator drugs to market implies a cost overrun calculated in 150 to 800 million dollars that would hinder their mainstay objective, i.e., "to regulate and reduce the medicine's price" [6]. The solution has been a very short, straightforward and inexpensive process created to approve generic versions of innovator products, which requires no comparative preclinical or clinical safety and/or efficacy studies, hoping that generics would generate results similar to those obtained with the innovator drug [7]. In consequence, therapeutic equivalence is assumed after demonstration of pharmaceutical equivalence and bioequivalence with respect to a gold standard, usually the innovator [8–10]. Furthermore, only the active pharmaceutical ingredient (API) is considered responsible for pharmaceutical equivalence, without special attention to binders, diluents, excipients (fillers), impurities, and contaminants present in all formulations that may vary widely between generics and innovators affecting safety and efficacy [3,11–13]. Of note, drug regulatory agencies (DRA) waive the requirement of bioequivalence for pharmaceutically equivalent intravenous solutions because their bioavailability is considered "self-evident" [14].

Aminoglycosides are concentration-dependent, highly bactericidal antibiotics that act mainly by inhibition of protein synthesis [15]. In many countries, gentamicin is the compound most frequently prescribed from this group to treat infections as



Conclusion: Pharmaceutical equivalence does not predict therapeutic equivalence of generic gentamicin. Stricter criteria based on solid experimental evidence should be required before approval for human use.

http://www.ncbi.nlm.nih.gov/pubmed?term=Determination%20of%20Therapeutic%20Equivalence%20of%20Generic%20Products%20

Rodriguez et al. BMC Infectious Diseases 2010, 10:153
http://www.biomedcentral.com/1471-2334/10/153

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

In vitro and in vivo comparison of the anti-staphylococcal efficacy of generic products and the innovator of oxacillin

Carlos A Rodriguez[1,3], Maria Agudelo[1,3], Andres F Zuluaga[1,3] and Omar Vesga*[1,2,3]

Abstract

Background: Oxacillin continues to be an important agent in the treatment of staphylococcal infections; many generic products are available and the only requirement for their approval is demonstration of pharmaceutical equivalence. We tested the assumption that pharmaceutical equivalence predicts therapeutic equivalence by comparing 11 generics with the innovator product in terms of concentration of the active pharmaceutical ingredient (API), minimal inhibitory (MIC) and bactericidal concentrations (MBC), and antibacterial efficacy in the neutropenic mouse thigh infection model.

Methods: The API in each product was measured by a validated microbiological assay and compared by slope

Results: 4 generic products failed pharmaceutical equivalence due to significant differences in potency; however, all products were undistinguishable from the innovator in terms of MIC and MBC.

results, bacteriostatic dose (BD) and dose needed to kill the first log of bacteria (1LKD) were also determined.

Results: 4 generic products failed pharmaceutical equivalence due to significant differences in potency; however, all products were undistinguishable from the innovator in terms of MIC and MBC. Independently of their status with respect to pharmaceutical equivalence or in vitro activity, all generics failed therapeutic equivalence in vivo, displaying significantly lower E_{max} and requiring greater BD and 1LKD, or fitting to a non-sigmoidal model.

Conclusions: Pharmaceutical or in vitro equivalence did not entail therapeutic equivalence for oxacillin generic products, indicating that criteria for approval deserve review to include evaluation of in vivo efficacy.

Background

Penicillinase-resistant penicillins, including the isoxazolyl penicillin oxacillin (OXA), have been the mainstay treatment of β-lactamase producing *Staphylococcus aureus* infections since the 1960s, although their usefulness is nowadays reduced by the emergence and worldwide dissemination of methicillin-resistant strains (MRSA) [1]. The patents of these drugs expired long ago and many generic products are currently available while the innovator has abandoned production of this essential antibiotic. The only requirement by drug regulatory agencies (DRA) to authorize marketing of generic intravenous drugs is the demonstration of pharmaceutical equivalence, defined as containing identical amounts of the same active ingredients in the same dosage form and manufactured in compliance with current Good Manufacturing Practices guidelines. Bioequivalence tests are waived, as bioavailability of intravenous formulations is by definition 100% [2-4], and therapeutic equivalence (defined as having the same efficacy and safety profile of the comparator) is assumed from pharmaceutical equivalence without further testing.

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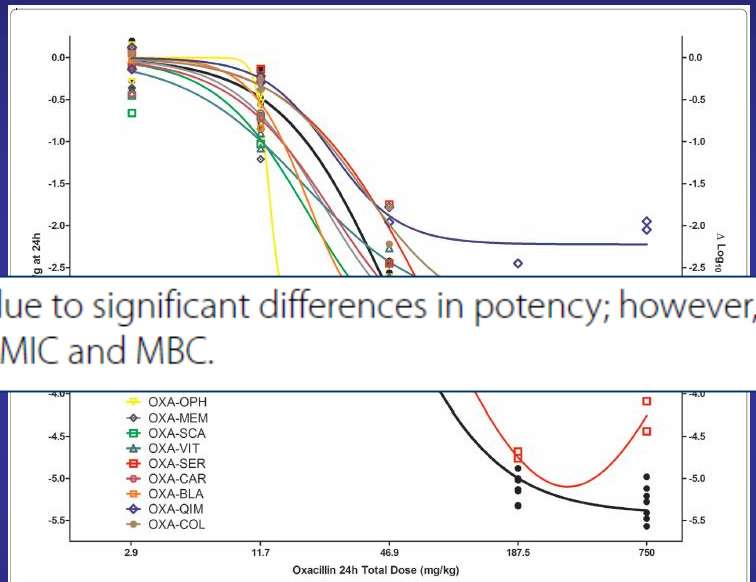

Figure 3 Dose-response relationship of the innovator and 9 generic products of oxacillin in the neutropenic mouse thigh infection model. OXA-BMS (innovator, black curve) and 8 generics fitted to Hill's sigmoid model, while generic product OXA-SER fitted to the Gaussian U-shaped model (red curve). Regardless of pharmaceutical equivalence and in vitro activity, all generics displayed significantly inferior bactericidal efficacy ($P < 0.0001$) or different pharmacodynamic behavior (Gaussian instead of sigmoid) compared with the innovator, thus lacking therapeutic equivalence.

Diaz et al. BMC Clinical Pharmacology 2011, 11:9
http://www.biomedcentral.com/1472-6904/11/9

BMC Clinical Pharmacology

RESEARCH ARTICLE Open Access

Comparative *in vitro* study of the antimicrobial activities of different commercial antibiotic products of vancomycin

Jorge A Diaz[1†], Edelberto Silva[1*†], Maria J Arias[2] and María Garzón[1]

Abstract

Background: One of the most critical problems about antimicrobial therapy is the increasing resistance to antibiotics. Previous studies have shown that there is a direct relation between erroneous prescription, dosage, route, duration of the therapy and the antibiotics resistance. Other important point is the uncertainty about the quality of the prescribed medicines. Some physicians believe that generic drugs are not as effective as innovator ones, so it is very important to have evidence that shows that all commercialized drugs are suitable for therapeutic use.

Methods: Microbial assays were used to establish the potency, the Minimal Inhibitory Concentrations (MICs), the Minimal Bactericidal Concentration (MBCs), the critical concentrations, and the production of spontaneous mutants that are resistant to vancomycin.

Results: The microbial assay was validated in order to determine the Vancomycin potency of the tasted samples. All the products showed that have potency values between 90 - 115% (USP requirement). The products behave similarly because the MICs, The MBCs, the critical concentrations, the critical concentrations ratios between

Conclusions: All products analyzed by microbiological tests, show that both trademarks and generics do not have statistical variability and the answer of antimicrobial activity Show also that they are pharmaceutical equivalents.

Background

Pharmaceutical products, especially antibiotics, must comply with standards of quality, efficacy and reliability, attributes that are determined by various authorities [[1,2], and [3]]. A discussion about the quality and efficacy of generic antibiotics has taken place in recent decades. This discussion has included presentations in congress and research articles in which the authors have shown that some products do not meet regulatory standards [4,5] and that their behavior is not similar in animal models [6,7]

Some antibiotics must be analyzed using biological assays (e.g., penicillin, amikacyn, vancomycin, and neomycin) [2]. These products are measured by their potency or biological activity compared against an international standard. Therefore, the commercial products must be similar in composition to the international reference standard [7]. With antibiotics like vancomycin, if the commercial products do not fulfill the requirements of pharmacopeia, their behavior and performance could put a patient's health in danger.

Biological assays and other analytical procedures must be validated before they are applied in the analysis of the content of the antibiotic under study because, otherwise, neither the information or data generated nor conclusions obtained will be reliable [3]. Our worry arises from the fact that some researchers confuse a "gold standard" with an international reference standard for quantification. A gold standard is something that is a defined commercial product used as reference of performance in comparative studies. It is not a reference standard, but another commercial product with its own variation. Gold standards are established for purposes of bioequivalence and bioavailability studies [2], but in the case of IV antibiotics, the bioavailability is 100%, and therefore, pharmacodynamic

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Generic Vancomycin Products Fail *In Vivo* despite Being Pharmaceutical Equivalents of the Innovator[V]

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Generic versions of intravenous antibiotics are not required to demonstrate therapeutic equivalence with the innovator because therapeutic equivalence is assumed from pharmaceutical equivalence. To test such assumptions, we studied three generic versions of vancomycin in simultaneous experiments with the innovator and determined the concentration and potency of the active pharmaceutical ingredient by microbiological assay, single-dose pharmacokinetics in infected mice, antibacterial effect by broth microdilution and time-kill curves (TKC), and pharmacodynamics against two wild-type strains of *Staphylococcus aureus* by using the neutropenic mouse thigh infection model. The main outcome measure was the comparison of magnitudes and patterns of *in vivo* efficacy between generic products and the innovator. Except for one product exhibiting slightly greater concentration, vancomycin generics were undistinguishable from the innovator based on concentration and potency, protein binding, *in vitro* antibacterial effect determined by minimal inhibitory or bactericidal concentrations and TKC, and serum pharmacokinetics. Despite such similarities, all generic products failed *in vivo* to kill *S. aureus*, while the innovator displayed the expected bactericidal efficacy: maximum antibacterial effect (E_{max}) (95% confidence interval [CI]) was 2.04 (1.89 to 2.19), 2.59 (2.21 to 2.98), and 3.48 (2.92 to 4.04) versus

Despite such similarities, all generic products failed *in vivo* to kill *S. aureus*, while the innovator displayed the expected bactericidal efficacy

The World Health Organization (WHO) and all drug regulatory agencies (DRA) support commercialization of generic medicines because they control costs and are irreplaceable therapeutic options in countries lacking the innovator product (10, 41). WHO defines two products as therapeutically equivalent "if they are pharmaceutically equivalent and, after administration in the same molar dose, their effects with respect to both efficacy and safety are essentially the same, as determined from appropriate bioequivalence, pharmacodynamic, clinical, or *in vitro* studies" (41). Parenteral formulations, however, are not required to demonstrate therapeutic equivalence because it "may be considered self-evident" (41).

Such assumptions have never been challenged, but there are reasons to do so for parenteral antimicrobials. First, many antibacterials are secreted in nature by microorganisms, and industrial production of the active pharmaceutical ingredient (API) involves complex processes for biosynthesis, purification, and manufacture, hard to replicate even for the designer (22). Second, two molecules may look similar without being identical, displaying different biological effects (2). Third, makers of generic drugs do not necessarily know the nature, composition, and pharmacological interactions of excipients employed by the innovator to avoid polymorphs of the API (33). Fourth, while most medicines interact with the host only, antimicrobials also confront the invader organism, a dynamic triangle with numerous possibilities of biologic variation (3, 11, 17). Thus, mixing the exactitude of chemistry with the variability of biology could generate unpredictable effects in seriously sick patients, but differences between the generic and the innovator might pass unnoticed among the complexity of infectious diseases in which death is one of the expected outcomes.

Vancomycin (VAN) is a fermentation product of *Amycolatopsis orientalis*, an actinomycete discovered in 1955 in a dirt sample sent from Borneo to scientists at Eli Lilly (24, 27). Infusion reactions were common initially, but technology led the innovator to a safer product (8). Differences in composition are well known (36) and even advertised (Baxter promotional material; Baxter, Bogota, Colombia), but DRA worldwide support commercialization of vancomycin generics based on scant *in vitro* data claiming unaltered efficacy (9). After 50 years of unparalleled performance of vancomycin against Gram-positive pathogens, *in vitro* susceptibility has certainly decreased, and nowadays more than 20 clinical studies blame vancomycin for ineffectiveness and claim success for new, very expensive replacements (15). Without exception, all these studies fail to mention the manufacturer of the vancomycin products involved, despite the fact that most hospitals around

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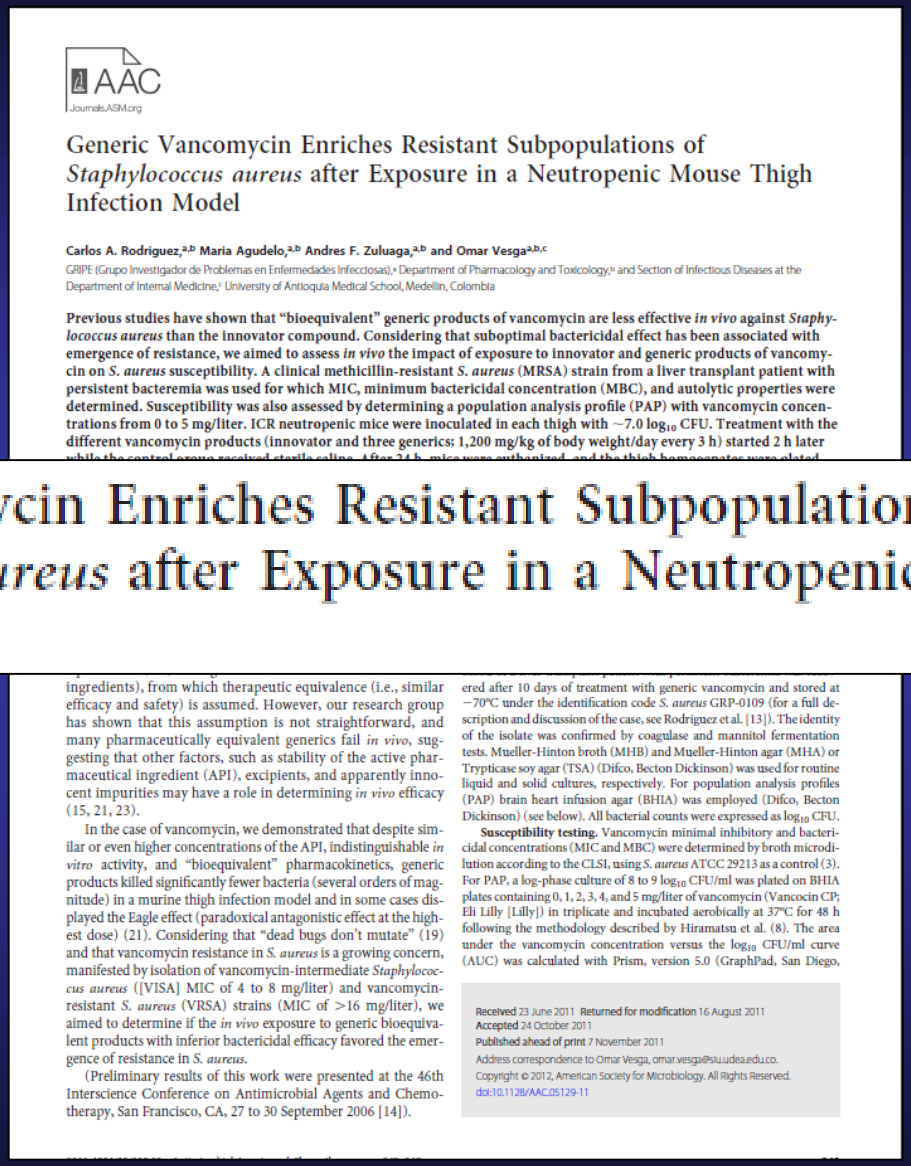
Vancomicina como Equivalente Farmacéutico mas no Terapéutico



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Generic Vancomycin Enriches Resistant Subpopulations of *Staphylococcus aureus* after Exposure in a Neutropenic Mouse Thigh Infection Model

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Previous studies have shown that "bioequivalent" generic products of vancomycin are less effective *in vivo* against *Staphylococcus aureus* than the innovator compound. Considering that suboptimal bactericidal effect has been associated with emergence of resistance, we aimed to assess *in vivo* the impact of exposure to innovator and generic products of vancomycin on *S. aureus* susceptibility. A clinical methicillin-resistant *S. aureus* (MRSA) strain from a liver transplant patient with persistent bacteremia was used for which MIC, minimum bactericidal concentration (MBC), and autolytic properties were determined. Susceptibility was also assessed by determining a population analysis profile (PAP) with vancomycin concentrations from 0 to 5 mg/liter. ICR neutropenic mice were inoculated in each thigh with ~7.0 $\log_{10}$ CFU. Treatment with the different vancomycin products (innovator and three generics: 1,200 mg/kg of body weight/day every 3 h) started 2 h later

Generic Vancomycin Enriches Resistant Subpopulations of *Staphylococcus aureus* after Exposure in a Neutropenic Mouse Thigh Infection Model

ingredients), from which therapeutic equivalence (i.e., similar efficacy and safety) is assumed. However, our research group has shown that this assumption is not straightforward, and many pharmaceutically equivalent generics fail *in vivo*, suggesting that other factors, such as stability of the active pharmaceutical ingredient (API), excipients, and apparently innocent impurities may have a role in determining *in vivo* efficacy (15, 21, 23).

