

# “Generics of antibiotics: Evidence-based approach”

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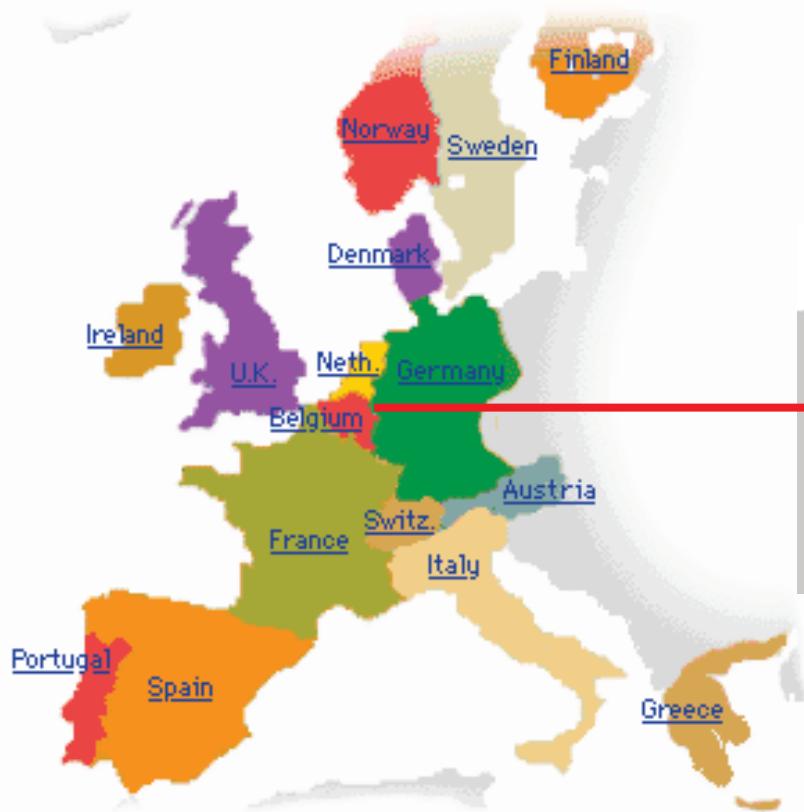
Round-Table  
Bayer Colombia  
Medellin, Colombia, 2 December 2015

# Disclosures and slides availability

- Research grants
  - Theravance, Astellas, Targanta, Cerexa/Forest, AstraZeneca, Bayer, GSK, Trius, Rib-X, Eumedica, Debiopharm
  - Belgian Science Foundation (*F.R.S.-FNRS*), Ministry of Health (*SPF*), Walloon and Brussels Regions, European Union (*FP7 programme*)
- Speaking fees
  - Bayer, GSK, Sanofi, Johnson & Johnson, OM-Pharma
- Decision-making and consultation bodies
  - European Committee for Antimicrobial Susceptibility Testing [EUCAST] (General Assembly and steering committee (2010-2012))
  - European Medicines Agency (external ad-hoc expert)
  - US National Institutes of Health (grant reviewing)
  - **Drive-AB [*Driving reinvestment in R&D and responsible use for antibiotics*]** (governance)

**Slides: <http://www.facm.ucl.ac.be> → Lectures**

# Belgium



# Belgium



10 millions inhabitants ...

10 Nobel prizes (10/850)

- **Peace**

- Institute of International Law, Ghent (1904)
- Auguste Beernaert (1909)
- Henri Lafontaine (1913)
- Father Dominique Pire (1958)

- **Literature**

- Maurice Maeterlinck, Ghent (1911)

- **Medicine**

- Jules Bordet, Brussels (1919)
- Corneille Heymans, Ghent (1938)
- Christian de Duve, Louvain (1974)
- Albert Claude, Brussels (1974)

- **Chemistry**

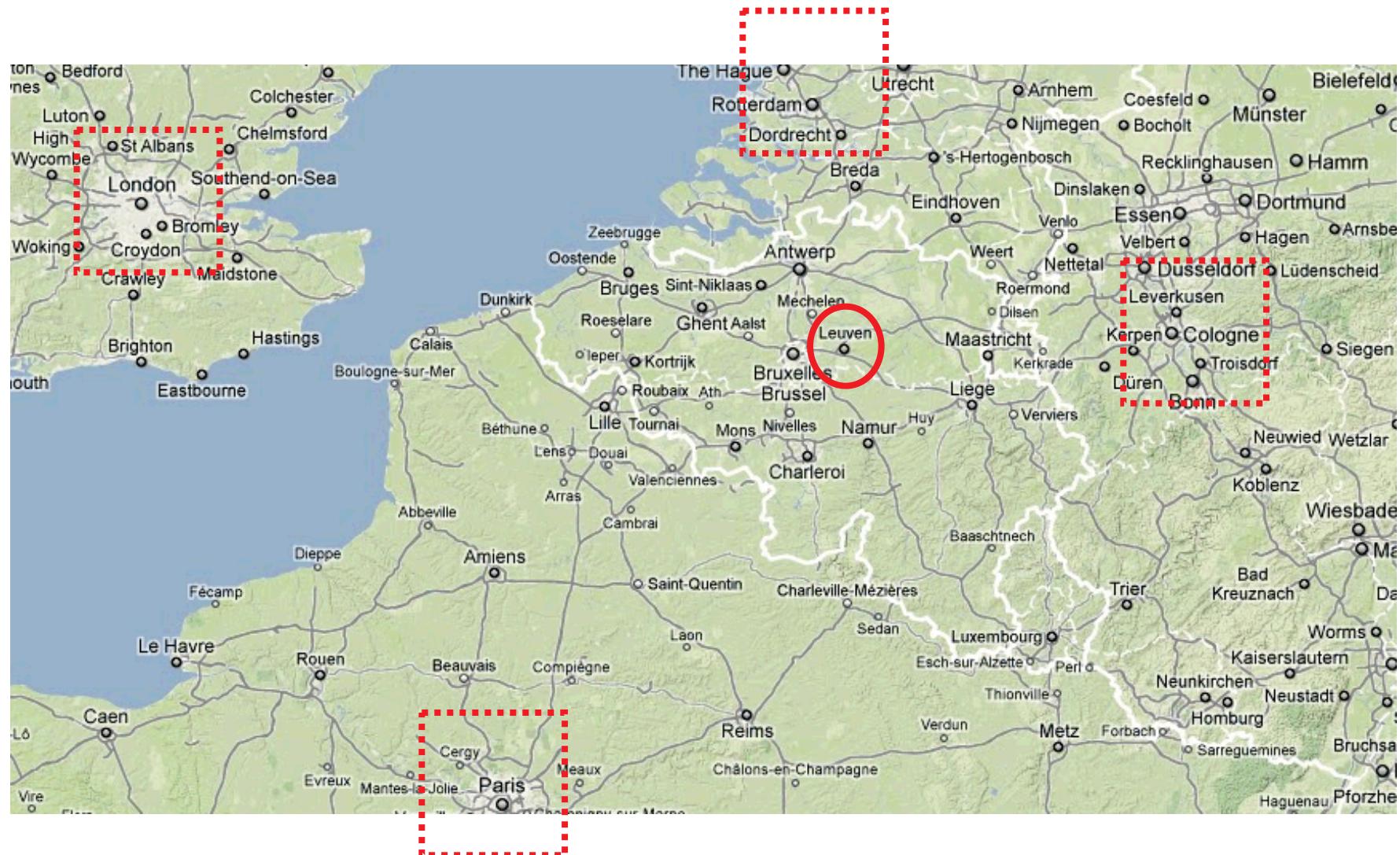
- Ilya Prigogine, Brussels (1977)

- **Physics**

- François Englert, Brussels (2013)

# The Catholic University of Louvain in brief (1 of 4)

- originally founded in **1425** in the city of **Louvain** (in French and English; known as **Leuven** in Flemish)



# The Catholic University of Louvain in brief (2 of 4)

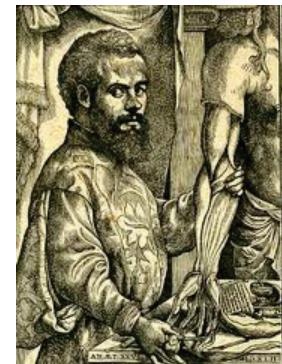
- It was one of the major Universities of the so-called "Low Countries" in the 1500 – 1800 period, with famous scholars and discoverers (Vesalius for anatomy, Erasmus for philosophy, ...). Teaching was in Latin, Greek, and Hebrew (College of the 3 languages...)