In the case of vancomycin, we demonstrated that despite similar or even higher concentrations of the API, indistinguishable *in vitro* activity, and "bioequivalent" pharmacokinetics, generic products killed significantly fewer bacteria (several orders of magnitude) in a murine thigh infection model and in some cases displayed the Eagle effect (paradoxical antagonistic effect at the highest dose) (21). Considering that "dead bugs don't mutate" (19) and that vancomycin resistance in *S. aureus* is a growing concern, manifested by isolation of vancomycin-intermediate *Staphylococcus aureus* ([VISA] MIC of 4 to 8 mg/liter) and vancomycin-resistant *S. aureus* (VRSA) strains (MIC of >16 mg/liter), we aimed to determine if the *in vivo* exposure to generic bioequivalent products with inferior bactericidal efficacy favored the emergence of resistance in *S. aureus*.

(Preliminary results of this work were presented at the 46th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, 27 to 30 September 2006 [14]).

ered after 10 days of treatment with generic vancomycin and stored at −70°C under the identification code *S. aureus* GRP-0109 (for a full description and discussion of the case, see Rodriguez et al. [13]). The identity of the isolate was confirmed by coagulase and mannitol fermentation tests. Mueller-Hinton broth (MHB) and Mueller-Hinton agar (MHA) or Trypticase soy agar (TSA) (Difco, Becton Dickinson) was used for routine liquid and solid cultures, respectively. For population analysis profiles (PAP) brain heart infusion agar (BHIA) was employed (Difco, Becton Dickinson) (see below). All bacterial counts were expressed as $\log_{10}$ CFU.

Susceptibility testing. Vancomycin minimal inhibitory and bactericidal concentrations (MIC and MBC) were determined by broth microdilution according to the CLSI, using *S. aureus* ATCC 29213 as a control (3). For PAP, a log-phase culture of 8 to 9 $\log_{10}$ CFU/ml was plated on BHIA plates containing 0, 1, 2, 3, 4, and 5 mg/liter of vancomycin (Vancocin CP; Eli Lilly [Lilly]) in triplicate and incubated aerobically at 37°C for 48 h following the methodology described by Hiramatsu et al. (8). The area under the vancomycin concentration versus the $\log_{10}$ CFU/ml curve (AUC) was calculated with Prism, version 5.0 (GraphPad, San Diego,

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Antimicrobial Agents and Chemotherapy p. 243–247

Antimicrobial Therapy with Generic Meropenem is a Risk Factor for Mortality in ICU-acquired Infections by *Pseudomonas aeruginosa* in Colombia

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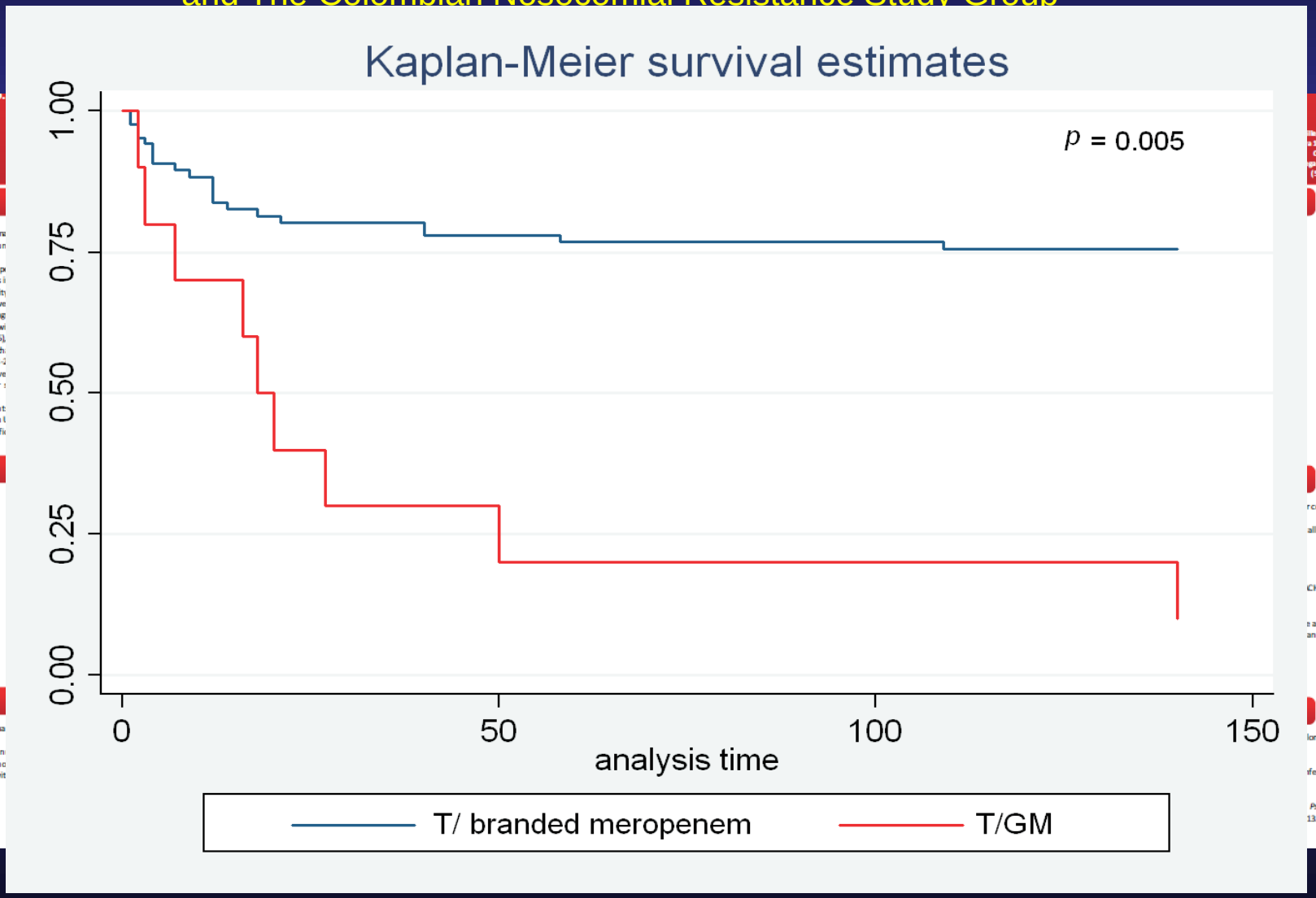
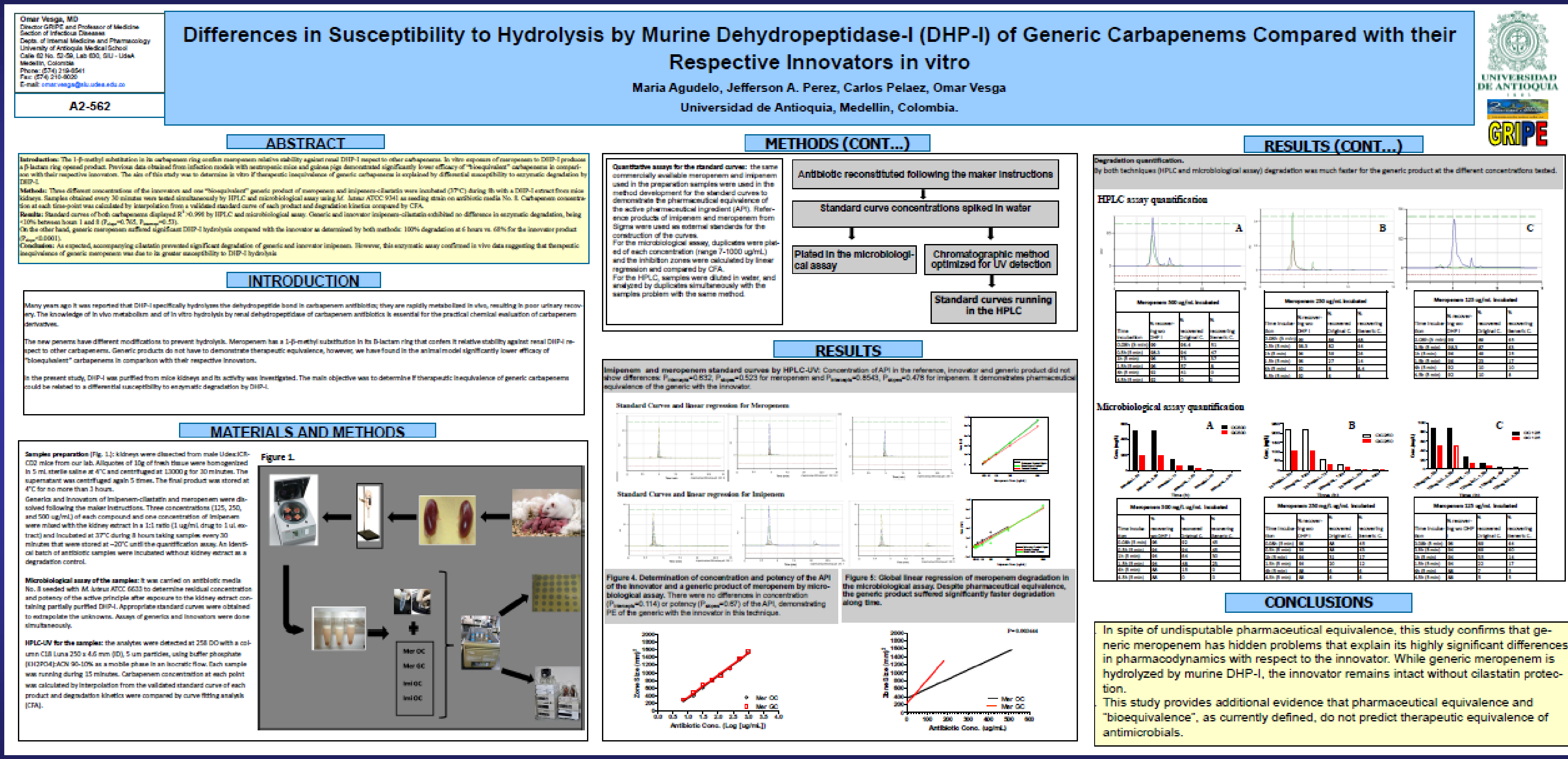
International Center for Medical Research & Training, CIDEIM, Cali, Colombia
and The Colombian Nosocomial Resistance Study Group



COMPARACIÓN ANTIBIÓTICOS GENÉRICOS VS INNOVADORES

Diferencias en la Susceptibilidad a Hidrólisis por Dehidropeptidasa Murina (DHP-I) de los Carbapenems Genéricos Comparados con el Respectivo Innovador in vitro

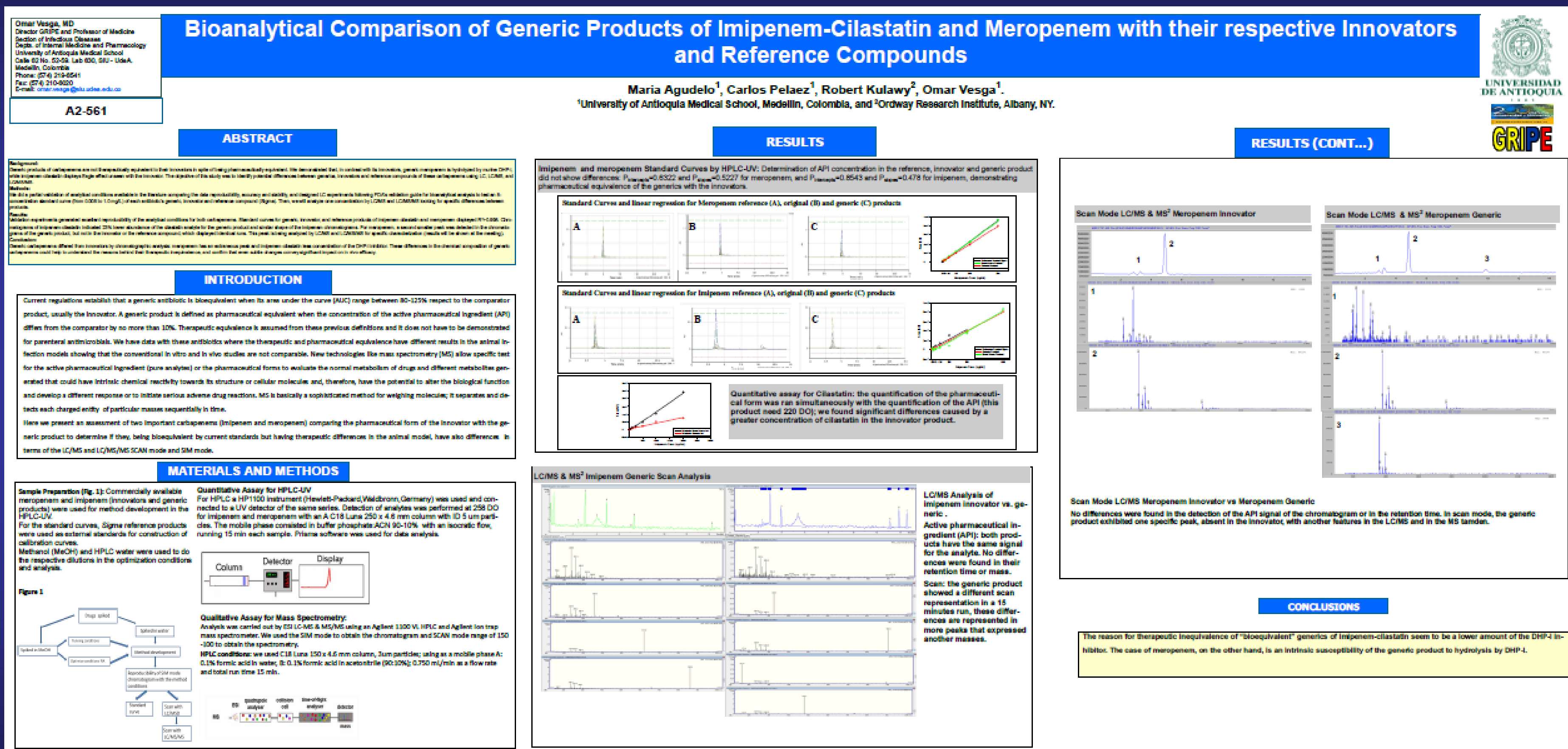


El Meropenem genérico presentó hidrólisis significativa por la DHP-I al comparar con el innovador.

Degradación a las 6 horas de 100% para el genérico vs. 68% para el producto innovador.

COMPARACIÓN ANTIBIÓTICOS GENÉRICOS VS INNOVADORES

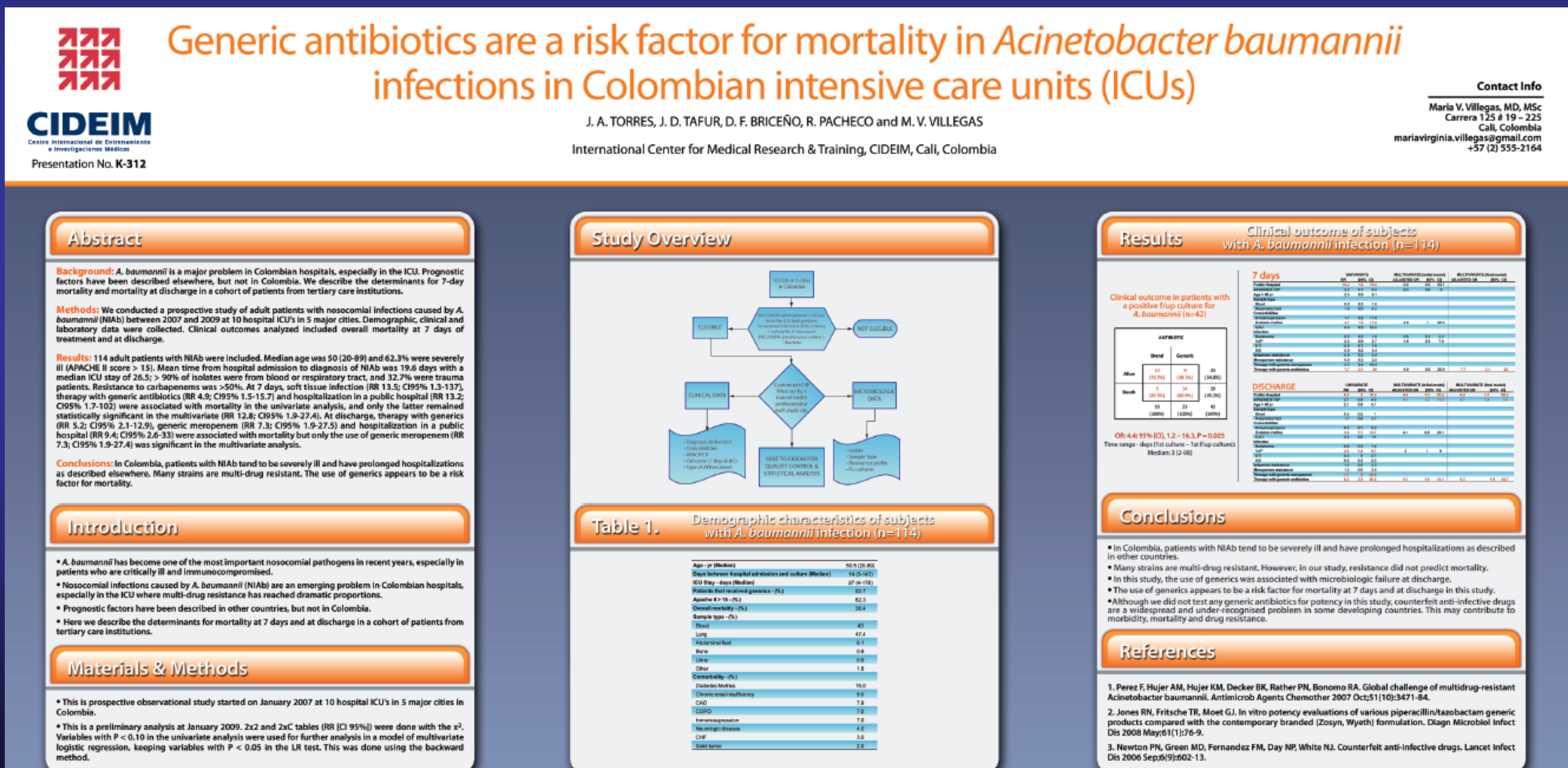
Comparación bioanalítica de Productos Genéricos de Imipenem-Cilastatina con sus Respectivos Compuestos Innovadores y de Referencia



- Los cromatogramas de Imipenem-Cilastatina mostraron 23% menos de Cilastatina en los productos genéricos.
- Estas diferencias podrían ayudar a entender las razones detrás de la inequivalencia terapéutica entre carbapenems innovadores y los genéricos.

Generics antibiotics are a risk factor for mortality in Acinetobacter baumanii infections in colombia intensive care units (UCI)

J.A.TORRES, J.D. TAFUR, F. BRICEÑO and M.V. VILLEGAS
International Center for Medical Research & Training, CIDEIM, Cali, Colombia



Comparación Medicamentos genéricos vs Innovadores

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ARTÍCULO ORIGINAL

Factores de riesgo asociados a mortalidad en infecciones relacionadas con la atención en salud en un hospital universitario de tercer nivel en Colombia

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Hospital Universitario del Valle 'Evaristo García', E.S.E., Cali, Colombia

Introducción. Las infecciones hospitalarias son una amenaza para la salud pública. A pesar de los esfuerzos para contenerlas, su incidencia sigue siendo grande y genera altos costos en la atención en salud.
Objetivo. Determinar los factores asociados a mortalidad en pacientes con diagnóstico de infecciones hospitalarias en nuestra institución.
Materiales y métodos. Se llevó a cabo un estudio prospectivo de cohortes entre enero y diciembre del 2011 por medio de la observación de 1.015 pacientes con diagnóstico de infección de acuerdo a los criterios del sistema de vigilancia hospitalaria sugeridos por los *Centers for Disease Control and Prevention* (CDC). Se excluyó a quienes no tenían cultivo microbiológico de la infección o habían tenido reingresos hospitalarios en menos de un año. Se evaluaron variables sociodemográficas y clínicas, perfiles de resistencia microbiológica y uso de antibióticos. La variable de desenlace fue la muerte. Se realizó un análisis de supervivencia para cada variable, estableciendo significación estadística con la prueba de *log-rank*, así como un análisis multivariado mediante regresión de Cox. Se consideraron significativos los valores de p menores de 0,05.

Conclusions: The use of generic molecules of antibiotics and inappropriate antibiotic treatments in patients with health care infections are modifiable factors to decrease mortality.

Conclusiones. El empleo de moléculas genéricas y el uso inadecuado de antibióticos en pacientes con infecciones hospitalarias son factores que pueden modificarse para disminuir la mortalidad.

Palabras clave: antibacterianos, infección hospitalaria, mortalidad.

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Mortality risk factors associated with healthcare infections in a tertiary level university hospital in Colombia

Introduction: Nosocomial infections are a public health threat. Despite multiple efforts, its incidence is still significant and it generates high costs in health care.
Objective: To determine risk factors associated with mortality in patients with healthcare infections in a tertiary level hospital in Colombia.
Materials and methods: A prospective cohort observational study was performed between January and December 2011. One thousand one hundred and fifteen patients with health care infections using the CDC definition criteria were included. Exclusion criteria were those patients with no microbiologic isolate associated with the infection or hospital readmissions in the last year. Socio-demographic and clinical variables, bacterial resistance profiles and antibiotic use were evaluated. Death was the primary outcome. Survival analysis for each variable was performed using statistical significance defined by the log-rank test. Multivariate and Cox regression analyses were done. Values of p less than 0.05 were considered statistically significant.
Results: Mean age was 43 years old (57% men and 47% women); 53% of patients had a medical condition and 47% surgical diagnosis; 54% of health care infections were surgical site infections and

Contribución de los autores:
Los autores contribuyeron en la misma proporción en la elaboración del planteamiento del problema, la definición de la metodología y el tipo de estudio y el establecimiento de objetivos. De igual forma, aportaron a la recolección y elaboración de la base de datos, el análisis estadístico de la información, la redacción de los resultados y la discusión.

Christian José Pallares, Biomédica 2014;34(Supl.1):148-55 - Factores asociados a mortalidad en infecciones hospitalarias

¿Porqué Analizar los Genéricos?

Predicting the clinical efficacy of generic formulations of ceftriaxone.

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Time above MIC (T>MIC) is regarded as the best pharmacokinetic/pharmacodynamic (PK/PD) parameter for predicting the clinical efficacy of cephalosporins. The concentration of non-protein-bound proprietary ceftriaxone (Rocephin, Roche) in body fluids exceeds this PK/PD criterion for the treatment of Streptococcus pneumoniae respiratory infections. However, the pharmaceutical quality of several generic products may be inferior to Rocephin. We have calculated the variations in fluid concentrations of 34 generic formulations of ceftriaxone and, by mathematical modelling, the implications for attainment of recommended PK/PD criteria, specifically: Treatment of S. pneumoniae infections based on the time that non-protein-bound ceftriaxone concentration in pleural fluid exceeds the CLSI (NCCLS) breakpoint of 4 mg/L for identification of resistant isolates. Impact upon Monte Carlo simulations in plasma for the treatment of S. pneumoniae infections based on T>MIC for 50% dosing interval. Rocephin exceeded the required PK/PD parameters at the mean and two standard deviation levels in both investigations. In contrast, most generic products failed to achieve required PK/PD levels in both investigations. As a consequence, some generic formulations of ceftriaxone may increase risks of clinical failure and/or emergence of resistant isolates.

¿Porqué Analizar los Genéricos?

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DIAGNOSTIC MICROBIOLOGY AND INFECTIOUS DISEASE

In vitro potency evaluations of various piperacillin/tazobactam generic products compared with the contemporary branded (Zosyn®, Wyeth) formulation

Ronald N. Jones[a,b,*], Thomas R. Fritsche[a], Gary J. Moet[a]

Abstract

Twenty-three generic intravenous piperacillin/tazobactam products were compared for in vitro activity to the branded formulation (Zosyn®, Wyeth, Philadelphia, PA) by disk diffusion and incremental broth microdilution assay methods. All but 1 lot demonstrated significantly decreased activity (−5 to −35%), necessitating further investigations regarding the chemical purity, potency, and therapeutic equivalence of these products worldwide. The average −16% activity across all generic lots was equivalent to underdosing piperacillin/tazobactam by 2.6 g daily for serious clinical infections (4.5 g Q8 h).

Keywords: Piperacillin/tazobactam; Generics; Branded agents; Activity in vitro

Piperacillin/tazobactam is a widely used intravenous penicillin/β-lactamase inhibitor combination delivered as an 8:1 ratio, usually 4 g of piperacillin and 0.5 g of tazobactam every 6 h (Jones and Barry, 1989; Knirk et al., 1989; Package Insert, 2007). Alternative dosing vials may contain 2 or 3 g of piperacillin and 0.25 or 0.375 g of tazobactam (Package Insert, 2007). The original worldwide sponsor/developer of this product (trade name Zosyn® or Tazocin®) was Wyeth Pharmaceuticals, Philadelphia, PA, and the patent rights to this combination vary geographically. Recently, generic formulations containing piperacillin/tazobactam have been introduced into various global markets but have been questioned as to bioequivalence when compared with the branded product (Yu et al., 2006). Also, the original sponsor's product (Zosyn®) has been reformulated to provide improved quality using proprietary techniques (Package Insert, 2007).

We studied "nonbranded" generic formulation samples of piperacillin/tazobactam for antimicrobial potency against 4 selected assay organisms (replicate testing) and directly compared them with the current Zosyn® formulation (Package Insert, 2007) purchased from a drug wholesale distributor in the United States. Generic piperacillin/tazobactam products (26 samples from 23 lots) were forwarded to JMI Laboratories, North Liberty, IA, from China (2 samples), Greece (3), India (5), Jordan (1), Philippines (10), Portugal (1), Spain (2), and Taiwan (2).

Reference susceptibility testing methods were applied as described by the Clinical and Laboratory Standards Institute (CLSI) M2-A9, M7-A7, and M100-S17 (CLSI, 2006a, 2006b, 2007). Broth microdilution tests (CLSI, 2006a) used reconstituted product sample vial contents as the stock solution to prepare panels having expanded log$_2$ dilution schedules over the MEC range of 32 to 0.188 μg/mL. The complete dilution schedule was 32, 28, 24, 20, 16, 14, 12, 10, 8, 7, 6, 5, 4, 3.5, 3, 2.5, 2, 1.75, 1.5, 1.25, 1, 0.875, 0.75, 0.625, 0.5, 0.438, 0.375, 0.313, 0.25, 0.219, 0.188, and a growth control. Four assay strains were used (Table 2), each having a reference piperacillin/tazobactam MEC between 1 and 4 μg/mL, 0.25 to 8 μg/mL using CLSI quality control

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¿Porqué Analizar los Genéricos?

In vitro potency evaluations of various piperacillin/tazobactam generic products compared with the contemporary branded (Zosyn(R), Wyeth) formulation.

Jones RN, Fritsche TR, Moet GJ.

JMI Laboratories, North Liberty, IA 52317, USA; Tufts University School of Medicine, Boston, MA 02111, USA.

Twenty-three generic intravenous piperacillin/tazobactam products were compared for in vitro activity to the branded formulation (Zosyn(R), Wyeth, Philadelphia, PA) by disk diffusion and incremental broth microdilution assay methods. All but 1 lot demonstrated significantly decreased activity (-5 to -35%), necessitating further investigations regarding the chemical purity, potency, and therapeutic equivalence of these products worldwide. The average -16% activity across all generic lots was equivalent to underdosing piperacillin/tazobactam by 2.6 g daily for serious clinical infections (4.5 g Q6 h).

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¿Porqué Analizar los Genéricos?

BJCP British Journal of Clinical Pharmacology

DOI:10.1111/j.1365-2125.2009.03399.x

Lack of pharmacokinetic bioequivalence between generic and branded amoxicillin formulations. A post-marketing clinical study on healthy volunteers

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Keywords
amoxicillin, bioequivalence, branded formulation, generic formulation, interchangeable drug, pharmacokinetics

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The mean pharmacokinetic profiles showed that the AUC value of branded amoxicillin was 8.5 and 5.4% greater than that estimated for generic A and B, respectively.

- Generic medicinal products are 'copies' of patented drugs and can be marketed at low cost following patent expiration of the brand-name preparations.
- Although the development of generic medicinal products is regulated by specific guidelines, a number of issues and concerns continue to undermine the confidence of physicians and patients in generic drugs.

WHAT THIS STUDY ADDS

- The present findings open interesting perspectives for the discussion of the quality of generic drugs in the postmarketing setting.
- In particular, our trial shows that postmarketing evaluation of bioequivalence between branded amoxicillin and its generic copies might result in lack of interchangeability.

AIMS
There are concerns about the quality of generic drugs in the postmarketing setting. The aim was to establish whether two generic formulations of amoxicillin, available on the Italian market, fulfil the criteria for clinical pharmacokinetic bioequivalence *vs.* the branded drug.

METHODS
Two generic amoxicillin products (generic A and B) were selected among four fast-release tablet formulations available on the Italian market. Twenty-four healthy adult volunteers of either sex participated to a single-dose, randomized, three-treatment, crossover, single-blind bioequivalence study designed to compare generic A and B with branded amoxicillin. Plasma samples were collected at preset times for 24 h after dosing, and assayed for amoxicillin levels by high-performance liquid chromatography.

RESULTS
Ninety percent confidence intervals of AUC ratios were 0.8238, 1.0502 (ratio 0.9302) and 0.8116, 1.1007 (ratio 0.9452) for generic A and B *vs.* branded amoxicillin, respectively. Ninety percent confidence intervals of C_{max} ratios were 0.7921, 1.0134 (ratio 0.8960) and 0.8246, 1.1199 (ratio 0.9610) for generic A and B *vs.* branded amoxicillin, respectively. The mean pharmacokinetic profiles showed that the AUC value of branded amoxicillin was 8.5 and 5.4% greater than that estimated for generic A and B, respectively. Few adverse events were recorded; these were not serious and occurred without apparent relationship to any specific amoxicillin formulation.

CONCLUSIONS
These results indicate that one of the two marketed amoxicillin generics analysed in the present study is not bioequivalent to the brand leader product for C_{max} on the basis of single-dose pharmacokinetic assessment.

British Journal of Clinical Pharmacology 2009, 34, 68:1 34-42

¿Porqué Analizar los Genéricos?

ANALYTICAL SCIENCES DECEMBER 2009, VOL. 25 1483

Notes

Terahertz Absorption Spectra of Original and Generic Ceftazidime

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The absorption spectra of ceftazidime and its generic versions (Modacin, Mosyl, and Mobenzocin) have been measured by terahertz time domain spectroscopy (THz-TDS). Differences in the THz absorption were observed between the original and generic versions. The results show small, but significant differences in the states of ceftazidime hydrate between the original and generic versions.

have been reported in many fields, such as medical diagnosis, pharmaceutical analysis, and security enhancement.[1-8] THz time domain spectroscopy (THz-TDS) using THz pulses generated by femtosecond laser pulses is useful for measuring the optical properties in wave number (frequency) ranges below 100 cm^{-1} (3 THz), and gives a better signal-to-noise ratio than far-infrared Fourier transform (FIR FT-IR) spectroscopy.[9,10] Absorption spectra in the THz range are very sensitive to differences in the crystal structure,[11] and are applied to study the polymorphs of medicines.[7] THz spectra are also sensitive to the states of assembled molecules. The assembly state is though to differ between optical isomers. In our previous paper,[12] we reported on the measurement of the absorption spectra of polycrystalline D-, L-, and DL-tartaric acid by THz-TDS. We found that the absorption spectra did not significantly differ between D- and L-tartaric acid. On the other hand, the absorption spectra differed remarkably between L- (or D-) and DL-tartaric acid. We demonstrated that a quantitative analysis of L-tartaric acid in mixture of L- and DL-tartaric acid is possible by using the partial least-squares method for their THz-TDS spectra. Similar results were reported between L- (or D-) and DL-alanine molecular crystal in a powder form.[13]

In this paper, we report on the difference between the THz spectra of original and generic versions of ceftazidime. We also mention here the possibility of applying THz-TDS to distinguish between original and generic medicines and to evaluate their stability.

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The absorption spectra were measured in a frequency range from near zero to 3 THz using a standard THz-TDS setup.[14] The pump source was a mode-locked Ti:sapphire laser, with a repetition rate of 82 MHz, a pulse of around 100 fs, and a center wavelength of around 800 nm. The emitter and detector were a dipole-type photoconductive antenna on low-temperature grown GaAs (LT-GaAs) substrates.[15] The antennae were excited and triggered by laser pulses with an average power of 10 mW. The bias voltage applied to the emitter photoconductive antenna was 20 $V_{p\text{-}p}$ and was modulated at 53 kHz. The THz radiation from the emitter was collected and focused on the sample by a parabolic mirror. The THz radiation transmitted through the sample was collected and focused by another parabolic mirror onto the detector photoconductive antenna. Hyper-spherical Si substrate lenses were used for both the emitter and the detector antennae to reduce the total reflection in the GaAs substrates and to increase the beam collection efficiency. The photoconductive current signal was detected with a lock-in amplifier, and its time-domain signal was obtained by scanning the optical delay of the probe pulse. By Fourier transforming the time-domain signal, the amplitude spectra were obtained. To reduce the absorption due to water vapor in the ambient air, the THz beam path was filled with dry air.