**The University in the 1500's**



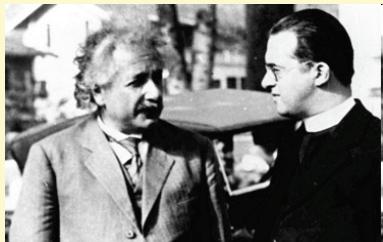
**Erasmus**



**Vesalius**

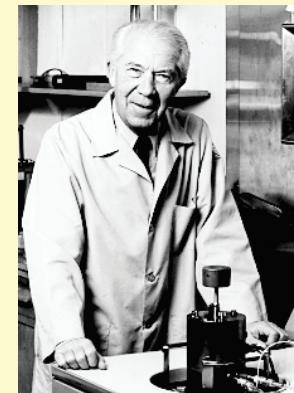
## The Catholic University of Louvain in brief (3 of 4)

- In the 19<sup>th</sup> century, teaching was in French but in the early 1900's, a Flemish-speaking section was opened. Courses were given in both languages, attracting many students and celebrities...



Prof. G. Lemaitre, professor of Physics and Mathematics at the University who, in the 1930's, made the first suggestion of the continuous expansion of the Universe ("big bang")  
(here in conversation with A. Einstein)

Professor C. de Duve, Professor of Biochemistry, obtained the Nobel Prize (Physiology and Medicine) in 1974 for his work on intracellular organelles (lysosomes, peroxisomes...)  
(here in front of a centrifuge)



- in 1968, the University was divided into
  - a French-speaking **Université catholique de Louvain**
  - a Flemish-speaking **Katholieke Universiteit Leuven...**

# The Catholic University of Louvain in brief (4 of 4)

- The Flemish-speaking **Katholieke Universiteit Leuven** has remained in Louvain (Leuven) and is named in English "Catholic University Leuven".
- The French-speaking **Université catholique de Louvain** has moved about 25 km South in a place called "Louvain-la-Neuve", with the "Health Sciences Sector" located in Brussels (Woluwe)



- Together, the two Universities have about **60,000 students**

# What do we do?

- Teaching of Pharmacology and Pharmacotherapy
- Post-graduate training on Drug Development
- Launching of Clinical Pharmacy in Europe
- Web-based courses on anti-infective Pharmacology
- 30 graduating students, doctoral fellows and post-graduate fellows working on anti-infective therapy (laboratory and clinical applications)
- improved schedules of aminoglycosides and  $\beta$ -lactams
- assessment of novel antibiotics
  - beta-lactams (e.g., ceftaroline...)
  - fluoroquinolones (e.g., delafloxacin...)
  - lipoglycopeptides (e.g., oritavancin)
  - ketolides ( e.g., solithromycin...)
  - oxazolidinones (e.g., tedizolid ...)
  - others...

[www.facm.ucl.ac.be](http://www.facm.ucl.ac.be)



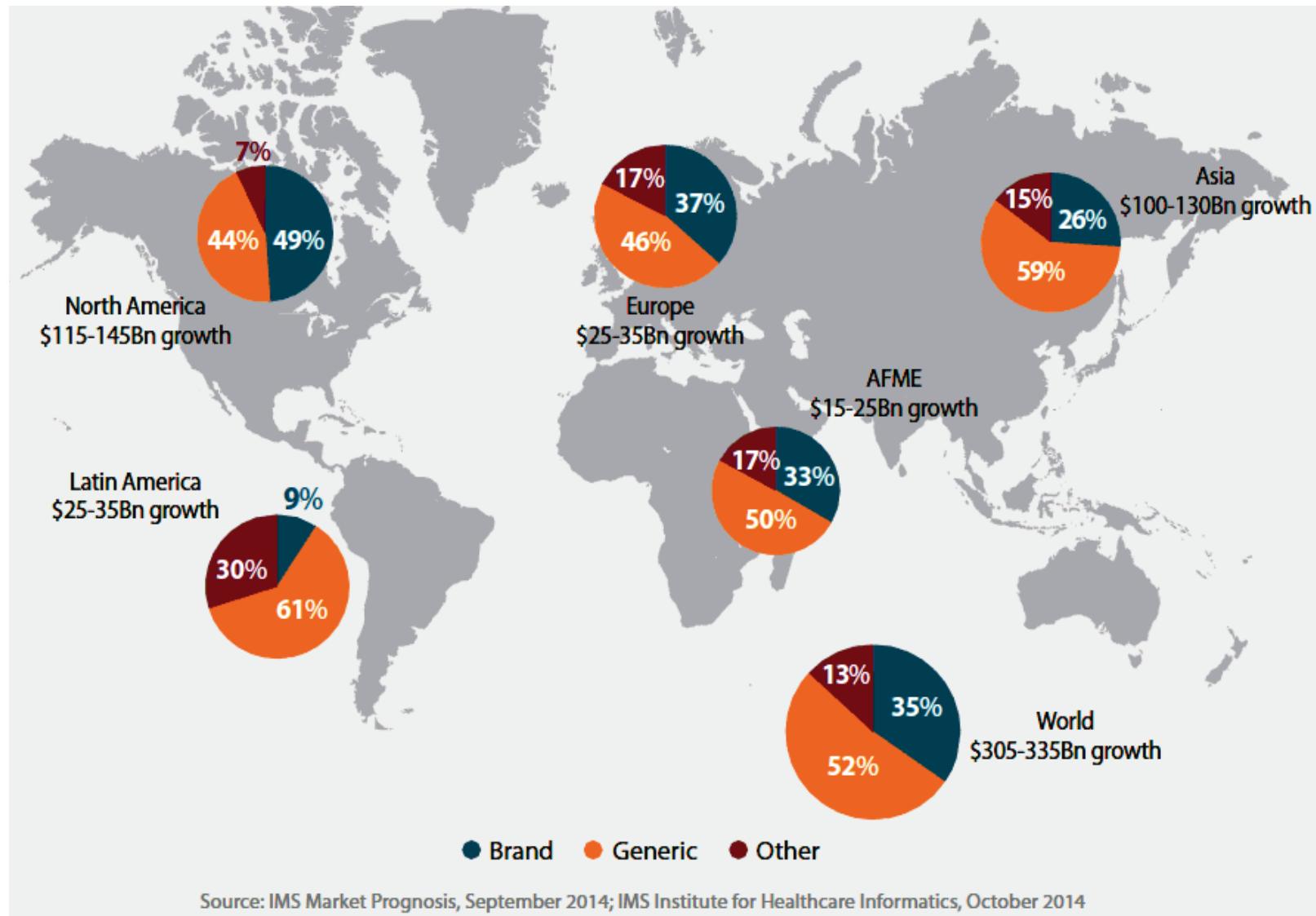
A partial view of our University Clinic (900 beds) and the Education and Research buildings (5,000 students), in the outskirts of Brussels, Belgium



- Editorial board of AAC and IJAA
- Member of the General Committee of EUCAST (for ISC) and of its Steering committee (2008-10)
- Member of the Belgian Antibiotic Policy Coordination Committee
- Founder and Past President of the International Society of Antiinfective Pharmacology (ISAP)

[www.isap.org](http://www.isap.org)

# Generic across the world ...



# Why choosing a "generic" antibiotic ?

1. Because it is like airlines: low cost is better
2. Because they have the same quality as the original ones
3. Because they can be produced locally (in my country) (as opposed to countries of "Big Pharma")
4. Because my patients / my hospital / my country has/have limited resources
5. Because "old antibiotics" (no longer under patent) cover most of my needs

Please, think about  
what YOU would choose !

# I guess the real and only justifiable answer is...

Your prescription,  
your choice.



\$71

Thirty-day  
prescription of one  
brand name drug



\$22

Thirty-day prescription  
of its generic equivalent



# What shall we discuss?

1. A **political choice** (US and EU ... and Asia ...)
2. Approach to PK **bioequivalence**
3. Approach to **microbiological equivalence**
4. Approach to **pharmacodynamic equivalence**
5. Problems related to **dissolution and stability**
6. **Impurities** and falsified medicines
7. The **hidden risks** of "low cost" antibiotics

# The US Law

PUBLIC LAW 98-417—SEPT. 24, 1984

98 STAT. 1585

Public Law 98-417  
98th Congress

## An Act

To amend the Federal Food, Drug, and Cosmetic Act to revise the procedures for new drug applications, to amend title 35, United States Code, to authorize the extension of the patents for certain regulated products, and for other purposes.

Sept. 24, 1984  
[S. 1538]

*Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled, That this Act may be cited as the "Drug Price Competition and Patent Term Restoration Act of 1984".*

Drug Price  
Competition and  
Patent Term  
Restoration Act  
of 1984.  
21 USC 301 note.

## TITLE I—ABBREVIATED NEW DRUG APPLICATIONS

<http://www.gpo.gov/fdsys/pkg/STATUTE-98/pdf/STATUTE-98-Pg1585.pdf>

- FDA works along the provisions of the **Drug Price Competition and Patent Term Restoration Act** ("Hatch-Waxman Act" [Public Law 98-417]), which encouraged the manufacture of generic drugs
- Marketers of generic drugs can file an **Abbreviated New Drug Application** (ANDAs) to seek FDA approval

# FDA requirements in a nutshell \*

- Published literature (for data for which the applicant has no right of reference to the original raw data supporting the application)
- FDA's findings (safety and effectiveness of the already approved drug)
- Comparison with the original NCE/NME (New Chemical Entity/New Molecular Entity) application for
  - dosage form, strength, route of administration
  - substitution of an active ingredient in a combination product or change such as different salt, ester, complex, ...
- **Bioequivalence study**

The proposed product does not need to be shown to be clinically **better** than the previously approved product; however, the application should not be used as a route of approval for poorly bioavailable generic drug products unable to meet the standards for bioequivalence.

\* 505 (B) (2) Application (Guidance to Industry)  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079345.pdf>

# In the European Union



►B

## DIRECTIVE 2001/83/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 6 November 2001

### on the Community code relating to medicinal products for human use

(OJ L 311, 28.11.2001, p. 67)

- \* Legislative act of the European Union that is then translated into country-specific laws for actual implementation, which may vary (in details) between countries (vs regulations that are self-executing and do not require local adaptations)

- ...the applicant shall not be required to provide the results of pre-clinical tests and of clinical trials if he can demonstrate that the medicinal product is a **generic** of a reference medicinal product...
- ... '**generic medicinal product**' shall mean a medicinal product which has the **same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product**, and whose **bioequivalence** with the reference medicinal product has been demonstrated by **appropriate bioavailability studies**...

[http://europa.eu/legislation\\_summaries/internal\\_market/single\\_market\\_for\\_goods/pharmaceutical\\_and\\_cosmetic\\_products/l21230\\_en.htm](http://europa.eu/legislation_summaries/internal_market/single_market_for_goods/pharmaceutical_and_cosmetic_products/l21230_en.htm)

# 1<sup>st</sup> round of conclusions and discussions

- The decision to go for generics is **political**
- It finds its origin and basis in
  - the **limited duration of the patent protection**  
(usually about 20 years post patent application → < 10 years after approval !!)
  - the fact that **drug production costs are usually very low**  
(often only a very minor fraction of the total requested by the innovator at the time of initial commercialization)
- The **only** incentive for going to generics **by governments** (and/or drug acquisition organizations) is only to acquire and provide drugs **more cheaply** to the population
- The opinion of the **clinically-active health professionals** is **rarely sought**, and patients' opinion never beyond pure economic considerations...

# What shall we discuss?

1. The US and the EU laws (as template)
2. **Approach to PK bioequivalence**



<http://www.choosinggenerics.ca/Bioequivalence.aspx>

Last visited: 15 March 2014

# Bioequivalence: principles (for oral drugs)

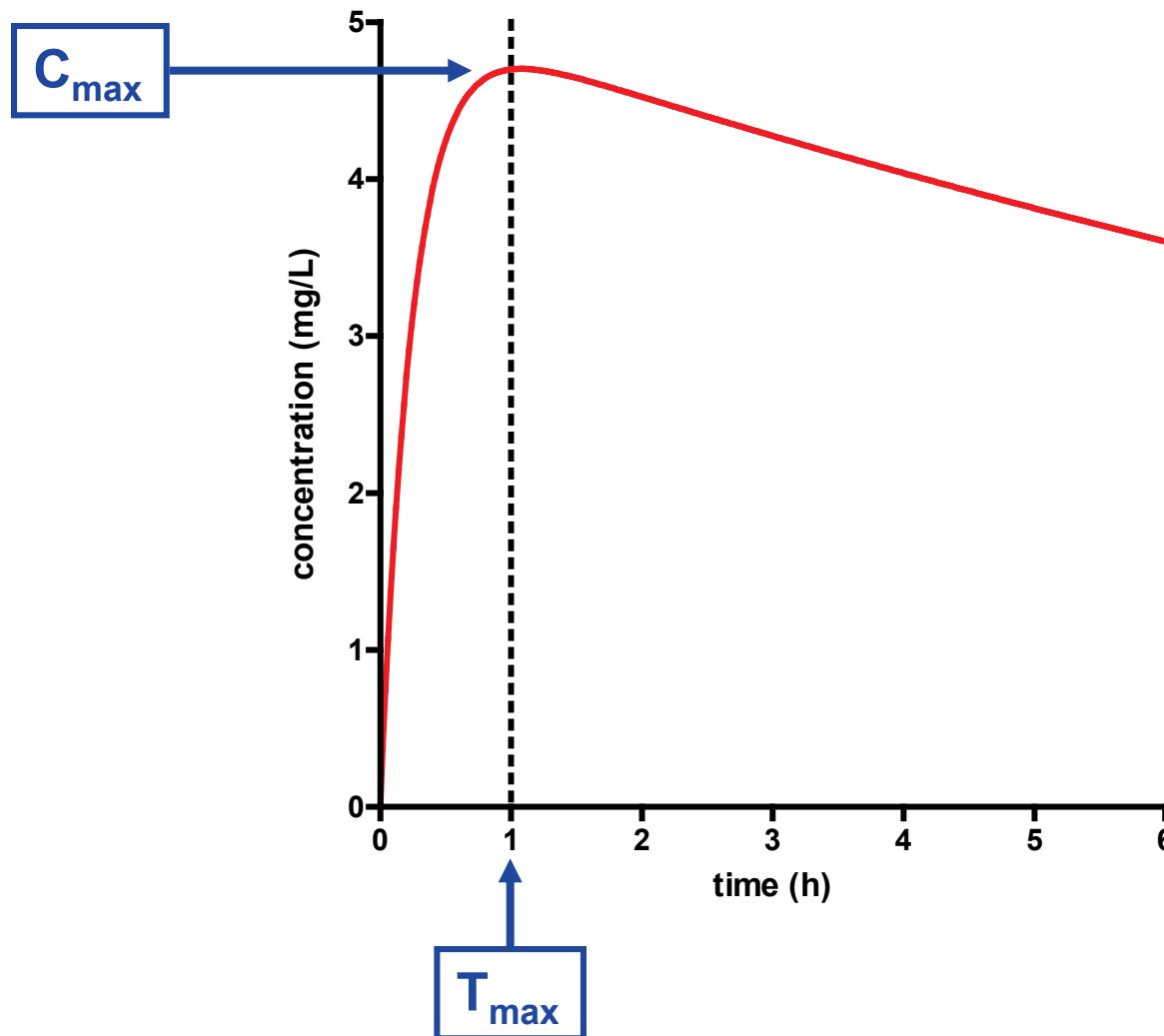
- Bioequivalence is an **accepted surrogate for therapeutic equivalence** <sup>1</sup> (including for branded drugs when the marketed form differs from the form used in development...)<sup>2</sup>
- Primary metrics are <sup>1,3</sup>
  - **AUC** (area under the plasma concentration–time profile of the active substance)  
→ **extent of absorption**
  - **C<sub>max</sub>** (the maximum plasma concentration of the active substance)  
→ **extent and rate of absorption**
  - **T<sub>max</sub>** (the time when C<sub>max</sub> is reached)  
→ **rate of absorption**

1. Hauschke et al. Bioequivalence Studies in Drug Development – Methods and Applications, John Wiley & Sons Ltd. (UK), 2007.