Medicine

Original and generic versions of ceftazidime hydrate ($C_{22}H_{22}N_6O_7S_2$, the structure is in Fig. 1), named Modacin from GlaxoSmithKline Co. Ltd., Mosyl from Sawai Pharmaceutical Co. Ltd., and Mobenzocin from Taiyo Yakuhin Co. Ltd., were used in this study. Modacin is the original medicine, while

Analytical Sciencies December 2009, vol 25 1483-85

“Cualquier ganancia potencial del uso de medicinas genéricas se justifica solamente si esas formas de presentación tienen el mismo valor terapéutico que el producto con marca registrada”

Drug and Ther Bull 1997;35 #2

Productos de Marca vs. Genéricos

Es muy difícil la reproducción exacta de un producto farmacéutico, por lo que se habla de:

1. Producto original, innovador o de marca.

2. Producto multifuente, copia o “genérico”.

El proceso de aprobación de un genérico

Aplicación Abreviada de Medicamento Nuevo (ANDA) requiere:

- La misma forma de dosis
- La misma ruta de administración
- La misma cantidad de ingrediente activo
- Cumplir las guías de buenas prácticas de manufactura
- Estudios de bioequivalencia

ANDA: Abbreviated New Drug Application

El proceso de aprobación de un genérico

La aplicación Abreviada de Medicamento Nuevo (ANDA), **NO** requiere:

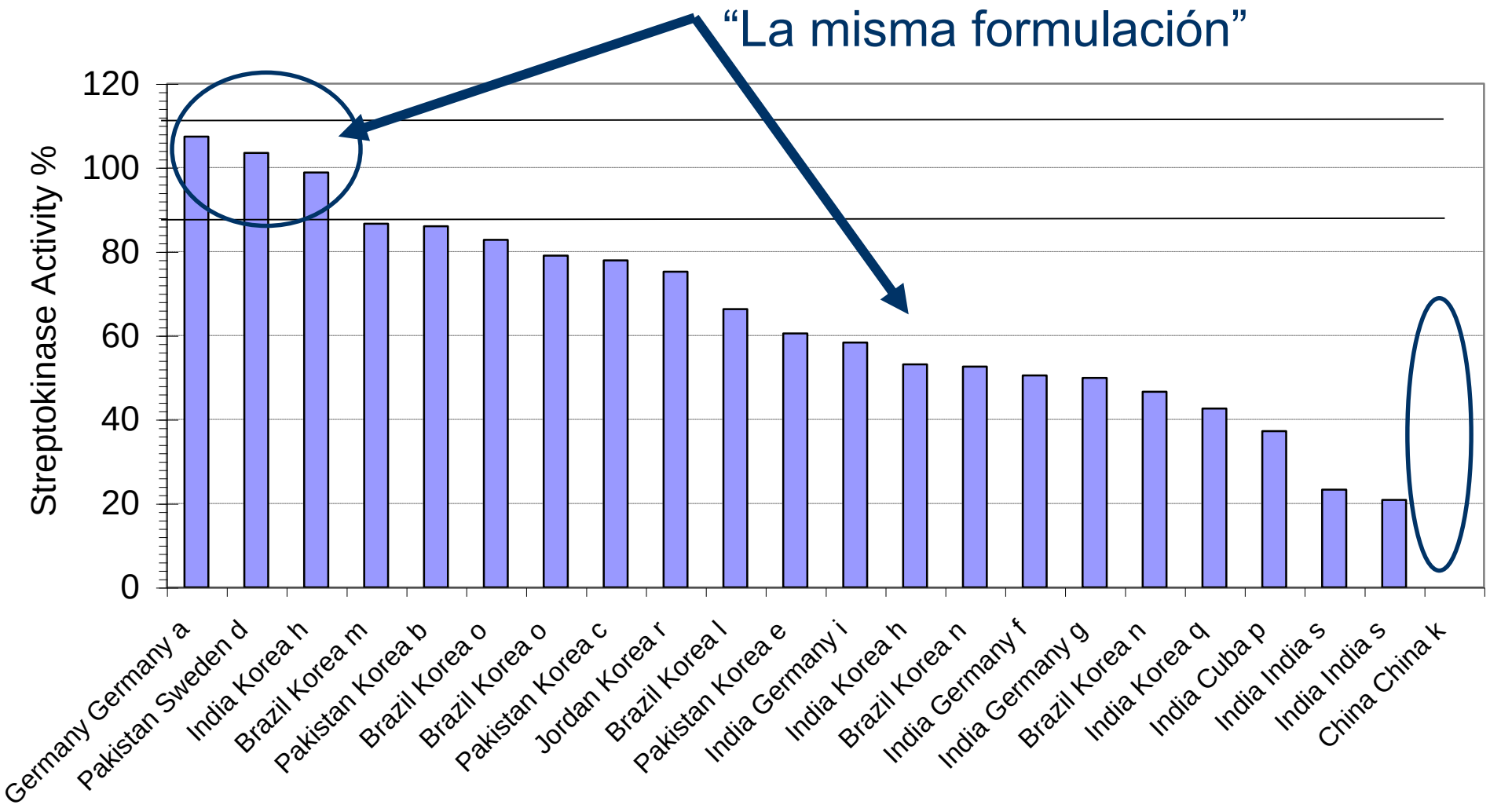
- Estudios de seguridad
- Estudios de eficacia
- Los mismos excipientes
- Demostración de equivalencia terapéutica

ANDA: Abbreviated New Drug Application

Excipientes

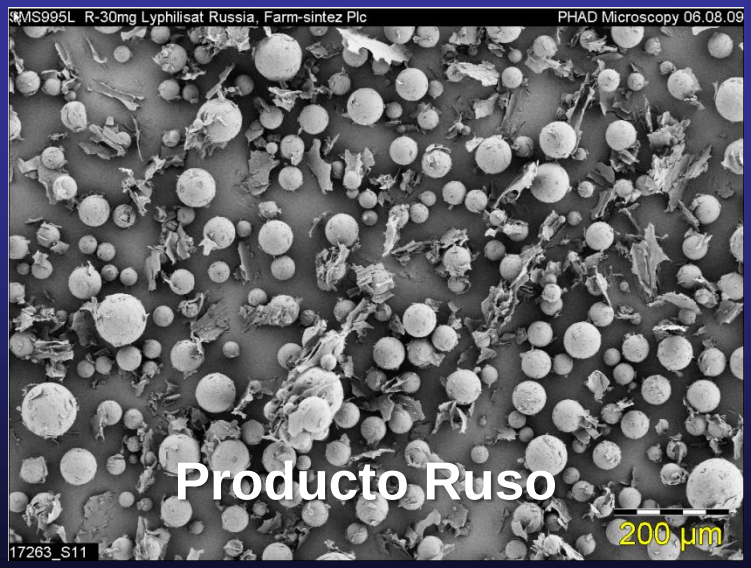
- Cambios en los excipientes pueden alterar:
  - La estabilidad de la formulación
  - Las interacciones medicamentosas
  - Los desenlaces clínicos
- Se necesita considerar
  - Los excipientes empleados
  - La cantidad usada
  - La calidad de los excipientes

Actividad de la estreptokinasa



Hermentin *et al*, European Heart Journal (2005) 26, 933–940

Microscopía electrónica de octreotide y copias



Cortesia Dr. Helmut Boehnke, Executive Director Technical Research & Development Cambridge,US June 28, 2010

Productos de Marca vs. Genéricos

Propiedades Polimórficas de los Fármacos

Estas diferencias influyen en:

Solubilidad y la velocidad de disolución:

Afecta la biodisponibilidad

Estabilidad del estado sólido:

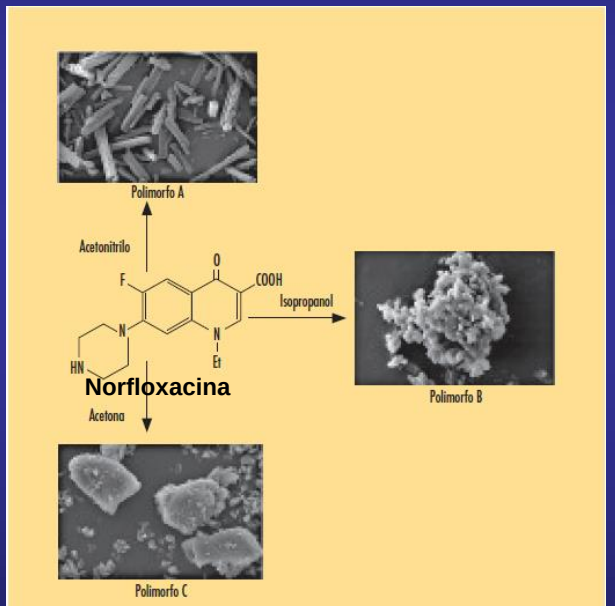
Afecta la potencia

Características de deformación:

Afecta la compactibilidad

Tamaño de partícula y forma:

Afecta la densidad del polvo



Diferentes morfologías observadas a través de microscopia electrónica de rastreo (SEM), correspondientes a los tres polimorfos del antibiótico Norfloxacino obtenidos por cristalización[17]

http://www.pcb.ub.edu/plataformes-mixtes/web/docs/4-IndustriaFarmaceutica.pdf

El Farmacéutico n.º 373 • **1 abril 2007**

Productos de Marca vs. Genéricos

Incluso las características del envase pueden llegar a afectar la potencia y eficacia de algunos antibióticos.

Registro INVIMA de Moxifloxacina Innovadora

Datos Generales del Producto

Expediente	19902058	**Nombre producto**	**AVELOX 400 MG COMPRIMIDOS**				
Registro Sanitario	INVIMA 2009 M-13626-R1	**Vencimiento**	2020/02/08	**Modalidad**	IMPORTAR Y VENDER	**Estado Registro**	Vigente
Observaciones	LAS CONTRAINDICACIONES Y ADVERTENCIAS DEBEN APARECER EN LAS ETIQUETAS Y EMPAQUES, MAS LA FECHA DE VENCIMIENTO Y EL NUMERO DE LOTE. EL TITULAR Y FABRICANTE AUTORIZADO EN EL REGISTRO SANITARIO, ADQUIEREN LA OBLIGACIÓN DE MANTENER LAS BUENAS PRACTICAS DE MANUFACTURA DURANTE LA VIGENCIA DEL REGISTRO SANITARIO						

Datos de Interés del Medicamento

Forma Farmaceutica	TN - TABLETAS CON O SIN RECUBR. QUE NO MODIFIQUEN LIBERACION FARMACO			**Franja**	VERDE
Indicaciones	AVELOX 400 MG COMPRIMIDOS CON CUBIERTA PELICULAR ESTÁ INDICADO PARA EL TRATAMIENTO DE LAS INFECCIONES BACTERIANAS SIGUIENTES CAUSADAS POR CEPAS SENSIBLES: - INFECCIONES DE LAS VÍAS RESPIRATORIAS: EXACERBACIÓN AGUDA DE BRONQUITIS CRÓNICA NEUMONÍA ADQUIRIDA EN LA COMUNICAD (NAC), INCLUYENDO LAS NAC CAUSADAS POR CEPAS MULTIRRESISTENTES SINUSITIS AGUDA - INFECCIONES NO COMPLICADAS DE LA PIEL Y ESTRUCTURAS DÉRMICAS. - ENFERMEDAD INFLAMATORIA PÉLVICA NO COMPLICADA (ES DECIR, INFECCIONES DEL APARATO GENITAL FEMENINO SUPERIOR, INCLUYENDO SALPINGITIS Y ENDOMETRITIS). - INFECCIONES COMPLICADAS DE LA PIEL Y ESTRUCTURAS DÉRMICAS (INCLUYENDO INFECCIONES DEL PIE DIABÉTICO). -INFECCIONES INTRAABDOMINALES COMPLICADAS, INCLUIDAS INFECCIONES POLIMICROBIANAS COMO ABSCESOS.				
Contraindicaciones	HIPERSENSIBILIDAD CONOCIDA A CUALQUIERA DE LOS COMPONENTES O A OTRAS QUINOLONAS. CONTRAINDICADO EN NIÑOS, ADOLESCENTES EN FASE DE CRECIMIENTO, EMBARAZO Y LACTANCIA. ADMINISTRESE CON PRECAUCION EN PACIENTES CON SINDROMES CONVULSIVOS Y ALTERACIONES SICOTICAS.				
Inserto ? ☑	**Vida Util**	60 MESES	**Condicion Venta**	CON FORMULA FACULTATIVA	Generico ? ☐
Via Administracion	PO - PO				

www.invima.gov.co

Registro INVIMA de Moxifloxacina Multifuente

Datos Generales del Producto

Expediente	19964309	**Nombre producto**	**MOXIFLOXACINA 400 MG TABLETAS RECUBIERTAS**				
Registro Sanitario	INVIMA 2006M-0005571	**Vencimiento**	2016/05/04	**Modalidad**	FABRICAR Y VENDER	**Estado Registro**	En tramite renov
Observaciones	LAS CONTRAINDICACIONES, ADVERTENCIAS, LA FECHA DE VENCIMIENTO Y EL NUMERO DE LOTE DEBEN APARECER EN LAS ETIQUETAS Y EMPAQUES. EL TITULAR Y FABRICANTE AUTORIZADO EN EL REGISTRO SANITARIO, ADQUIEREN LA OBLIGACIÓN DE MANTENER LAS BUENAS PRACTICAS DE MANUFACTURA DURANTE LA VIGENCIA DEL REGISTRO SANITARIO.						

Datos de Interés del Medicamento

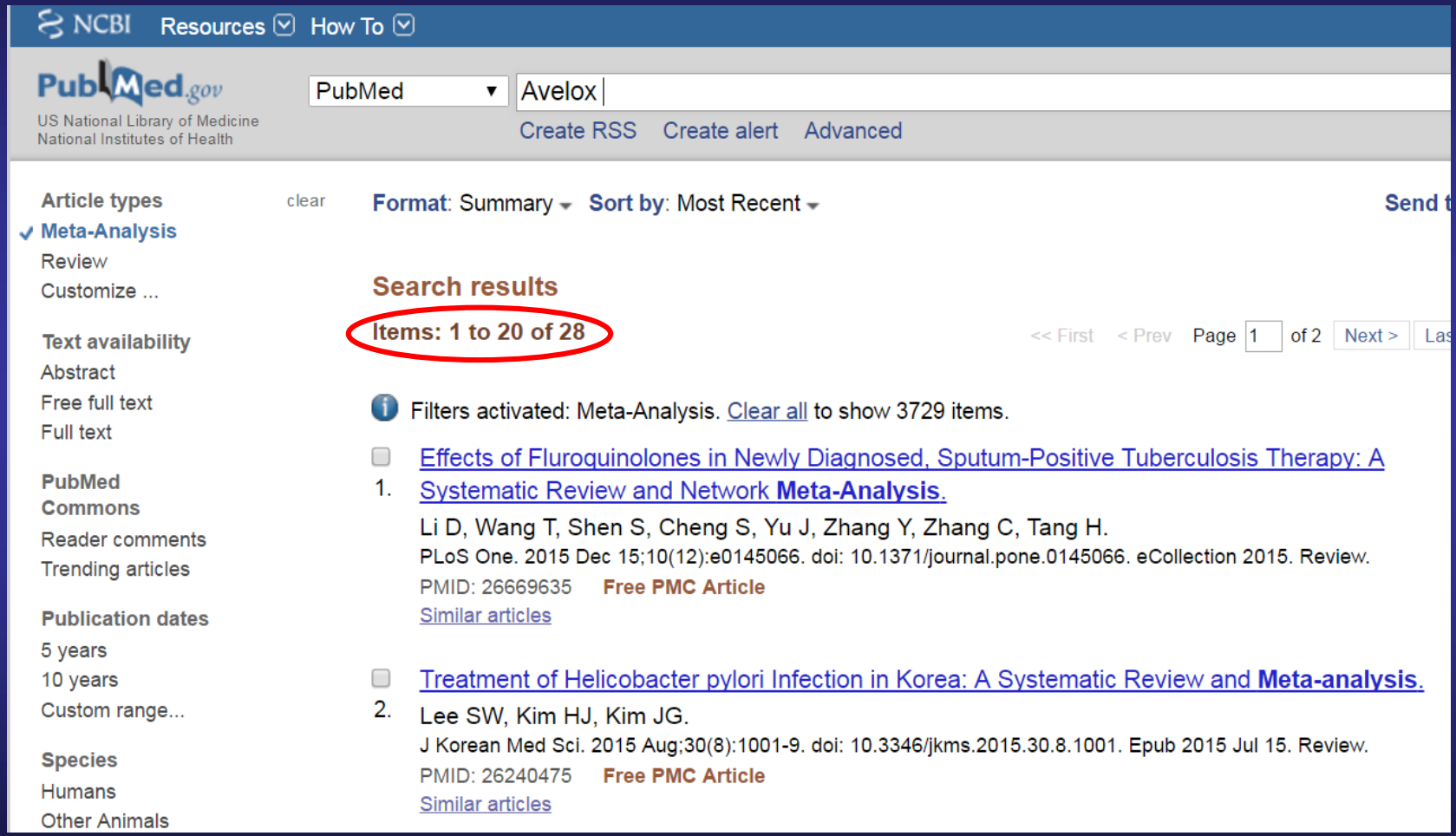
Forma Farmaceutica	TN - TABLETAS CON O SIN RECUBR. QUE NO MODIFIQUEN LIBERACION FARMACO			**Franja**	NINGUNA
Indicaciones	TRATAMIENTO ALTERNATIVO DE INFECCIONES BACTERIANAS DEL TRACTO RESPIRATORIO EN PACIENTES MAYORES DE 18 AÑOS.				
Contraindicaciones	HIPERSENSIBILIDAD A CUALQUIERA DE SUS COMPONENTES U OTRAS QUINOLONAS. CONTRAINDICADO EN NIÑOS ADOLESCENTES EN FASE DE CRECIMIENTO. EMBARAZO Y LACTANCIA. ADMINISTRESE CON PRECAUCION EN PACIENTES CON SINDROME CONVULSIVOS Y ALTERACIONES SICOTICAS. RIESGO DE EXACERBACIÓN DE LA MIASTENIA GRAVE ASOCIADA A FLUOROQUINOLONAS.				
Inserto ? ☐	**Vida Util**	DOS 2 AÑOS	**Condicion Venta**	CON FORMULA FACULTATIVA	Generico ? ☑
Via Administracion	PO - PO				

www.invima.gov.co

Publicaciones en PubMed de Moxifloxacina Innovadora

www.pubmed.com

Publicaciones en PubMed de Moxifloxacina Innovadora



www.pubmed.com

Comparación Entre Antibióticos Genéricos vs Innovadores

Incidencia de infecciones postquirúrgicas en pacientes sometidos a bypass coronario (CABG) recibiendo profilaxis antimicrobiana con cefuroxima original o genérica.

J Infect. 2008 Jan;56(1):35-9. Epub 2007 Nov 5.

Incidence of postoperative infections in patients undergoing coronary artery bypass grafting surgery receiving antimicrobial prophylaxis with original and generic cefuroxime.

Mastoraki E, Michalopoulos A, Kriaras I, Mouchtouri E, Falagas ME, Karatza D, Geroulanos S.

Department of Surgical Intensive Care Unit, Onassis Cardiac Surgery Center, 356 Sygrou Ave, 17674 Athens, Greece.

Erratum in

J Infect. 2008 May;56(5):399. Falagas, Matthew [corrected to Falagas, Matthew E].

Abstract

OBJECTIVE: The aim of this study was to compare the incidence of post-operative infections in patients undergoing coronary artery bypass grafting (CABG) surgery who received generic cefuroxime (gCFX) instead of original cefuroxime (oCFX) as antimicrobial prophylaxis.

METHODS: The study had two parts, a prospective and a retrospective one (4 weeks with oCFX followed by 4 weeks with gCFX in each part; total study duration of 16 weeks). The studied patient population was 618 consecutive adult patients who underwent on pump CABG surgery. Patients were divided into two groups according to type of formulation they received: 313 patients received oCFX and 305 gCFX.