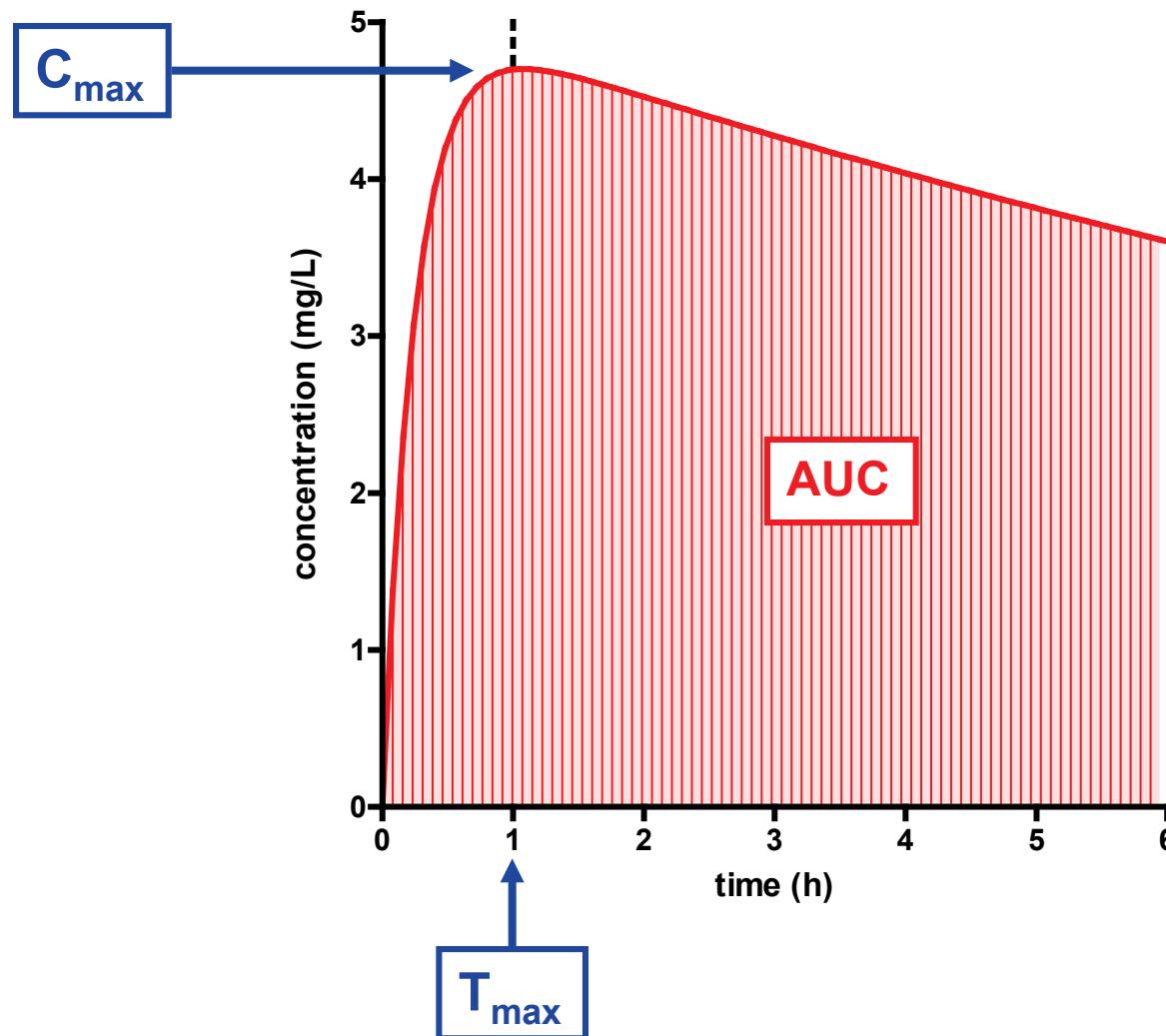
2. Benet LZ: Understanding bioequivalence testing. Transplant.Proc. 31 (Suppl 3A): 7S-9S, 1999.

3. Niazi SK: Handbook of Bioequivalence Testing, "Drugs and the Pharmaceutical Sciences", vol. 171, Informa Healthcare (New York), 2007.

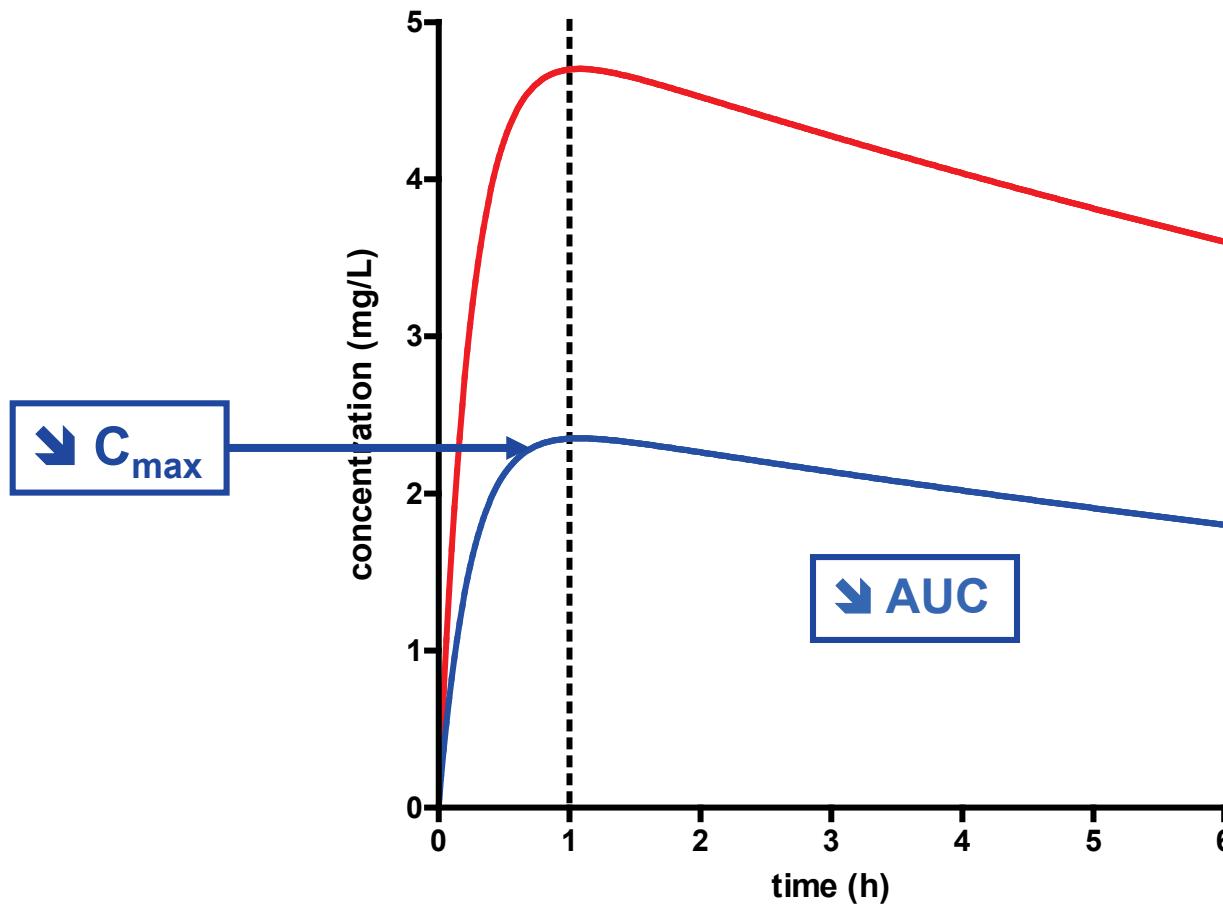
# AUC – C<sub>max</sub> – T<sub>max</sub>



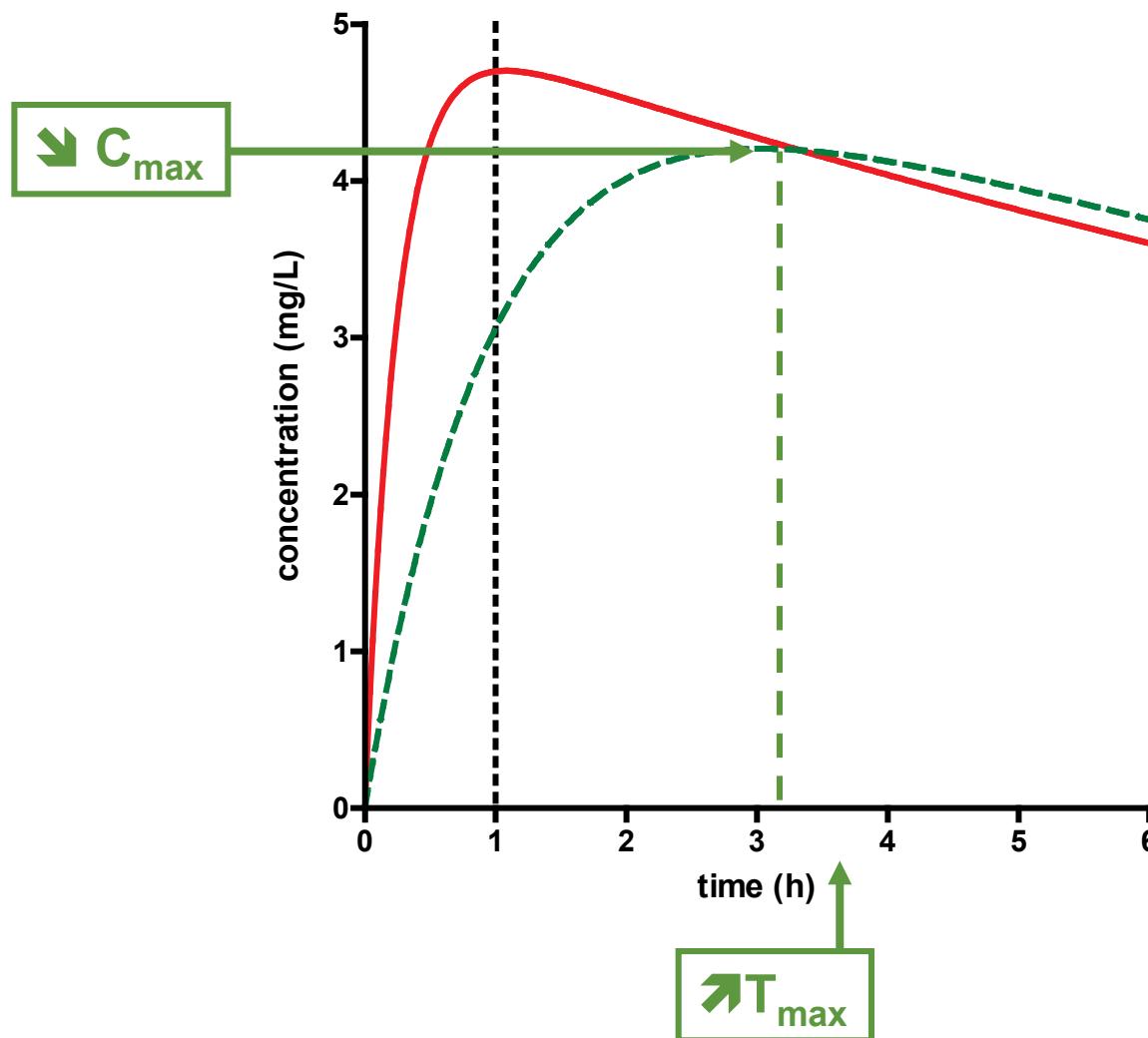
# AUC – C<sub>max</sub> – T<sub>max</sub>



# What if the absorption is decreased ?

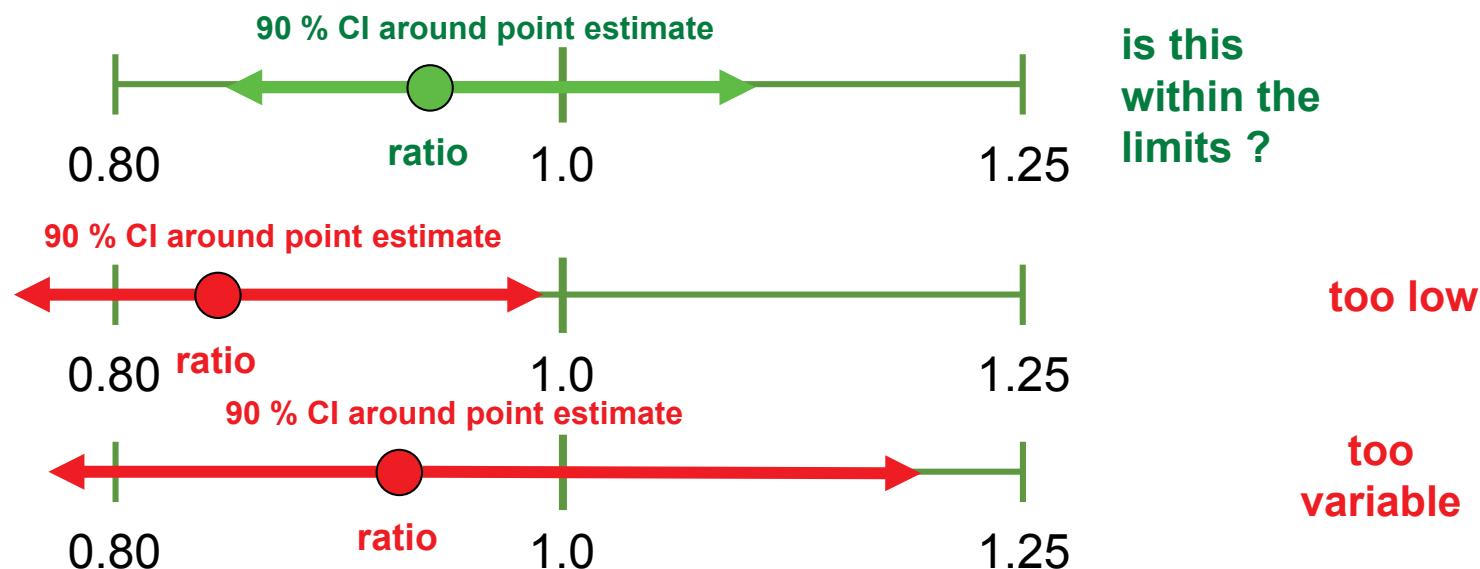


# What if absorption is delayed ?



# Criteria of bioequivalence (EMA\* / FDA\*\*)

- Calculate the **90% confidence interval** around the **geometric mean ratios** of **both AUC** and **C<sub>max</sub>** for Test (generic) and Reference (innovator).
- The 90% confidence intervals should, in most cases, be **within the 0.80 – 1.25 acceptance limits**.

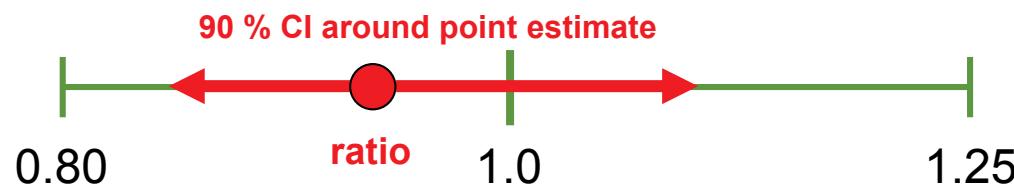


\* Guideline to the Investigation of Bioequivalence, London, 20 January 2010 - Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr \*\*  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2010/01/WC500070039.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf)

\*\* Guidance for Industry (BIOEQUIVALENCE GUIDANCE) - Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070124.pdf>  
<http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm052363.pdf>

# Criteria of bioequivalence (EMA / FDA)

- Calculate the **90% confidence interval** around the **geometric mean ratios** of **both AUC** and **C<sub>max</sub>** for Test (generic) and Reference (innovator).
- The 90% confidence intervals should, in most cases, be **within the 0.80 – 1.25 acceptance limits**.



Notes:

1. if both **AUC** and **C<sub>max</sub>** are within range, the generic should have the same bioavailability as the reference
2. statistical evaluation of **T<sub>max</sub>** only makes sense if there is a clinically relevant claim for rapid release or action or signs related to adverse effects (see next slide)
3. for drugs with narrow therapeutic index, EMA recommends "tightened" acceptance intervals, **Health Canada** requires **0.9 – 1.12**, but **FDA** accepts **0.8 – 1.25**

# Caveats !

- Bioequivalence studies are NOT required for drugs administered by the intravenous route ! (since that route provides, by definition a 100 % bioavailability and, therefore, full bioequivalence !)
  - Only demonstration that the drug has the **same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product** is required.
- Complex drugs (such as biologicals, fractionated heparins, etc. ) may require and will pass through more stringent requirements <sup>1-3</sup>

<sup>1</sup> Tothfalusi et al. Eur J Health Econ (2014) 15 (Suppl 1):S5–S11

<sup>2</sup> Ahn & Lee, Ungyong Tonggye Yongu (2011) 24(3): 495–503

<sup>3</sup> Lee et al. Nature Biotechnology (2013) 31:220-226

# What shall we discuss?

1. A political decision (US and EU laws as an example)
2. Approach and limits to PK bioequivalence studies
3. **Approach to microbiological and therapeutic equivalence**
  - MIC
  - PK/PD animal models
  - clinical data (case reports)



<http://www.umu.se/english/research/research-excellence/strong-research/Infection+Biology>  
Last visited: 25 March 2014



<http://www.gaebler.com/How-to-Start-a-Laboratory-Animals-Business.htm>  
Last accessed: 29 March 2014



<http://www.buzzle.com/articles/staph-infections-staph-infection-treatment-and-symptoms.html>  
Last visited: 25 March 2014

# Potency (piperacillin)

Using the incremental MIC assay (Jones RN et al., *Diagn Microbiol Infect Dis* 2008; 61:76–79).