RESULTS: Eight (2.5%) and 39 (12.8%) patients in the oCFX and gCFX group, respectively, developed postoperative infections ($p<0.001$). There were 6 (1.9%) surgical site infections in the oCFX group and 31 (10.1%) in the gCFX group ($p<0.001$). Bacteremia occurred in 2 (0.6%) patients in the oCFX group and in 8 (2.6%) patients in the gCFX group ($p=0.1$). In addition, septic shock occurred in 6 cases (2.0%, $p=0.04$) and multiple organ failure in another 4 patients (1.3%, $p=0.1$) in the gCFX group. The most common pathogens isolated were Gram-positive cocci in both groups.

CONCLUSIONS: This study revealed a higher incidence of postoperative infections in adult patients undergoing CABG surgery receiving gCFX compared to oCFX as antimicrobial prophylaxis. The findings of our study provide additional evidence regarding the problem of substandard drugs, in our case a formulation of a generic antibiotic, even in developed countries. ULTRAMINI-SUMMARY: The incidence of post-operative infections following CABG surgery was higher in adult patients receiving generic instead of original cefuroxime as antimicrobial prophylaxis. The findings of our study provide additional evidence regarding the problem of substandard drugs, in our case a formulation of a generic antibiotic, even in developed countries.

313 pacientes recibieron cefuroxima original y 305 la cefuroxima genérica.

Desarrollaron infecciones postquirúrgicas 8 pacientes (2.5%) con cefuroxima original y 39 (12.8%) con el genérico.

Mastoraki E, Michalopoulos A, Kriaras I, Mouchtouri E, Falagas ME, Karatza D, Geroulanos S. Infect. 2008 Jan;56(1):35-9. Epub 2007 Nov 5.

Los Países Difieren en los Requisitos Aprobatorios

Los requisitos de registro para genéricos emplean generalmente los estudios del producto de referencia	EMA[1]	FDA[2]	Países en desarrollo
Pruebas de bioadisponibilidad y bioequivalencia con supervisión del comité de etica	✓	✓	Requerimientos poco comunes En algunos países no se requieren
Evaluación de la calidad del ingrediente activo incluyendo la identificación y cuantificación de las impurezas (ej. Impurezas genotóxicas)	✓	✓	
Pre and post aprobación cuando cambia la fuente del ingrediente activo	✓	✓	
La identificación y cualificación de los productos de degradación en el medicamento, no solo pruebas de estabilidad	✓	✓	No se requiere
BPM estrictas e inspecciones de campo a las plantas productoras del medicamento	✓	✓	Algunos países lo solicitan
Pruebas de laboratorio al producto terminado	✓	✓	Algunos países lo solicitan

[1] EMA = European Medicines Agency
[2] FDA = US. Food and Drug Administration


Marcas
Copias
✓ Innovación
✓ Estudios
✓ Pruebas
✓ Estándares
✗ Precio
✓ Precio
✓ Accesibilidad
✓ Competencia
✗ Costos indirectos
✗ Falta de estudios

Similar ≠ Lo mismo

≠

Similar significa diferente

Estereoisomería y Antibióticos

Journal of Antimicrobial Chemotherapy (1996) **37**, 7–32

Review

Drug chirality: a consideration of the significance of the stereochemistry of antimicrobial agents

A. J. Hutt[a] and J. O'Grady[b]

[a]*Department of Pharmacy, King's College London, Manresa Road, London SW3 6LX;*
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Approximately 25% of drugs are marketed as either racemates or mixtures of

The significance of stereoisomerism in antimicrobial agents is addressed in this review using examples drawn from the β-lactams, as being representative of semisynthetic agents, and the quinolones, as examples of synthetic agents.

epimerization, e.g. carbenicillin, in the case of others there are potential advantages with the use of single isomers, e.g. ofloxacin. However, in the case of latamoxef, a compound which undergoes in-vivo epimerization with a half-life similar to its apparent serum elimination half-life the situation is by-no-means clear cut. These agents emphasise the importance of considering each compound individually, i.e. on a case-by-case basis, before deciding to use a single isomer or stereoisomeric mixture.

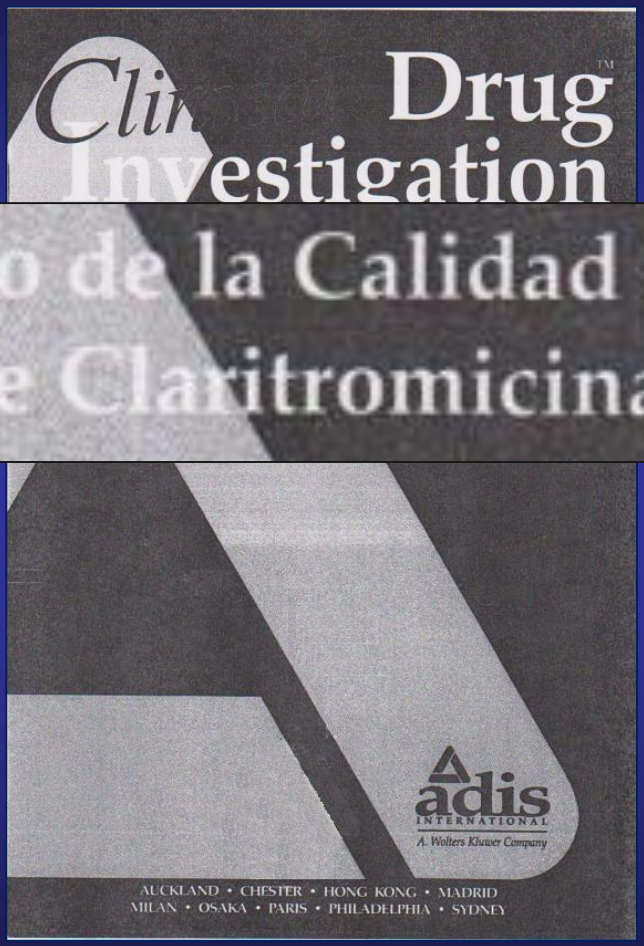
Introduction

Over the last ten years drug chirality has become a 'big issue', not only within the scientific and medical communities but also in the 'quality' lay press (Hawkes, 1993; Moran, 1993) and popular scientific press (Mason, 1984; Matteson, 1991). This interest in chirality has arisen as a result of recent advances in the areas of stereoselective synthesis and stereospecific analysis of chiral drug molecules. As a result of these advances, and the increasing realisation of the significance of the pharmacodynamic and pharmacokinetic differences between the enantiomers of chiral drugs, there has been increasing concern over the use of racemates, and other stereoisomeric mixtures, in therapeutics. The use of such mixtures may present problems, particularly if the adverse affects, or toxicity, of the administered agent is associated with the less active, or inactive, isomer or does not show stereoselectivity.

0305–7453/96/010007 + 26 $12.00/0

Journal of Antimicrobial Chemotherapy (1996) **37**, 7–32

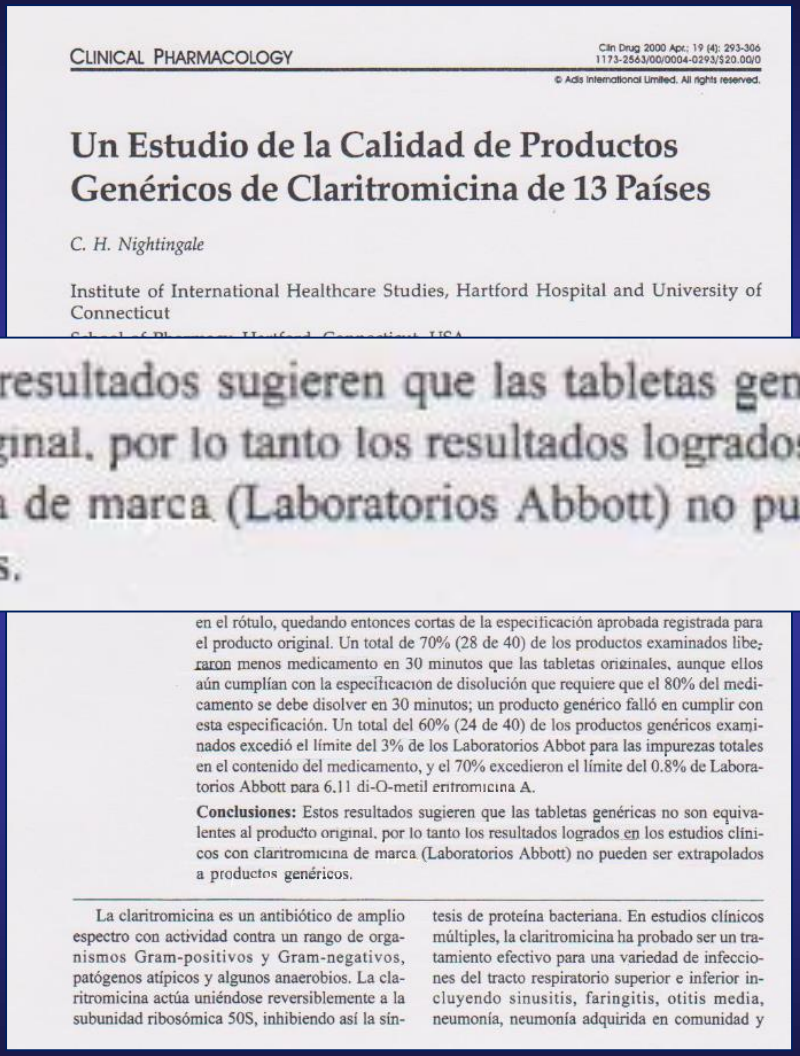
Productos de Marca vs. Genéricos



Un Estudio de la Calidad de Productos Genéricos de Claritromicina de 13 Países

Clinical Drug Investigation. April 2000 Vol19 No 4 (pp 293-306)

Productos de Marca vs. Genéricos



CLINICAL PHARMACOLOGY

Clin Drug 2000 Apr; 19 (4): 293-306
1173-2563/00/0004-0293/$20.00/0

Un Estudio de la Calidad de Productos Genéricos de Claritromicina de 13 Países

C. H. Nightingale

Institute of International Healthcare Studies, Hartford Hospital and University of Connecticut

Conclusiones: Estos resultados sugieren que las tabletas genéricas no son equivalentes al producto original, por lo tanto los resultados logrados en los estudios clínicos con claritromicina de marca (Laboratorios Abbott) no pueden ser extrapolados a productos genéricos.

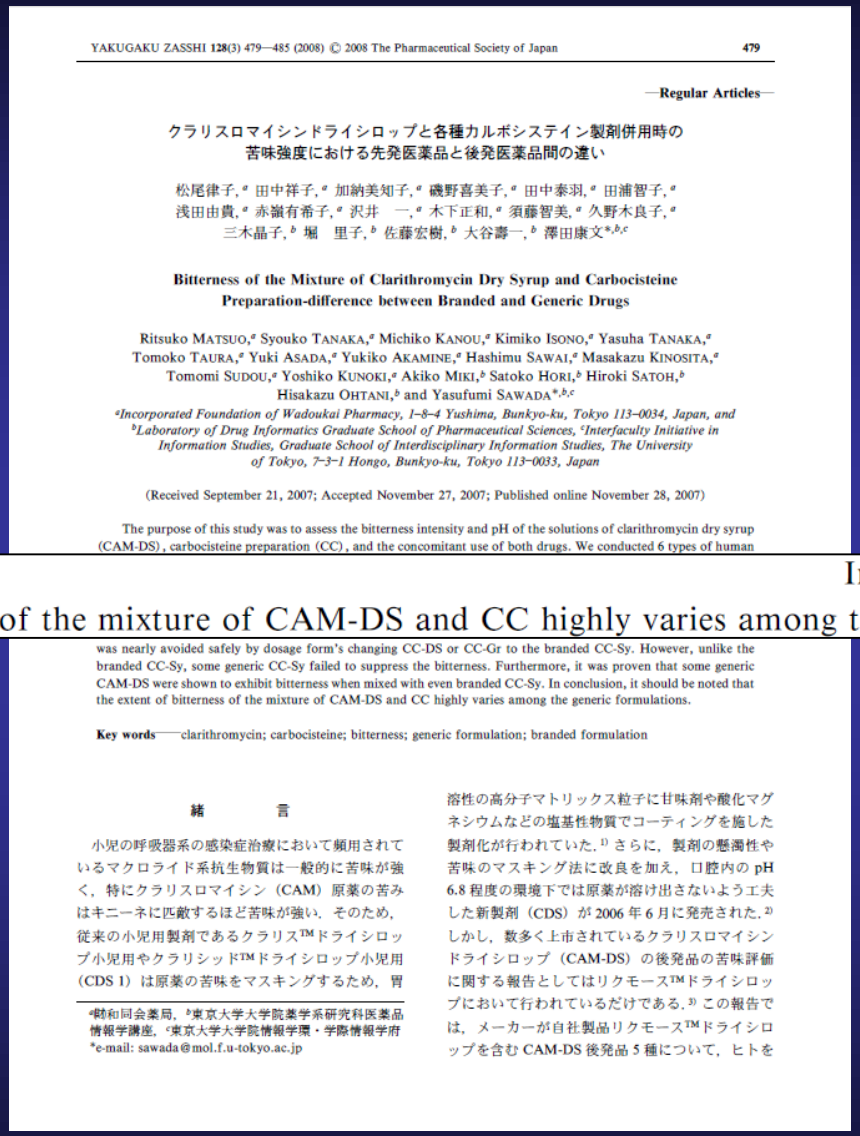
en el rótulo, quedando entonces cortas de la especificación aprobada registrada para el producto original. Un total de 70% (28 de 40) de los productos examinados liberaron menos medicamento en 30 minutos que las tabletas originales, aunque ellos aún cumplían con la especificacion de disolución que requiere que el 80% del medicamento se debe disolver en 30 minutos; un producto genérico falló en cumplir con esta especificación. Un total del 60% (24 de 40) de los productos genéricos examinados excedió el límite del 3% de los Laboratorios Abbot para las impurezas totales en el contenido del medicamento, y el 70% excedieron el límite del 0.8% de Laboratorios Abbott para 6.11 di-O-metil eritromicina A.

Conclusiones: Estos resultados sugieren que las tabletas genéricas no son equivalentes al producto original, por lo tanto los resultados logrados en los estudios clínicos con claritromicina de marca (Laboratorios Abbott) no pueden ser extrapolados a productos genéricos.

La claritromicina es un antibiótico de amplio espectro con actividad contra un rango de organismos Gram-positivos y Gram-negativos, patógenos atípicos y algunos anaerobios. La claritromicina actúa uniéndose reversiblemente a la subunidad ribosómica 50S, inhibiendo así la síntesis de proteína bacteriana. En estudios clínicos múltiples, la claritromicina ha probado ser un tratamiento efectivo para una variedad de infecciones del tracto respiratorio superior e inferior incluyendo sinusitis, faringitis, otitis media, neumonía, neumonía adquirida en comunidad y

Clinical Drug Investigation. April 2000 Vol19 No 4 (pp 293-306)

Palatabilidad de la suspensión de claritromicina innovadora Vs. genéricos



YAKUGAKU ZASSHI 128(3) 479—485 (2008) © 2008 The Pharmaceutical Society of Japan 479

—Regular Articles—

クラリスロマイシンドライシロップと各種カルボシステイン製剤併用時の
苦味強度における先発医薬品と後発医薬品間の違い

松尾律子,[a] 田中祥子,[a] 加納美知子,[a] 磯野喜美子,[a] 田中泰羽,[a] 田浦智子,[a]
浅田由貴,[a] 赤嶺有希子,[a] 沢井 一,[a] 木下正和,[a] 須藤智美,[a] 久野木良子,[a]
三木晶子,[b] 堀 里子,[b] 佐藤宏樹,[b] 大谷壽一,[b] 澤田康文*,[b,c]

Bitterness of the Mixture of Clarithromycin Dry Syrup and Carbocisteine Preparation-difference between Branded and Generic Drugs

Ritsuko MATSUO,[a] Syouko TANAKA,[a] Michiko KANOU,[a] Kimiko ISONO,[a] Yasuha TANAKA,[a]
Tomoko TAURA,[a] Yuki ASADA,[a] Yukiko AKAMINE,[a] Hashimu SAWAI,[a] Masakazu KINOSITA,[a]
Tomomi SUDOU,[a] Yoshiko KUNOKI,[a] Akiko MIKI,[b] Satoko HORI,[b] Hiroki SATOH,[b]
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(Received September 21, 2007; Accepted November 27, 2007; Published online November 28, 2007)

The purpose of this study was to assess the bitterness intensity and pH of the solutions of clarithromycin dry syrup (CAM-DS), carbocisteine preparation (CC), and the concomitant use of both drugs. We conducted 6 types of human

In conclusion, it should be noted that the extent of bitterness of the mixture of CAM-DS and CC highly varies among the generic formulations.

was nearly avoided safely by dosage form's changing CC-DS or CC-Gr to the branded CC-Sy. However, unlike the branded CC-Sy, some generic CC-Sy failed to suppress the bitterness. Furthermore, it was proven that some generic CAM-DS were shown to exhibit bitterness when mixed with even branded CC-Sy. In conclusion, it should be noted that the extent of bitterness of the mixture of CAM-DS and CC highly varies among the generic formulations.