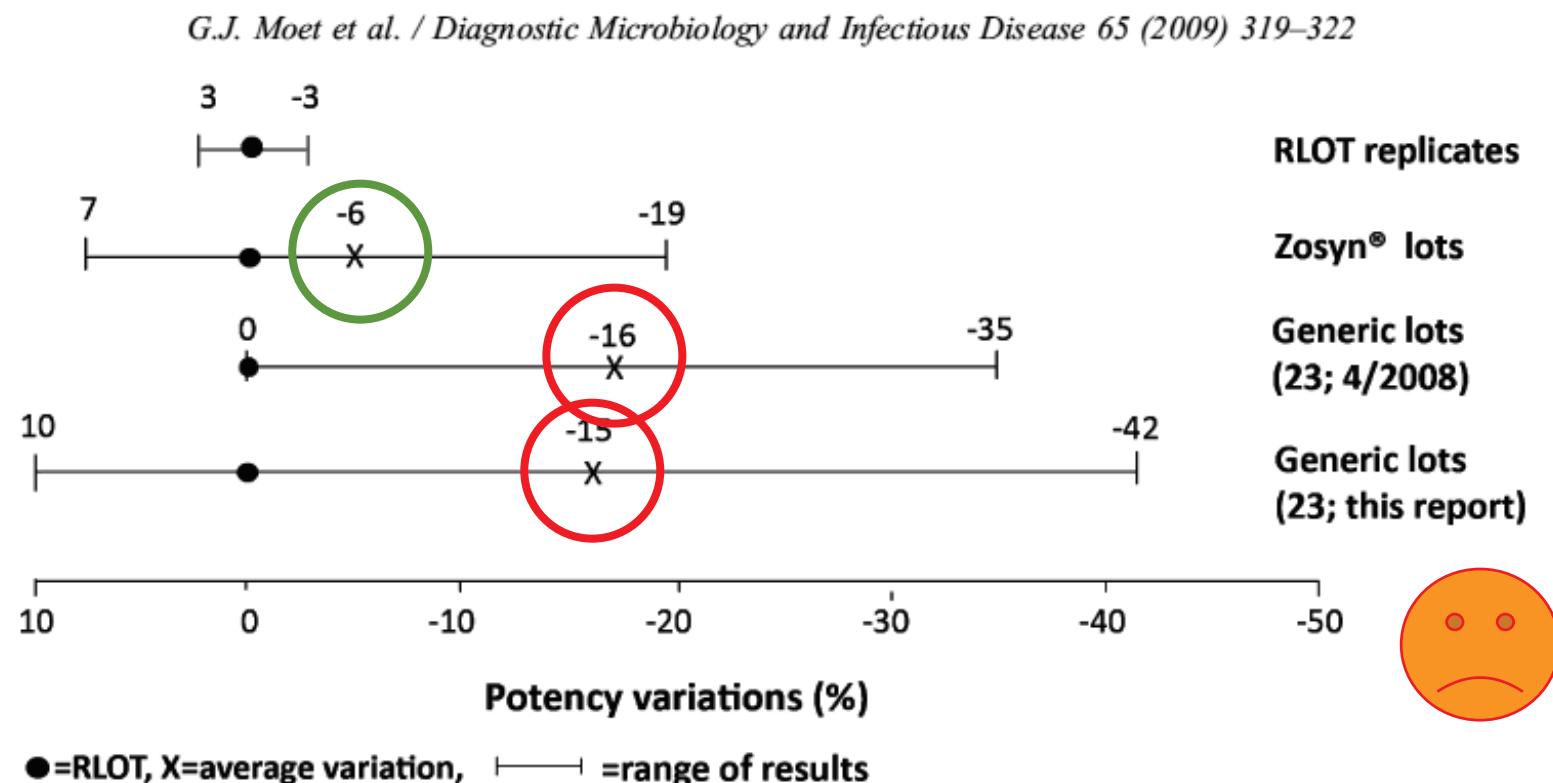


Fig. 1. Extent of potency variations among 4 groups of experiments with piperacillin/tazobactam intravenous injection lots.

Moet et al. Diagnostic Microbiology and Infectious Disease 2009;65: 319–322

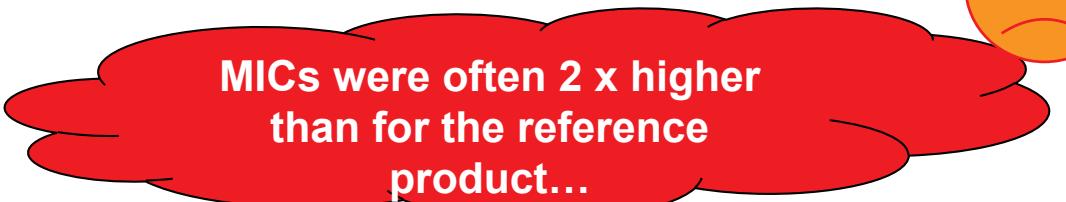
# MIC values (vancomycin)

**Table 1** Comparison of antimicrobial activity against various clinical isolates in a brand name and generic antibiotics

Antibiotic	Pathogen (no.)	No. of generic markers	Nonidentical rate of the MIC value of all generics (mean $\pm$ SD)	MIC distribution (%) of the most different generic versus brand name drug						
				1/8	1/4	1/2	1 <sup>a</sup>	2	4	8
Vancomycin	MRSA (90)	5	25.00 $\pm$ 15.52	—	—	—	54.4	45.6	—	—
Teicoplanin	MRSA (147)	7	28.09 $\pm$ 10.29	—	—	—	59.2	40.1	0.7	—
Cefotiam	<i>Staphylococcus aureus</i> (100)	7	8.71 $\pm$ 3.04	—	—	—	87.0	13.0	—	—
	<i>Escherichia coli</i> (100)	7	12.00 $\pm$ 5.89	—	—	—	77.0	22.0	1.0	—
Ceftriaxone	<i>Streptococcus pneumoniae</i> (126)	6	12.70 $\pm$ 4.77	—	—	—	81.7	18.3	—	—
Ceftazidime	<i>Pseudomonas aeruginosa</i> (100)	2	3.00 $\pm$ 2.83	—	—	—	95.0	5.0	—	—
Meropenem	<i>P. aeruginosa</i> (100)	7	18.57 $\pm$ 3.46	—	—	—	78.0	19.0	2.0	1.0
Imipenem	<i>P. aeruginosa</i> (100)	4	9.00 $\pm$ 2.58	—	—	—	88.0	11.0	1.0	—

MRSA methicillin-resistant *Staphylococcus aureus*<sup>a</sup> Note that the distribution of one minimal inhibitory concentration (1 MIC) shows the identical rate with the brand drug: MIC was determined by broth micro-dilution method using powder in each drug trial

Fujimura & Watanabe J Infect Chemother (2012) 18:421–427

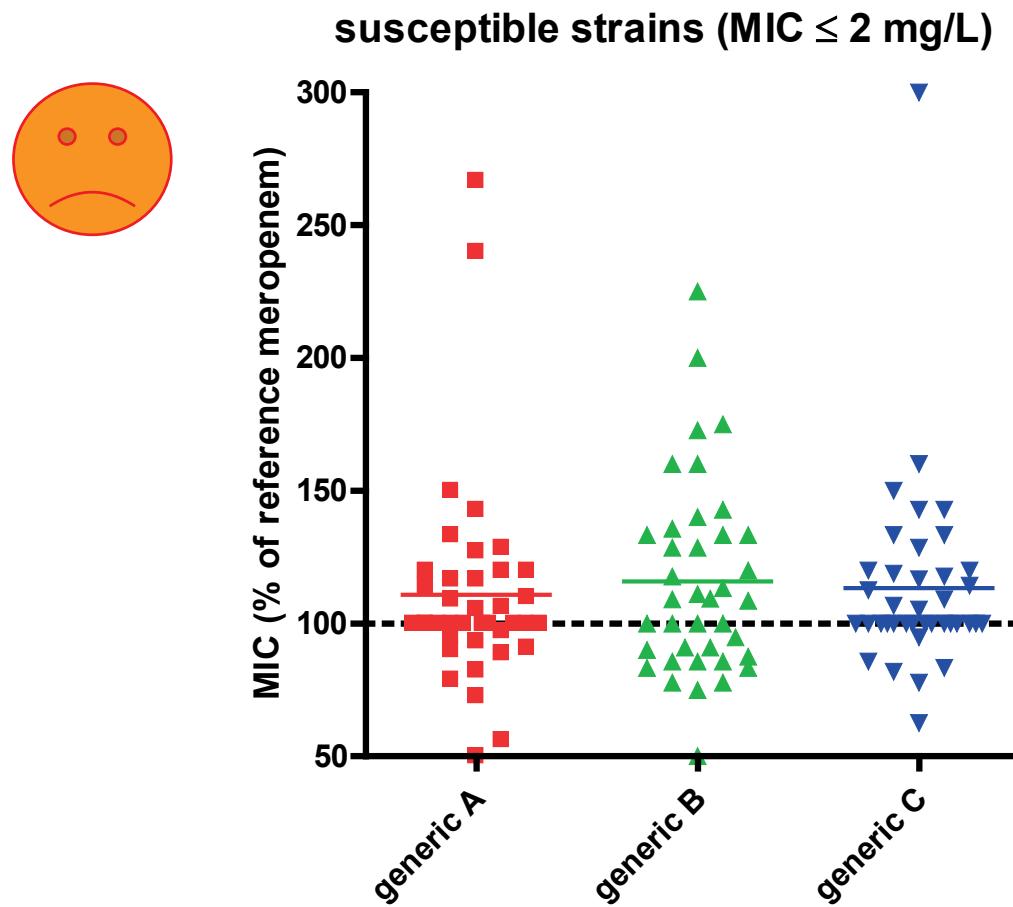


**MICs were often 2 x higher  
than for the reference  
product...**



# MIC values (meropenem) in Belgium

*MICs determined by arithmetic dilutions in comparison  
with the originator MERONEM®*



Van Bambeke et al., in preparation

# Vancomycin: evidence of non-therapeutic equivalence revealed by a PK/PD animal model in Colombia

Neutropenic mouse thigh infection model

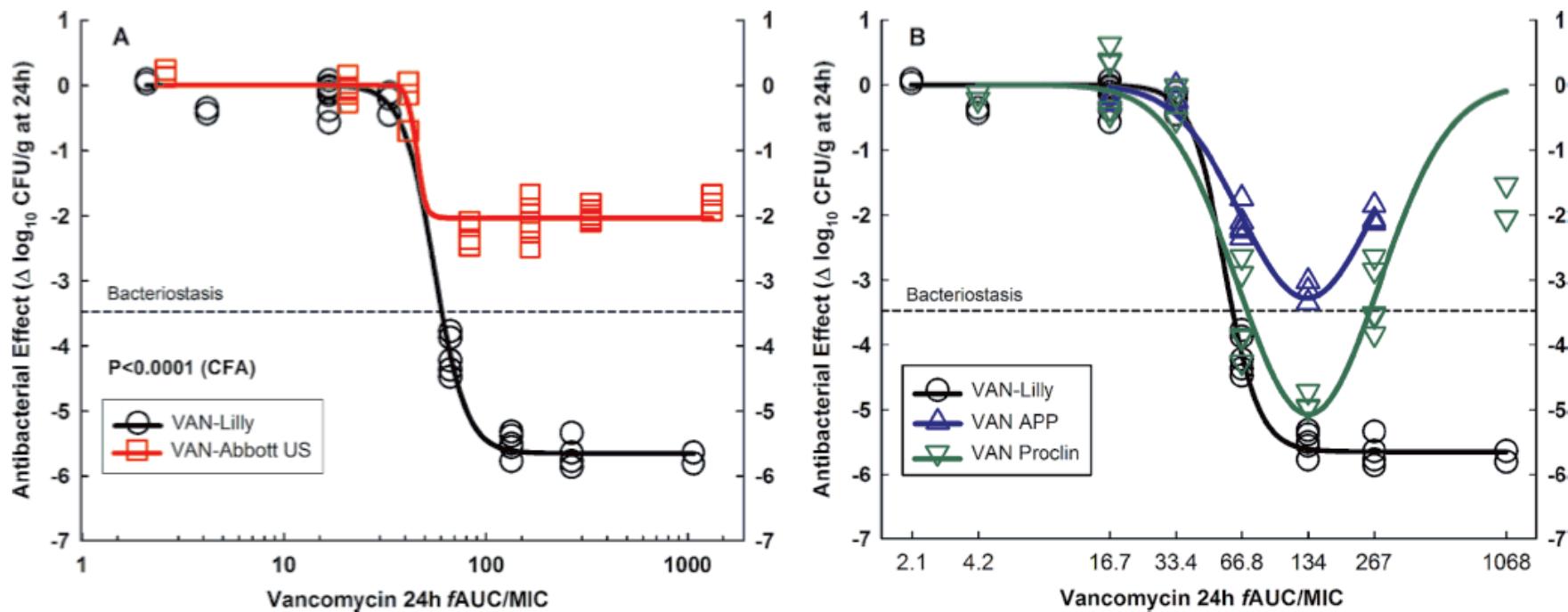
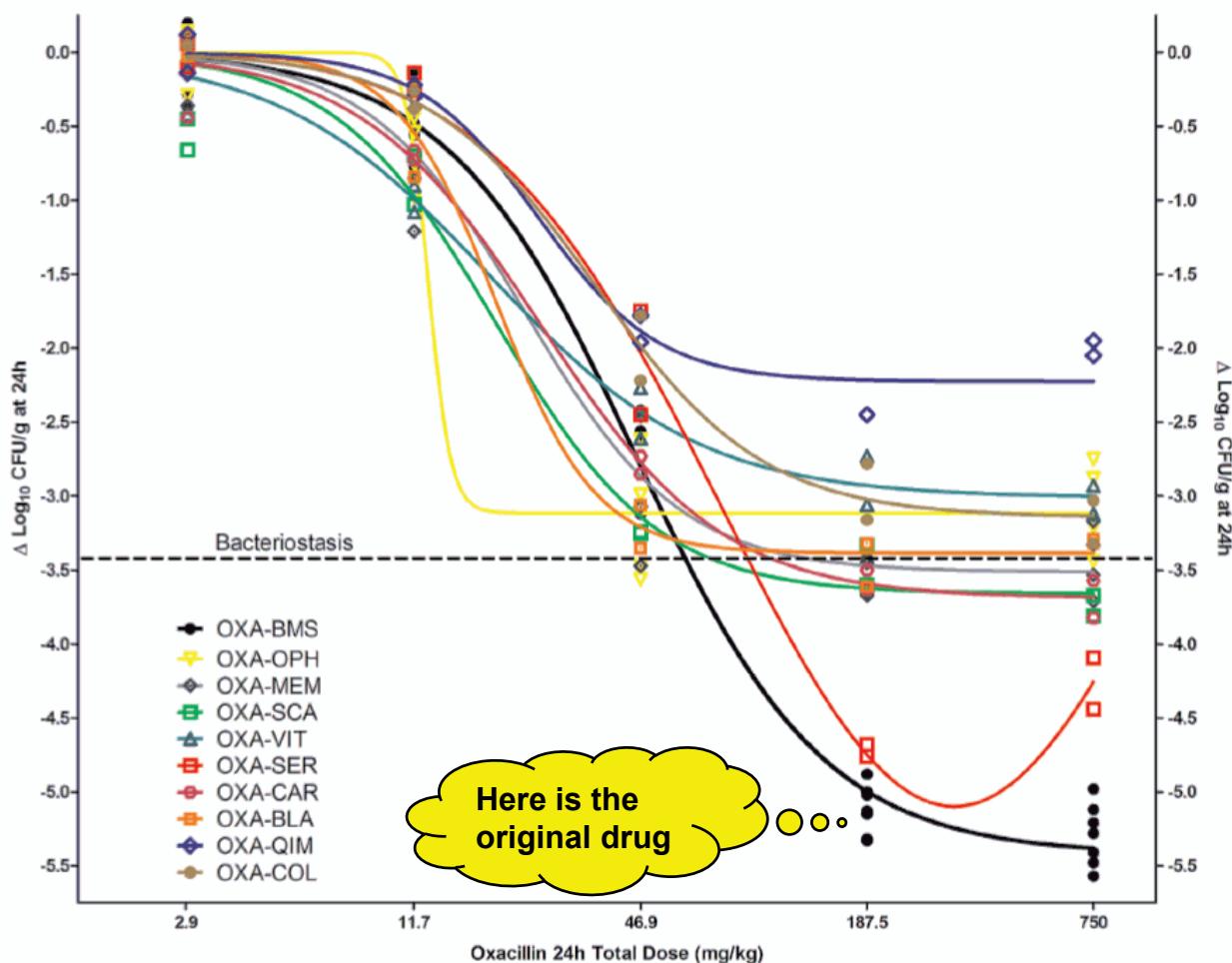


FIG. 1. *In vivo* efficacy against *S. aureus* GRP-0057 (years 2002 and 2003) at a low inoculum ( $4.30 \pm 0.05 \log_{10}$  CFU per thigh when subcutaneous treatment q1h started). Vancomycin generic products are compared with the innovator (VAN-Lilly) in dose-effect experiments (2.34 to 1,200 mg/kg per day) using the neutropenic mouse thigh infection model (each data point represents the mean CFU/g of both thighs from a single mouse). (A) Pharmacodynamic patterns of VAN-Abbott US and VAN-Lilly fitted to the Hill model. Despite containing a significantly greater concentration of API (125%), VAN-Abbott US was completely ineffective *in vivo*. VAN-Abbott US is shown in a separate graph because of its greater AUC/MIC ratio than that of VAN-Lilly (123%; their dosing regimens were identical). (B) VAN-APP and VAN-Proclin were both pharmaceutically equivalent to VAN-Lilly, but neither was therapeutically equivalent due to their marked Eagle effect. The curve for VAN-APP ends at 300 mg/kg (fAUC/MIC, 267 h) because this product was discontinued and the remaining amount was insufficient for the highest doses.