Key words——clarithromycin; carbocisteine; bitterness; generic formulation; branded formulation

緒 言

小児の呼吸器系の感染症治療において頻用されているマクロライド系抗生物質は一般的に苦味が強く，特にクラリスロマイシン（CAM）原薬の苦みはキニーネに匹敵するほど苦味が強い．そのため，従来の小児用製剤であるクラリス™ドライシロップ小児用やクラリシッド™ドライシロップ小児用（CDS 1）は原薬の苦味をマスキングするため，胃溶性の高分子マトリックス粒子に甘味剤や酸化マグネシウムなどの塩基性物質でコーティングを施した製剤化が行われていた.[1] さらに，製剤の懸濁性や苦味のマスキング法に改良を加え，口腔内の pH 6.8 程度の環境下では原薬が溶け出さないよう工夫した新製剤（CDS）が 2006 年 6 月に発売された.[2] しかし，数多く上市されているクラリスロマイシンドライシロップ（CAM-DS）の後発品の苦味評価に関する報告としてはリクモース™ドライシロップにおいて行われているだけである.[3] この報告では，メーカーが自社製品リクモース™ドライシロップを含む CAM-DS 後発品 5 種について，ヒトを

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The Pharmaceutical Society of Japan. 128 (3) 479 -485 (2008)

Un genérico debería contar con estudios de biodisponibilidad y bioequivalencia

Int J Clin Pharmacol Ther. 2005 Aug;43(8):399-404.

Comparative bioavailability of clarithromycin formulations in healthy brazilian volunteers.

Ruenis AP, Moreno RA, Abib-Júnior E, Simões RP, Franco LM, Groppo FC, Baglie S, Franco GC, Rosalen PL.

Piracicaba Dental School, State University of Campinas (UNICAMP), Piracicaba, SP, Brazil.

Abstract

OBJECTIVE: To compare the bioavailability of clarithromycin 500 mg tablets (Merck S.A Industrias Quimicas, Sao Paulo, SP, Brazil, used as test formulation) and Klaricid (Abbott Laboratórios do Brasil Ltda, Sao Paulo, SP, Brazil, used as reference formulation) in 24 healthy volunteers.

MATERIAL AND METHODS: The study was conducted using an open, randomized, two-period crossover design with one-week interval between doses. Blood samples were collected at pre-dose, 0.33, 0.66, 1, 1.33, 1.66, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 20 and 24 hours after the administration. AUC was calculated by the trapezoidal rule extrapolation method. Cmax and tmax were compiled from the plasmatic concentration-time data. Analysis of variance was carried out using logarithmically transformed AUC(0-inf), AUC(0-24 h), Cmax and untransformed tmax.

RESULTS: Intraindividual coefficient of variation (CV%) values were 14.25% and 12.62%, respectively for Cmax and AUC(0-24 h). The geometric mean values (+/- SD) for AUC(0-24 h) (microg x h/ml), AUC(0-inf) (microg x h/ml), and Cmax (microg/ml) for test medication were 18.56 (+/- 6.87), 18.8 (+/- 5.70) and 2.45 (+/- 0.88); the obtained values for reference medication were 18.29 (+/- 5.39), 19.10 (+/- 7.21) and 2.5 (+/- 0.69). 90% CI for clarithromycin geometric mean of AUC(0-24 h), AUC(0-inf) and Cmax ratios (test/reference) were: 93.6-105.9%, 93.8-106.2% and 89- 103.2%. CCONCLUSION The test medication was considered bioequivalent to the reference medication based on the rate and extent of absorption.

PMID: 16119515 [PubMed - indexed for MEDLINE]

…pero los estudios de biodisponibilidad y de bioequivalencia, no garantizan la efectividad de los antibióticos.

Registro sanitario de claritromicina innovadora (Klaricid®)

Datos Generales del Producto

Expediente	54709	**Nombre producto**	**KLARICID IV**				
Registro Sanitario	INVIMA 2006 M-005882 R1	**Vencimiento**	2016/09/11	**Modalidad**	IMPORTAR Y VENDER	**Estado Registro**	Vigente
Observaciones	LAS CONTRAINDICACIONES Y ADVERTENCIAS DEBEN APARECER EN LAS ETIQUETAS Y EMPAQUES, MÁS LA FECHA DE VENCIMIENTO.						

Datos de Interés del Medicamento

Forma Farmaceutica	PO - POLVOS	**Franja**	VERDE
Indicaciones	TRATAMIENTO DE LAS INFECCIONES CAUSADAS POR GÉRMENES SENSIBLES A LA CLARITROMICINA		
Contraindicaciones	HIPERSENSIBILIDAD DE LOS ANTIBIÓTICOS MACRÓLIDOS, LOVASTAINA Y SIMVASTATINA,EMBARAZO Y LACTANCIA. ADMINÍSTRESE CON PRECAUCIÓN EN PACIENTES CON DISFUNCIÓN HEPÁTICA ADVERTENCIAS Y PRECAUCIONES LA INFORMACIÓN RELACIONADA CON HIPOGLICEMIANTES ORALES/ INSULINAS: INFORMACIÓN DE INTERACCIÓN Y RECOMENDACIÓN PARA EL MONITOREO CUIDADOSO DE LA GLUCOSA. - ANTICOAGULANTES ORALES: INFORMACIÓN ACERCA DEL RIESGO DE HEMORRAGIA CON EL USO CONCOMITANTE DE WARFARINA, MONITOREO CUIDADOSO DE LOS TIEMPOS INR Y DE PROTROMBINA.- INHIBIDORES DE LA HMG-COA REDUCTASA: DESCRIPCIÓN DE LA INTERACCIÓN Y POTENCIAL DE LA RABDOMIÓLISIS, ENTRE OTRAS,		
Inserto ? ☑	**Vida Util** 4 AÑOS	**Condicion Venta**	CON FORMULA FACULTATIVA	Generico ? ☐	
Via Administracion	IV - INTRAVENOSA				

Presentaciones Comerciales

Presentacion Comercial

Expediente	Consec	Termino	Unidad / Medida	Cantidad	Descripcion	Fecha insc	Estado	Fecha Inactiv
000054709	01	0168	mg	500,00	CAJA POR UN VIAL POR 15 CC, CONTIENE CLARITROMICINA 500MG(POLVO LIOFILIZADO) PARA RECONSTITUIR A 10 ML., CAJA POR UN VIAL	2006/11/10	Activo	

www.invima.gov.co - registros sanitarios

Registro sanitario de otra claritromicina copia

Datos Generales del Producto

Expediente	19961536	**Nombre producto**	**CLARITROMICINA 500MG POLVO LIOFILIZADO PARA RECONSTITUR A SOLUCION INYECTABLE I.V.**				
Registro Sanitario	INVIMA 2006M-0005477	**Vencimiento**	2016/03/30	**Modalidad**	IMPORTAR Y VENDER	**Estado Registro**	Vigente
Observaciones	LAS CONTRAINDICACIONES Y ADVERTENCIAS DEBEN APARECER EN LOS MATERIALES DE EMPAQUE MAS LA FECHA DE VENCIMIENTO MAS UNA FRANJA VERDE CON LA LEYENDA: MEDICAMENTO ESENCIAL.						

Datos de Interés del Medicamento

Forma Farmaceutica	PL - POLVO LIOFILIZADO			**Franja**	VERDE
Indicaciones	TRATAMIENTO DE LAS INFECCIONES CAUSADAS POR GÉRMENES SENSIBLES A LA CLARITROMICINA				
Contraindicaciones	HIPERSENSIBILIDAD DE LOS ANTIBIÓTICOS MACRÓLIDOS, EMBARAZO Y LACTANCIA.				
Inserto ? ☑	**Vida Util**	DOS 2 AÑOS	**Condicion Venta**	CON FORMULA FACULTATIVA	Generico ? ☑
Via Administracion	IV - INTRAVENOSA				

Presentaciones Comerciales

Presentacion Comercial

Expediente	Consec	Termino	Unidad / Medida	Cantidad	Descripcion	Fecha insc	Estado	Fecha Inactiv
019961536	01	0168	mg	25000,00	CAJA POR 50 FRASCOS DE VIDRIO DE CAPACIDAD 20ML. CADA FRASCO CONTIENE 500MG DE CLARITROMICINA	2006/11/10	Activo	
019961536	02	0168	mg	50000,00	CAJA POR 100 FRASCOS DE VIDRIO DE CAPACIDAD 20ML. CADA FRASCO CONTIENE 500MG DE CLARITROMICINA	2006/11/10	Activo	
019961536	03	0168	mg	500,00	CAJA POR UN FRASCO DE VIDRIO DE CAPACIDAD 20ML. CADA FRASCO CONTIENE 500MG DE CLARITROMICINA	2007/02/01	Activo	

www.invima.gov.co - registros sanitarios

Flebitis por Claritromicina

Recomendaciones Hospital San Vicente Fundación

- Se debe reconstituir en agua estéril para inyección, luego de reconstituido puede ser diluido en Solución Salina al 0.9% o en Dextrosa al 5%.
- La concentración máxima para la administración de la solución es de 2 mg/ml.
- El tiempo de infusión mínimo debe ser de una hora.
- El medicamento siempre se debe proteger de la luz, luego de la dilución la solución es estable por 6 horas a temperatura ambiente.
- No administrar antes, durante o después de: Ceftazidima, Cefuroxima, Heparina, Fenitoina sódica y Furosemida

Lacy FCh, Amstrong LI, Goldman Mp, Lance LI. Drug Information Handbook with International Trade names index. 19 ed. Ohio: Lexi-Comp Inc; 2010-2011
Trissel, Lawrence A. Handbook on injectable drugs. 13 ed. American Society of Health-System Pharmacists, 2005.

Productos de Marca vs. Genéricos

Cuando un medicamento genérico o copia tiene menos vida útil que el de marca o se contraindica en menores de edad, debe asumirse que no tiene la misma estabilidad que el innovador y se debe vigilar la aparición de material particulado.

Drug excipients. Adv Drug Deliv Rev. 2007 Dec 22;59(15):1482-503.

The effects of pharmaceutical excipients on drug disposition. Rev Med Brux. 2001 Dec;22(6):513-20.

Generics: essentially similar, bioequivalent but not identical. Regul Toxicol Pharmacol. 2000 Oct;32(2):210-8..

Adverse effects of pharmaceutical excipients in drug therapy. Med Toxicol Adverse Drug Exp. 1988 Mar-Apr;3(2):128-65.

Registros Sanitarios de Piperacilina-Tazobactam

Su búsqueda enlistó **12** registros para el grupo **MEDICAMENTOS** Fecha/Hora sistema: 2010/09/02 12:41

Expediente	Nombre del Producto	Registro sanitario	Estado Registro	Fecha Vencimien
19941580	PIPERACILINA - TAZOBACTAM INYECTABLE	INVIMA 2004M-0003522	Vigente	2014/07/21
19953325	PIPERACILINA TAZOBACTAM 4.5G POLVO PAA RECOSTITUIR A SOLUCION INYECTABLE	INVIMA 2006M-0005629	Vigente	2016/05/08
19961814	PIPERACILINA Y TAZOBACTAM 4.5 G	INVIMA 2006M-0005799	Vigente	2016/06/02
19969105	PIPERACILINA 4G + TAZOBACTAM 0,5G POLVO ESTERIL PARA RECONSTITUIR A SOLUCION INYECTABLE	INVIMA 2006M-0006639	Vigente	2016/12/13
19974254	PIPERACILINA+ TAZOBACTAM 4.5 G INYECTABLE	INVIMA 2007M-0007071	Vigente	2017/06/22
19976389	PIPERACILINA + TAZOBACTAM 4.5G POLVO ESTERIL PARA RECONSTITUIR A SOLUCION INYECTABLE	INVIMA 2007M-0007340	Vigente	2017/10/11
19981396	PIPERACILINA TAZOBACTAM 4,5G	INVIMA 2007M-0007593	Vigente	2017/12/18
19988366	PIPERACILINA + TAZOBACTAM 4,5 G POLVO ESTERIL PARA INYECCION	INVIMA 2008M-0007812	Vigente	2018/03/13
20005167	PIPERACILINA 4.0 G + TAZOBACTAM 0.5 G	INVIMA 2009M-0009761	Vigente	2019/07/01
20005170	PIPERACILINA 4,0 G + TAZOBACTAM 0,5 G	INVIMA 2009M-0009747	Vigente	2019/07/01
20006873	PIPERACILINA 4G + TAZOBACTAM 0,5G POLVO ESTERIL PARA RECONSTITUIR A SOLUCION INYECTABLE	INVIMA 2010M-0010754	Vigente	2020/05/13
20010839	PIPERACILINA (SODICA) 4G + TAZOBACTAM (SODICO) 0.5 G	INVIMA 2010M-0010804	Vigente	2020/06/02

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Registros sanitarios de Piperacilina-Tazobactam Antibiótico Innovador

Datos de Interés del Medicamento

Forma Farmaceutica	PL - POLVO LIOFILIZADO	**Franja**	VERDE
Indicaciones	TRATAMIENTO DE LAS SIGUIENTES INFECCIONES BACTERIANAS SISTÉMICAS Y/O LOCALES CAUSADAS POR MICROORGANISMOS GRAM-POSITIVOS Y GRAM-NEGATIVOS AERÓBICOS Y ANAERÓBICOS SUSCEPTIBLES A PIPERACILINA / TAZOBACTAM O PIPERACILINA: ADULTOS: INFECCIONES DEL TRACTO RESPIRATORIO INFERIOR, INFECCIONES DEL TRACTO URINARIO, INFECCIONES INTRA-ABDOMINALES, INFECCIONES DE LA PIEL Y TEJIDOS BLANDOS, SEPTICEMIA BACTERIANA, INFECCIONES GINECOLÓGICAS, INCLUYENDO ENDOMETRITIS POSPARTO Y ENFERMEDAD PÉLVICA INFLAMATORIA (EPI), NEUTROPENIA FEBRIL EN COMBINACIÓN CON UN AMINOGLICÓSIDO, INFECCIONES ÓSEAS Y ARTICULARES, INFECCIONES POLIMICROBIANAS (AEROBIOS Y ANAEROBIOS GRAM-POSITIVOS / GRAM-NEGATIVOS). NIÑOS: NEUTROPENIA FEBRIL EN PACIENTES PEDIÁTRICOS EN COMBINACIÓN CON UN AMINOGLICOSIDO, INFECCIÓN INTRA-ABDOMINAL EN NIÑOS DE 2 AÑOS O MAYORES. "INFECCIONES DE PIEL Y TEJIDO BLANDO NO COMPLICADAS Y COMPLICADAS QUE INCLUYE: CELULITIS, ABSCESOS CUTÁNEOS, INFECCIONES EN PIE DIABÉTICO/ ISQUÉMICO CAUSADAS POR MICROORGANISMOS RESISTENTES A LA PIPERACILINA Y STAPHYLOCOCCUS AUREUS PRODUCTOR DE ß-LACTAMASAS"		
Contraindicaciones	PACIENTES CON HISTORIA DE REACCIONES ALERGICAS A CUALQUIERA DE LAS PENICILINAS, CEFALOSPORINAS O INHIBIDORES DE BETALACTAMASA. PUEDE OCASIONAR COLITIS SEUDOMEMBRANOSA.		
Inserto ? ☑	**Vida Util** TRES AÑOS	**Condicion Venta**	CON FORMULA FACULTATIVA — Generico ? ☐
Via Administracion	IV - INTRAVENOSA		

Hace referencia a su empleo en infecciones intra-abdominales en niños

www.invima.gov.co - registros sanitarios

Registro Sanitarios de Piperacilina-Tazobactam Copia

Datos Generales del Producto

Expediente	19953325	Nombre producto	PIPERACILINA TAZOBACTAM 4.5G POLVO PAA RECOSTITUIR A SOLUCION INYECTABLE				
Registro Sanitario	INVIMA 2006M-0005629	Vencimiento	2016/05/08	Modalidad	IMPORTAR Y VENDER	Estado Registro	Vigente
Observaciones	LAS CONTRAINDICACIONES Y ADVERTENCIAS DEBEN APARECER EN LAS ETIQUETAS Y EMPAQUES MAS LA FECHA DE VENCIMIENTO Y UNA FRANJA VERDE CON LA LEYENDA MEDICAMENTO ESENCIAL.						

Datos de Interés del Medicamento

Forma Farmaceutica	PO - POLVOS	Franja	VERDE
Indicaciones	TRATAMIENTO DE INFECCIONES PRODUCIDAS POR GÉRMENES SUSCEPTIBLES A PIPERACILINA/TAZOBACTAN CAUSADAS POR GÉRMENES PRODUCTORES DE BETALACTAMASA.		
Contraindicaciones	PACIENTES CON HISTORIA DE REACCIONES ALÉRGICAS A CUALQUIERA DE LAS PENICILINAS, CEFALOSPORINAS O INHIBIDORES DE BETALACTAMASA. PUEDE OCASIONAR COLITIS PSEUDOMEMBRANOSA. INFECCIONES INTRAABDOMINALES SEVERAS EN NIÑOS.		

Inserto ? ☑	Vida Util	2 AÑOS	Condicion Venta	CON FORMULA FACULTATIVA	Generico ? ☑

!Contraindicado en infecciones intra-abdominales en niños!

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Registro Sanitario de Otra Piperacilina-Tazobactam "Multifuente"

Datos de Interés del Medicamento

Forma Farmaceutica	PO - POLVOS	**Franja**	VERDE
Indicaciones	TRATAMIENTO DE LAS SIGUIENTES INFECCIONES BACTERIANAS SISTÉMICAS Y/O LOCALES CAUSADAS POR MICROORGANISMOS GRAM-POSITIVOS Y GRAM-NEGATIVOS AERÓBICOS Y ANAERÓBICOS SUSCEPTIBLES A PIPERACILINA / TAZOBACTAM O PIPERACILINA: ADULTOS: INFECCIONES DEL TRACTO RESPIRATORIO INFERIOR, INFECCIONES DEL TRACTO URINARIO, INFECCIONES INTRA-ABDOMINALES, INFECCIONES DE LA PIEL Y TEJIDOS BLANDOS, SEPTICEMIA BACTERIANA, INFECCIONES GINECOLÓGICAS, INCLUYENDO ENDOMETRITIS POSPARTO Y ENFERMEDAD PÉLVICA INFLAMATORIA (EPI), NEUTROPENIA FEBRIL EN COMBINACIÓN CON UN AMINOGLICÓSIDO, INFECCIONES ÓSEAS Y ARTICULARES, INFECCIONES POLIMICROBIANAS (AEROBIOS Y ANAEROBIOS GRAM-POSITIVOS / GRAM-NEGATIVOS). NIÑOS: NEUTROPENIA FEBRIL EN PACIENTES PEDIÁTRICOS EN COMBINACIÓN CON UN AMINOGLICOSIDO, INFECCIÓN INTRA-ABDOMINAL EN NIÑOS DE 2 AÑOS O MAYORES. "INFECCIONES DE PIEL Y TEJIDO BLANDO NO COMPLICADAS Y COMPLICADAS QUE INCLUYE: CELULITIS, ABSCESOS CUTÁNEOS, INFECCIONES EN PIE DIABÉTICO/ ISQUÉMICO CAUSADAS POR MICROORGANISMOS RESISTENTES A LA PIPERACILINA Y STAPHYLOCOCCUS AUREUS PRODUCTOR DE ß-LACTAMASAS"		
Contraindicaciones	PACIENTES CON HISTORIA DE REACCIONES ALÉRGICAS A CUALQUIERA DE LAS PENICILINAS, CEFALOSPORINAS O INHIBIDORES DE BETALACTAMASA. PUEDE OCASIONAR COLITIS PSEUDOMEMBRANOSA. INFECCIONES INTRAABDOMINALES SEVERAS EN NIÑOS.		
nserto ? ☐	**Vida Util** DOS 2 AÑOS	**Condicion Venta**	CON FORMULA FACULTATIVA — Generico ? ☑
Via Administracion	IV - INTRAVENOSA		

!Contraindicado en infecciones intra-abdominales en niños!

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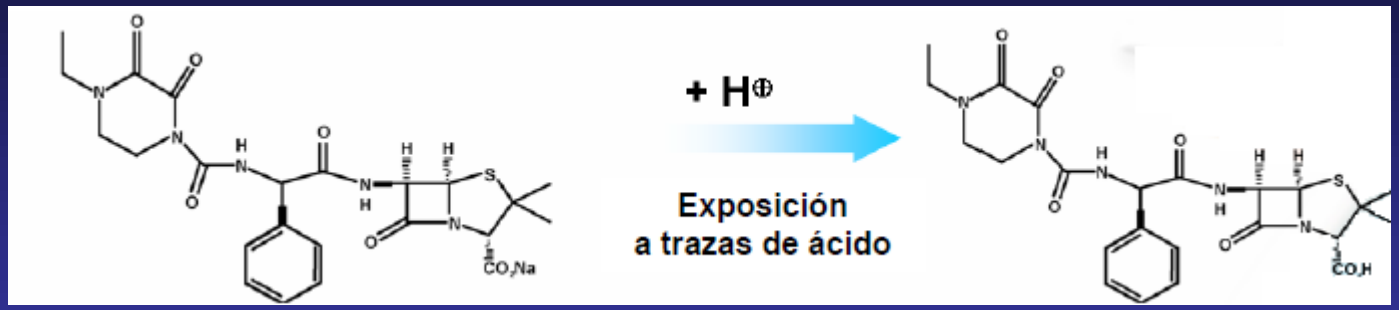
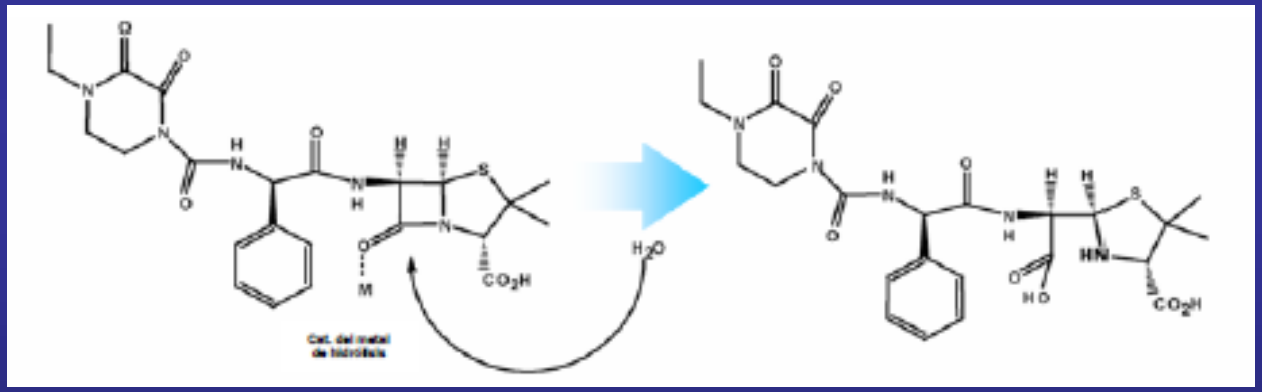
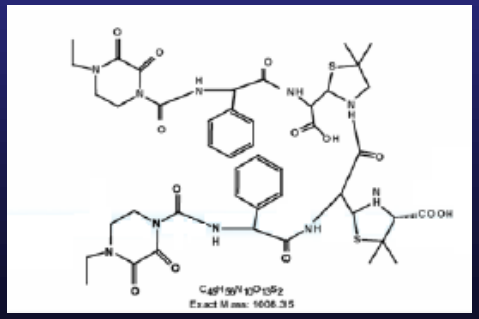
Causas de la Variación de las Partículas



Piperacilina-COO-Na+ con variaciones de pH se convierte a piperacilina menos soluble

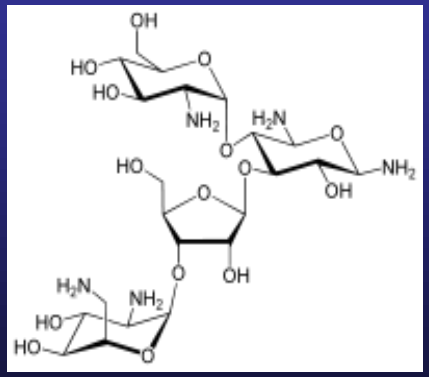


La reacción catalizada del metal produce un dímero insoluble



Diluyentes Comerciales con pH Bajo

- **Iones Metálicos (particularmente zinc):**
  - Potencian la apertura del anillo de beta-lactamasa de la piperacilina, un precursor de la formación de dímeros
  - La degradación de la piperacilina contribuye a la formación de complejos insolubles



Data on File, Wyeth Pharmaceuticals Inc., Philadelphia, Pa.

Concentraciones de Zinc en los Diluyentes

Figura 1: Nveles de Zinc Detectados en la Inyección de Cloruro de Sodio 0.9%, Muestras USP

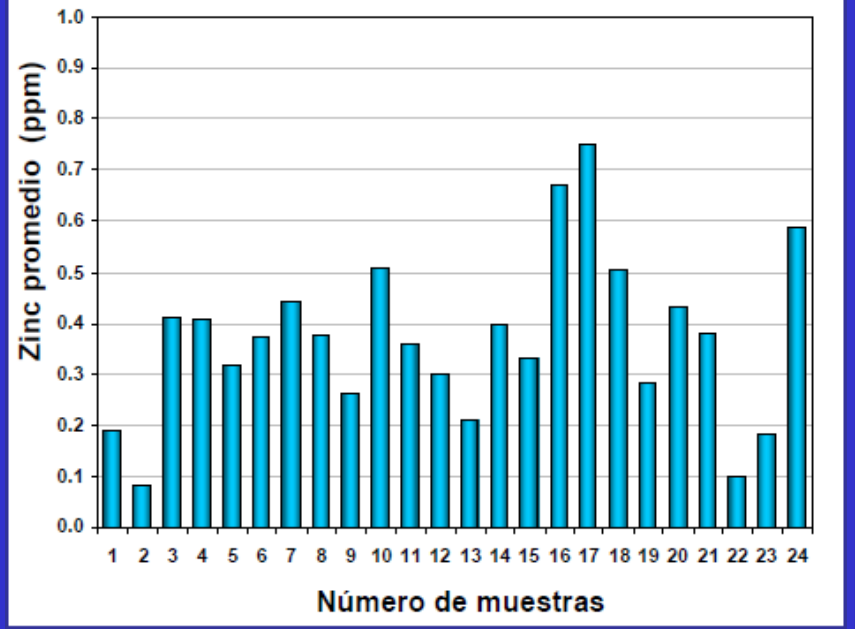
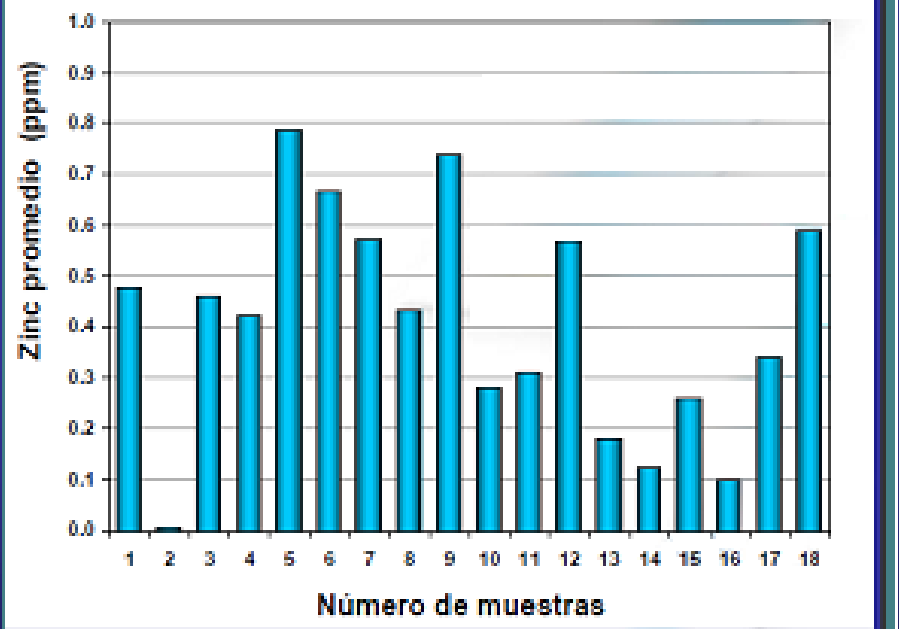


Figura 2: Niveles de Zinc Detectados en la Inyección de Dextrosa 5%, Muestras USP



USP Data on file. Wyeth Pharmaceuticals Inc., Philadelphia, Pa.

Implicaciones del material particulado

El material particulado suministrado IV puede causar:

- Flebitis
- Granulomas pulmonares
- Disfunción pulmonar grave
- Disminución de la densidad capilar funcional (músculo estriado post-isquémico)

Lehr HA, et al. *Am J Resp Crit Care Med*. 2002; 165: 518

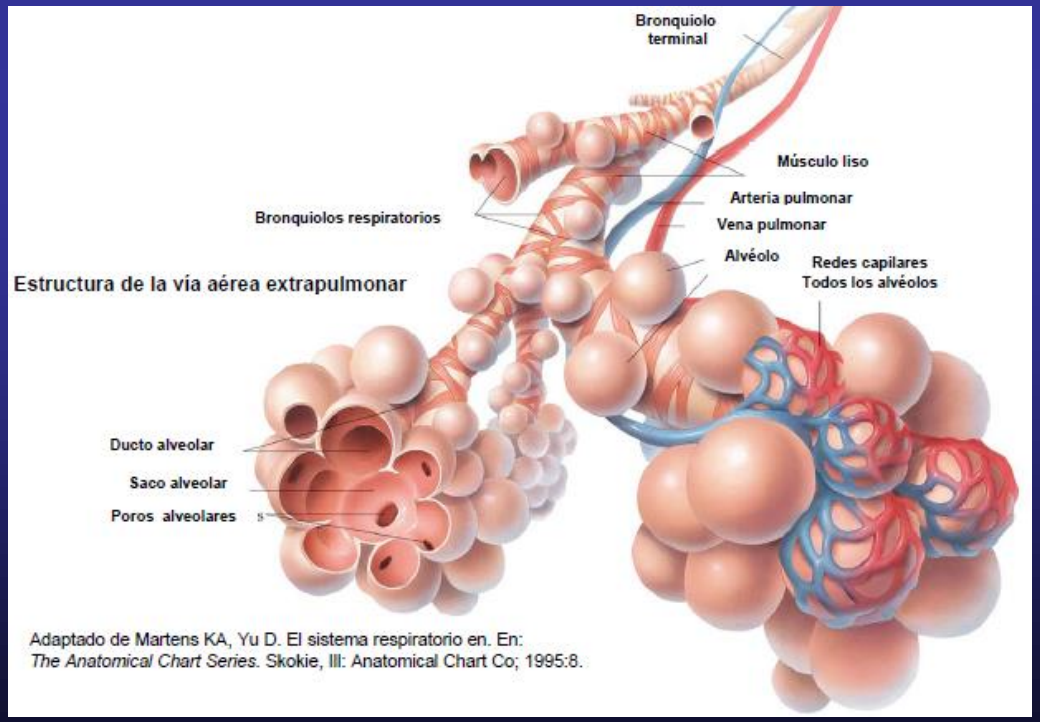
Potencial daño inducido por el material particulado

Bloqueo mecánico de arteriolas y capilares de pequeño calibre.

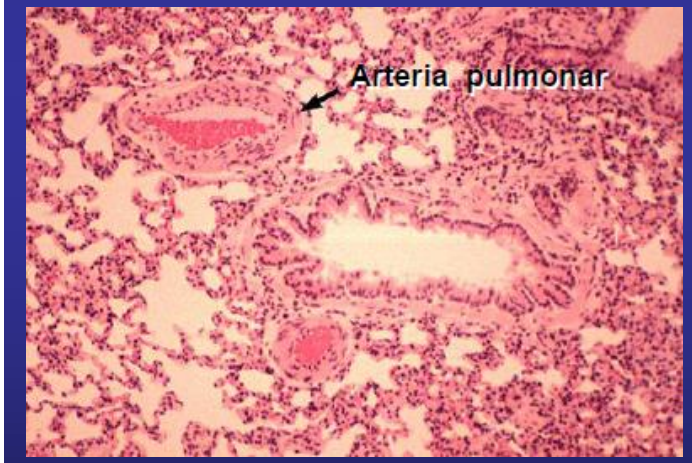
Activación de plaquetas y/o neutrófilos.

Generación de microtrombos oclusivos.

Efectos indirectos sobre la actividad vasomotora.



Adaptado de Martens KA, Yu D. El sistema respiratorio en. En: *The Anatomical Chart Series*. Skokie, Ill: Anatomical Chart Co; 1995:8.



Fotomicrografía de la arteria pulmonar con autorización.George TJ, Wojciech P. Revisión de Histología. Derechos de autor ©2000. Página Web de la Universidad de FloridaWebsite. Disponible en: http://medinfo.ufl.edu/year1/histo/images/b3b.jpg. AccesoMarzo 21, 2007.

Registro de Cefalexina Innovador (Keflex®) Vs. Copia

Datos Generales del Producto

Expediente	87108	Nombre producto	KEFLEX 500 MG				
Registro Sanitario	INVIMA 2005 M-001775-R1	Vencimiento	2015/06/29	Modalidad	IMPORTAR Y VENDER	Estado Registro	Vigente
Observaciones	LAS CONTRAINDICACIONES Y ADVERTENCIAS DEBEN APARECER EN LAS ETIQUETAS Y EMPAQUES MAS LA FECHA DE VENCIMIENTO Y UNA FRANJA VERDE CON LA LEYENDA "MEDICAMENTO ESENCIAL" . ALMACENADO EN SU EMPAQUE Y ENVASE ORIGINAL A UNA TEMPERATURA NO MAYOR A 30°C						

Datos de Interés del Medicamento

Forma Farmaceutica	TN - TABLETAS CON O SIN RECUBR. QUE NO MODIFIQUEN LIBERACION FARMACO			Franja	VERDE
Indicaciones	INFECCIONES PRODUCIDAS POR GÉRMENES SENSIBLES A LA CEFALEXINA.				
Contraindicaciones	HIPERSENSIBILIDAD A LAS CEFALOSPORINAS Y/ O PENICILINAS. ADMINÍSTRESE CON PRECAUCIÓN A PACIENTES CON INSUFICIENCIA RENAL.				
Inserto ? ☑	Vida Util	DOS(2)AÑOS	Condicion Venta	CON FORMULA FACULTATIVA	Generico ? ☐
Via Administracion	PO - ORAL				

Innovador

Datos Generales del Producto

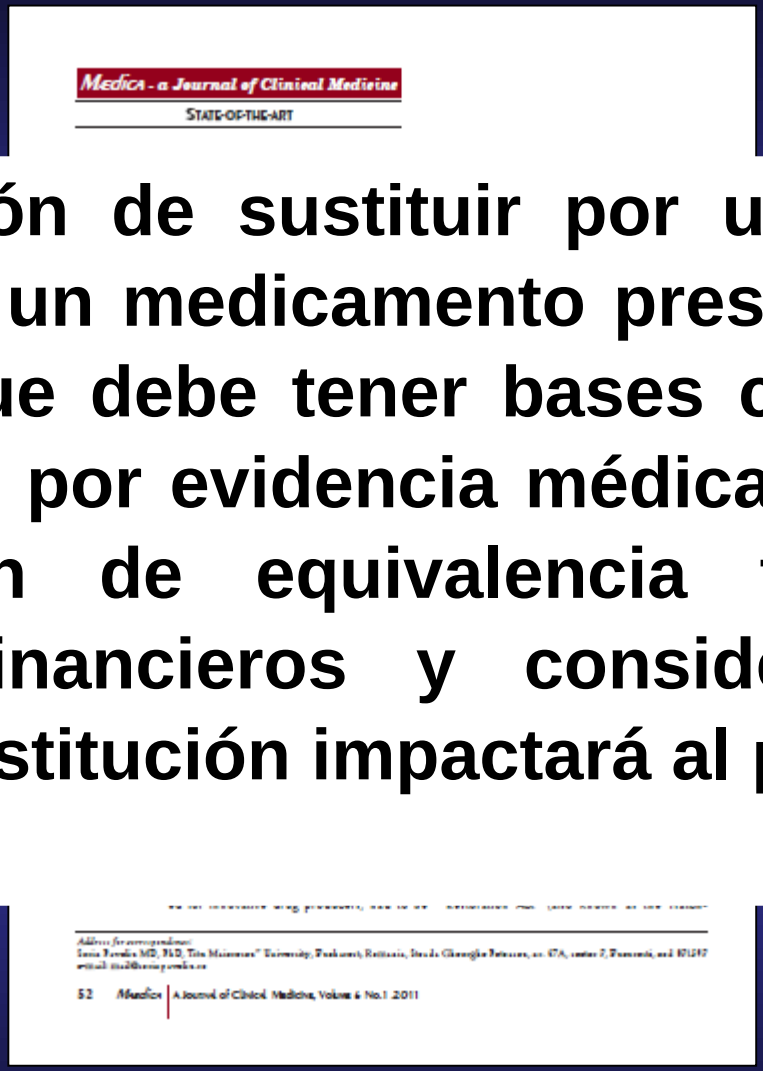
Expediente	25353	Nombre producto	CEFALEXINA CAPSULAS X 500 MG.				
Registro Sanitario	INVIMA 2008M-010172 -R1	Vencimiento	2018/05/30	Modalidad	FABRICAR Y VENDER	Estado Registro	Vigente
Observaciones	LAS CONTRAINDICACIONES Y ADVERTENCIAS DEBEN APARECER EN LAS ETIQUETAS Y EMPAQUES MAS LA FECHA DE VENCIMIENTO Y UNA FRANJA VERDE EN SENTIDO HORIZONTAL CON LA LEYENDA EN SU INTERIOR MEDICAMENTO ESENCIAL.						

Datos de Interés del Medicamento

Forma Farmaceutica	CD - CAPSULA DURA			Franja	VERDE
Indicaciones	INFECCIONES PRODUCIDAS POR GERMENES SENSIBLES A LA CEFALEXINA				
Contraindicaciones	HIPERSENSIBILIDAD A LAS CEFALOSPORINAS Y/ O PENICILINAS, ADMINISTRESE CON PRECAUCION A PACIENTES CON INSUFICIENCIA RENAL . CONTIENE TARTRAZINA QUE PUEDE PRODUCIR REACCIONES ALERGICAS TIPO ANGIOEDEMA,ASMA,URTICARIA Y SHOCK ANAFILACTICO.				
Inserto ? ☐	Vida Util	TRES3 AÑOS	Condicion Venta	CON FORMULA FACULTATIVA	Generico ? ☑
Via Administracion	PO - ORAL				

Copia

El Tema de la Sustitución por Genéricos


Maedica - a Journal of Clinical Medicine

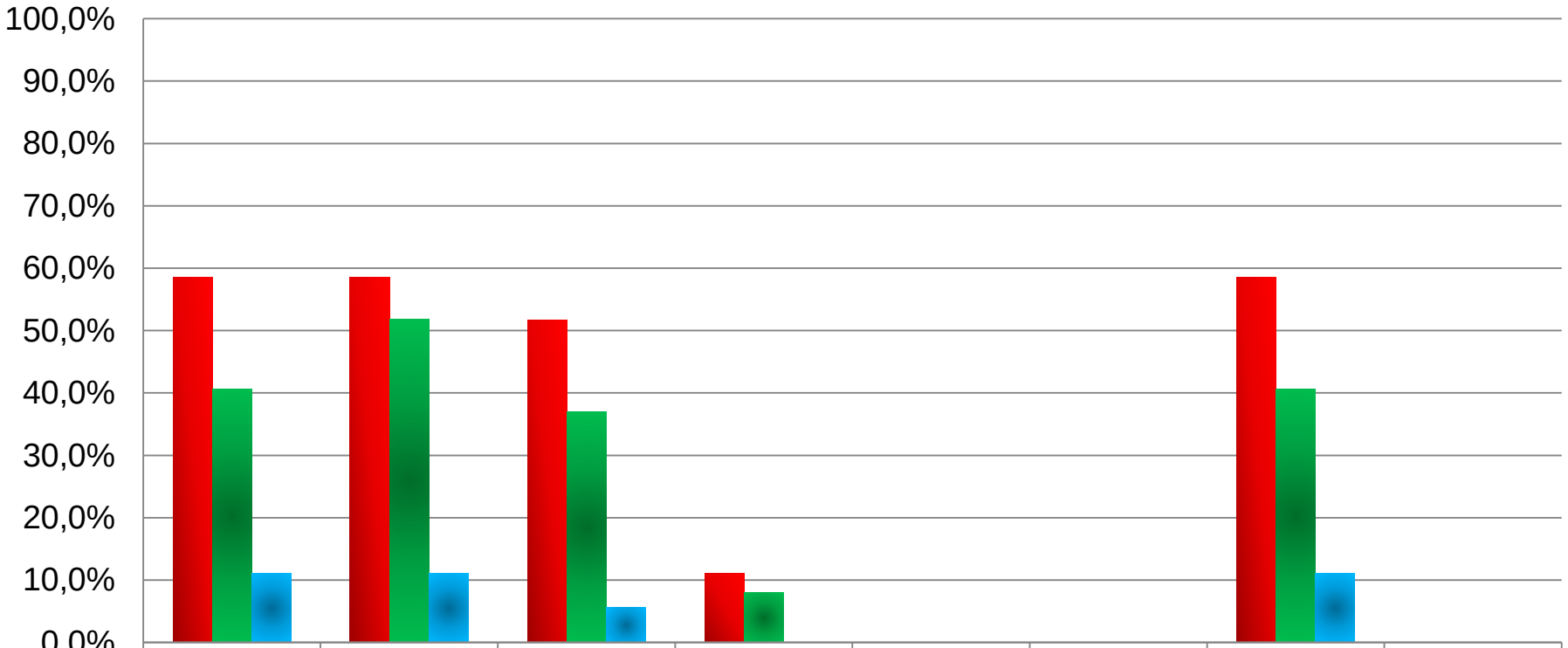
STATE-OF-THE-ART

“La decisión de sustituir por un producto alternativo un medicamento prescrito, es un proceso que debe tener bases clínicas, ser respaldado por evidencia médica apropiada, información de equivalencia terapéutica, factores financieros y consideración de cómo la sustitución impactará al paciente”.

52 Maedica | A Journal of Clinical Medicine, Volume 6 No.1 2011

Maedica (Buchar). 2011 Jan;6(1):52-8.

Perfil de resistencia S. aureus en UCI adultos HGM



	Cefazolina	Eritromicina	Clindamicina	Rifampicina	Trimetropim Sulfa	Linezolid	Oxacilina	Vancomicina
2005	58,6%	58,6%	51,7%	11,1%	0,0%	0,0%	58,6%	0,0%
2006	40,7%	51,9%	37,0%	8,0%	0,0%	0,0%	40,7%	0,0%
2007	11,1%	11,1%	5,6%	0,0%	0,0%	0,0%	11,1%	0,0%

Cortesía Dra. Marta Vallejo – M.D. Cirujana General – Epidemióloga Hospital General de Medellín

Similitud Entre Medicamentos

1º. Evaluación técnica:

Equivalencia farmacéutica

2º. Estudios de biodisponibilidad y bioequivalencia:

Equivalencia biológica

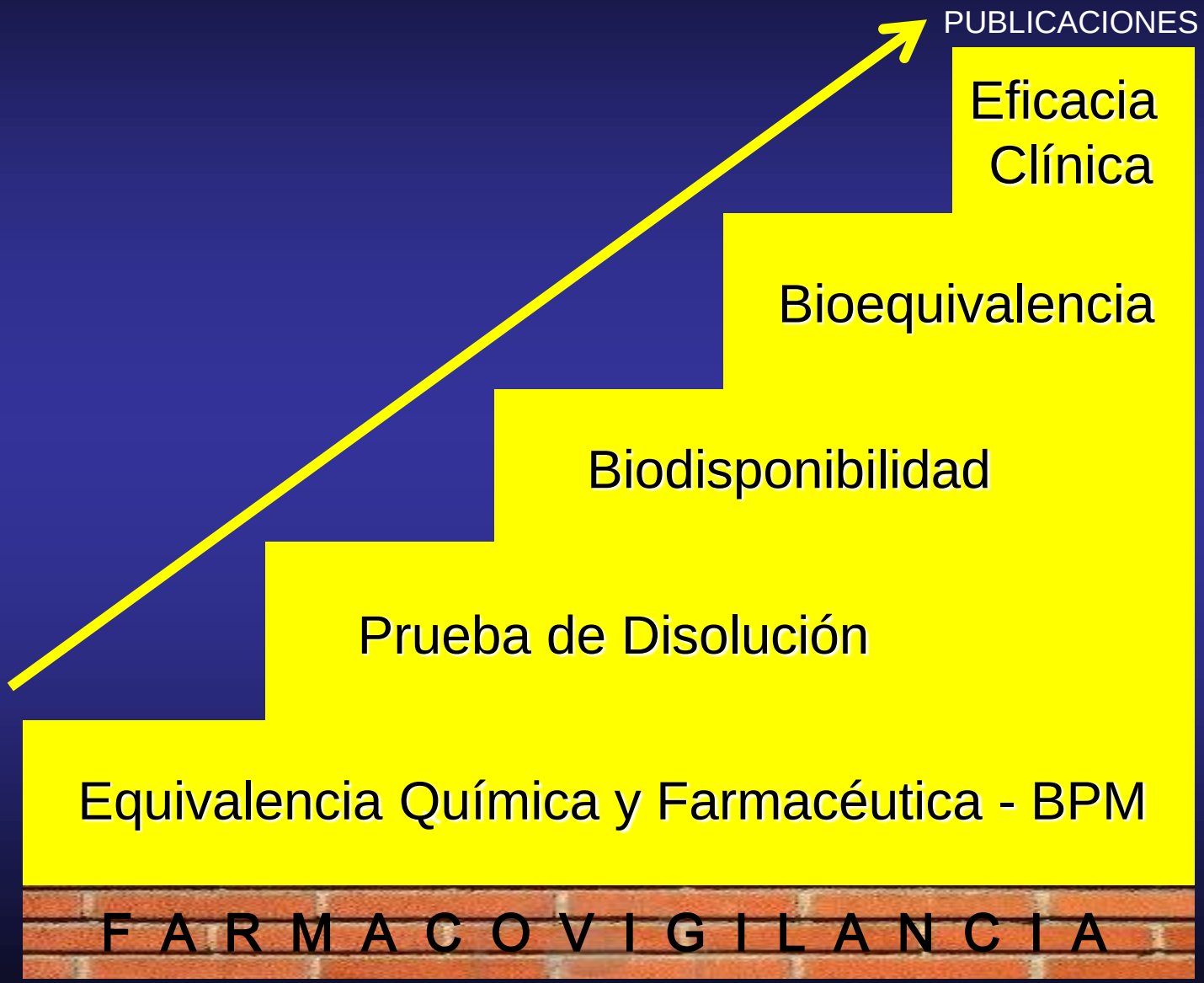
3º. Intercambiabilidad:

Uso clínico

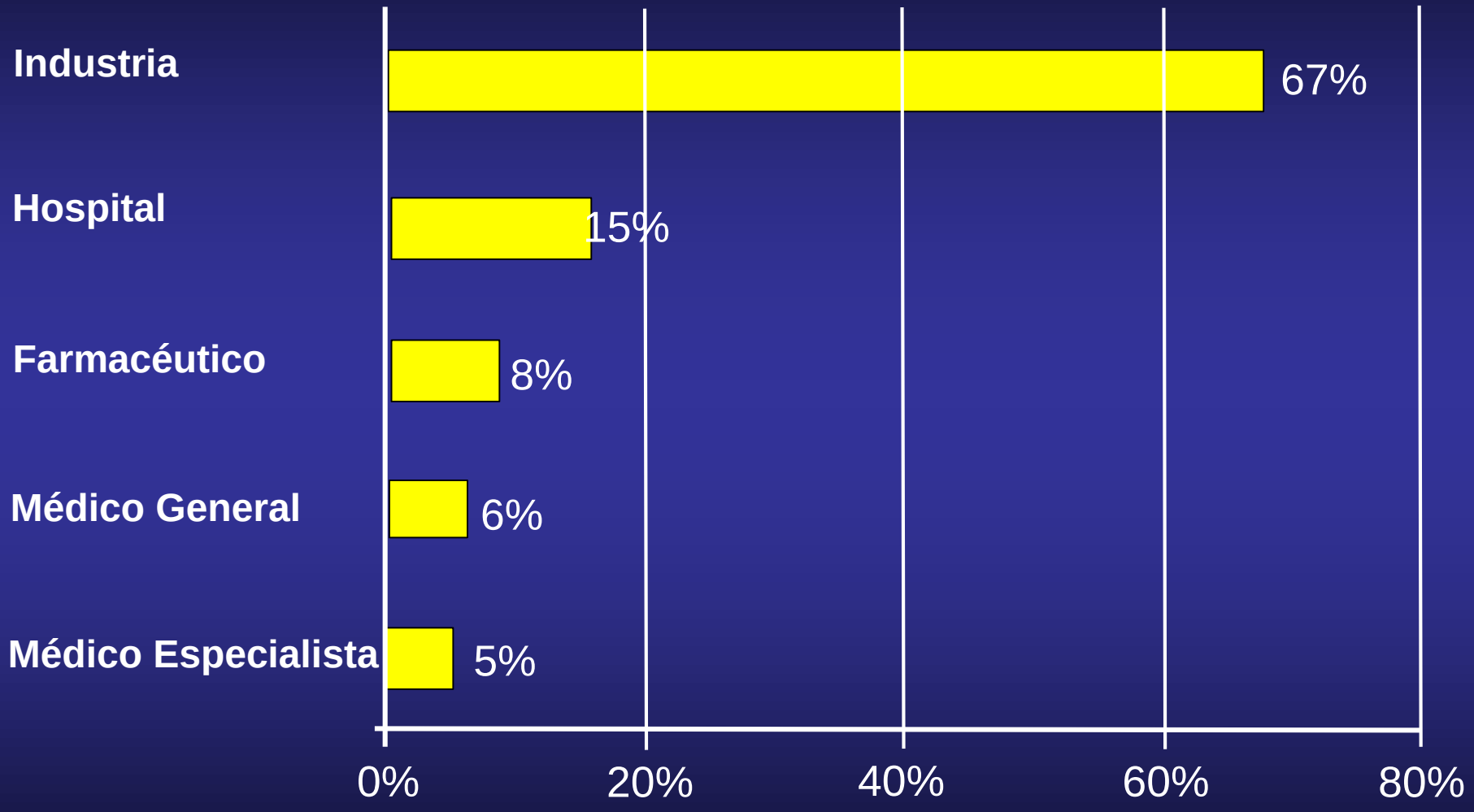
Equivalentes Terapéuticos

- Deben ser:
  - **Seguros**
  - **Efectivos**
  - **Bioequivalentes**
  - **Etiquetados y con BPM**
- Deben tener igual:
  - **Principio activo**
  - **Cantidad**
  - **Forma farmacéutica**
  - **Efecto terapéutico**

Proceso que Garantiza la Calidad de un Medicamento



Fuentes del Reporte de Farmacovigilancia



Fuente INVIMA

Fallo Terapéutico en Antibioticoterapia

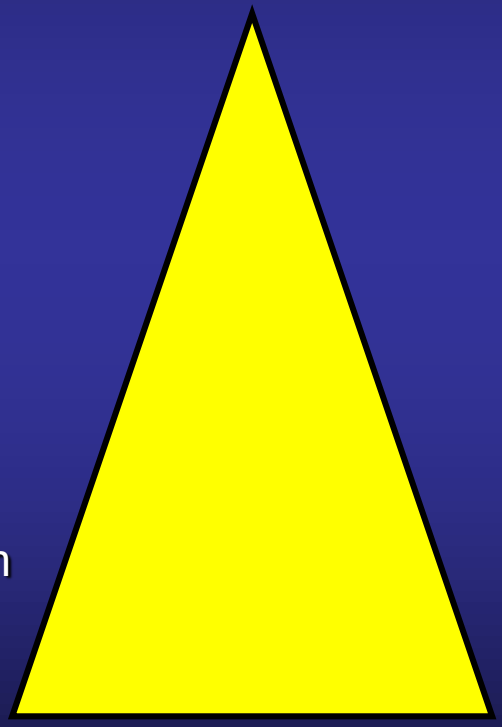
FACTORES DELHUESPED

- Diagnóstico incorrecto
- Adherencia
- Reacción adversa
- Gravedad
- Respuesta inmune

FACTORES DEL MEDICAMENTO

Cadena de Procesos:

- Manufactura
- Equivalencia farmacéutica
- Equivalencia biológica
- Biodisponibilidad
- Bioequivalencia
- Almacenamiento y transporte
- Control de Calidad y Regulación
- Estudios de efectividad clínica



FACTORES DEL USO

- Selección del antibiótico
- Resistencia
- Interacción
- Dosis
- Tiempo de tratamiento
- Dispensación

RESPUESTA

Reglas de Oro para el uso de Antibióticos en Infecciones

1. Conocer la epidemiología local.
2. Iniciar pronto y en forma acertada.
3. Escoger el antibiótico de acuerdo al germen y su mecanismo de resistencia.
4. Con cultivo (+) de-escalar.
5. Usar dosis, intervalos y tiempos óptimos de tratamiento.
6. Utilizar medicamentos de calidad.

CIDEIM

“Un farmacéutico no debe comprar, vender o suministrar ningún producto medicinal cuando exista alguna razón para dudar de su calidad y seguridad”.

Código de Etica
Royal Pharmaceutical Society of Great Britain. 1992:7

GRACIAS

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