Vesga et al. Antimicrob Agents Chemother. 2010; 54:3271–3279.

# Oxacillin: evidence of non-equivalence in animal PK/PD model

Neutropenic mouse thigh infection model



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

# But pharmacodynamics equivalence can also be demonstrated



Antimicrob Agents Chemother 59:53–58.

## Impact on Resistance of the Use of Therapeutically Equivalent Generics: the Case of Ciprofloxacin

Carlos A. Rodriguez,<sup>a,b</sup> Maria Agudelo,<sup>a,b,d</sup> Andres F. Zuluaga,<sup>a,b</sup> Omar Vesga<sup>a,b,c,d</sup>

GRIPE: Grupo Investigador de Problemas en Enfermedades Infecciosas,<sup>a</sup> Department of Pharmacology,<sup>b</sup> and Department of Internal Medicine,<sup>c</sup> School of Medicine, University of Antioquia, Medellin, Colombia; Infectious Diseases Unit, Hospital Universitario San Vicente Fundación, Medellin, Colombia<sup>d</sup>

# But pharmacodynamics equivalence can also be demonstrated



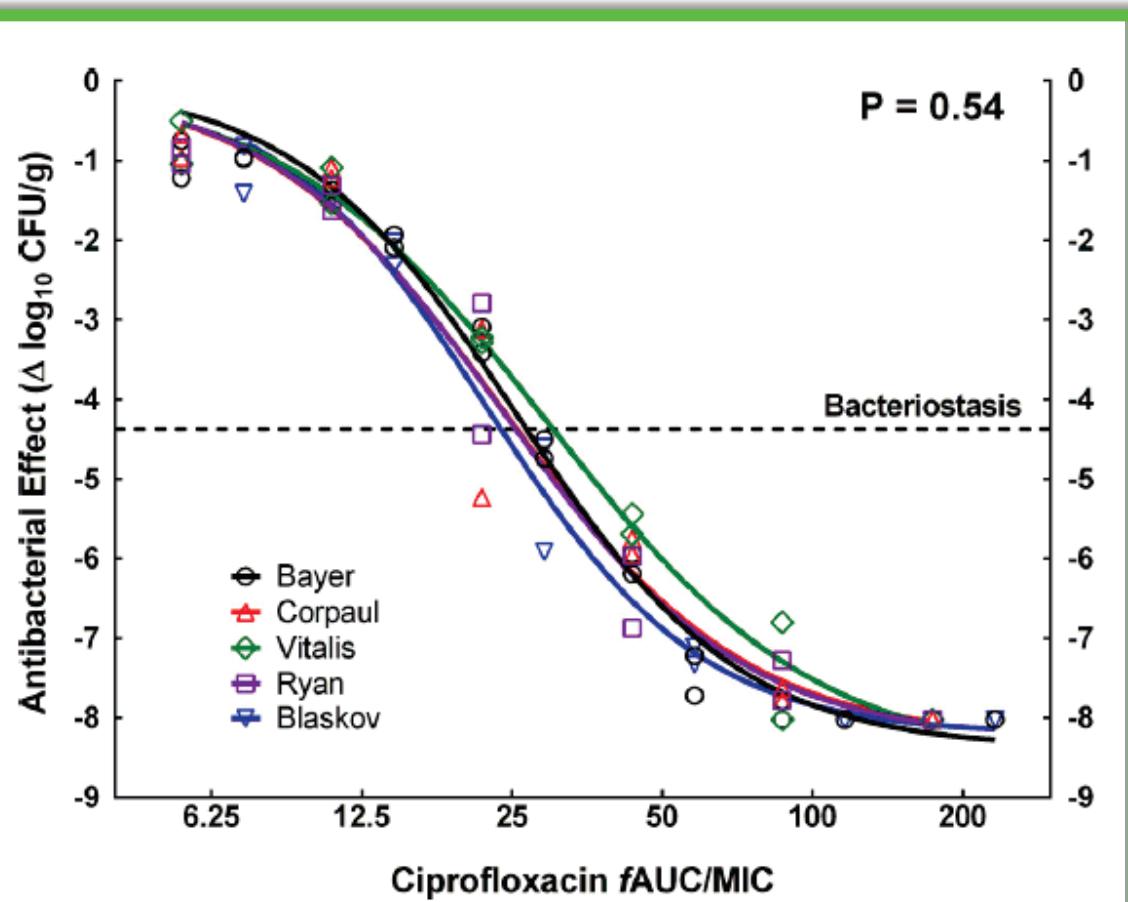
## Antimicrob Agents Ch

### Impact on Resistance of the Use of Generic Ciprofloxacin Generics: the Case of Ciprofloxacin

Carlos A. Rodriguez,<sup>a,b</sup> Maria Agudelo,<sup>a,b,d</sup> Andres F. Zu

GRIPE: Grupo Investigador de Problemas en Enfermedades Infecciosas,<sup>a</sup> Department of Infectious Diseases, University of Antioquia, Medellin, Colombia; Infectious Diseases Unit, Hospital Universitario San Ignacio, Bogotá, Colombia

Same authors as those  
describing the non-  
therapeutic equivalence  
of vancomycin and  
oxacillin !



**FIG 1** *In vivo* exposure-response relationship of ciprofloxacin against *P. aeruginosa* PAO1, comparing the innovator and four generic products. Global CFA indicated that all data belonged to the same population and could be described by a single curve, confirming the therapeutic equivalence of the generics. Stasis was achieved with a fAUC/MIC value of ~27 and 99.9% kill with a fAUC/MIC value of ~75.

# Clinical alerts (efficacy and safety) ?

## Safety and efficacy of generic drugs with respect to brand formulation

Luca Gallelli<sup>1</sup>, Caterina Palleria<sup>1</sup>, Antonio De Vuono<sup>2</sup>, Laura Mumoli<sup>1</sup>, Piero Vasapollo<sup>2</sup>, Brunella Piro<sup>3</sup>, Emilio Russo<sup>1</sup>

<sup>1</sup>Department of Health Science, Regional Center on drug information, Mater Domini University Hospital, Italy and Chair of Pharmacology, School of Medicine, University of Catanzaro, <sup>2</sup>Department of General Medicine, ASP Cosenza, <sup>3</sup>Department of Pharmacovigilance, ASP Cosenza, Italy

J Pharmacol Pharmacother. 2013 Dec;4(Suppl 1):S110-4.

“In this case-review, we report the lack of efficacy during treatment with generic formulations of fluoroquinolones and discuss the relative reasons also considering the limitations of this legal approach.”

# Clinical alerts (efficacy and safety) ?

## Safety and efficacy of generic drugs compared to brand formulation

Luca Gallelli<sup>1</sup>, Caterina Palleria<sup>1</sup>, Antonio De Vuono<sup>2</sup>, Ilenia Sartori<sup>1</sup>,  
Emilio Russo<sup>1</sup>

<sup>1</sup>Department of Health Science, Regional Center on drug information, Maggiore School of Medicine, University of Catanzaro, <sup>2</sup>Department of General Medicine, University of Cosenza, Italy

J Pharmacol Pharmacother. 2013 Dec;4(Suppl 1):

In this case-review, we report a case of lack of efficacy during treatment with generic formulations and discuss the relative reasons, highlighting the importance of this legal approach.

### CONCLUSION

In conclusion, the use of generic drugs could be related with an increased days of disease (time to relapse) or might lead to a therapeutic failure; on the other hand, a higher drug concentration might expose patients to an increased risk of dose-dependent side-effects. Overall, it is advisable to well evaluate the effects of generic formulations during the therapeutic treatment.

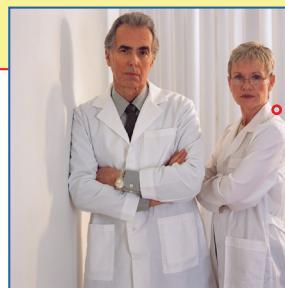
In agreement with Manning and Smith,<sup>[41]</sup> it is necessary to underline the importance that clinician's change their attitude toward pharmacovigilance and post-marketing surveillance systems, which can help to identify the lack of efficacy during the treatment with generic formulations.

### ACKNOWLEDGMENTS

The Italian Drug Agency (Agenzia Italiana del Farmaco) is kindly acknowledged for its financial and technical support.

## 2nd round of conclusions and discussions

- There are contradictory observations about the **pharmacodynamic and therapeutic equivalence** of generic antibiotics, (even from the same investigators when comparing different products !)
- The reasons for a non-equivalence remain often obscure but may be related to **differences in biophysical properties** that will impact on the inter- and intra-organ bioavailability, which **cannot be detected by simple measurements of serum levels**
- This needs to be further studied, but, at this point, is beyond the clinician's grip !



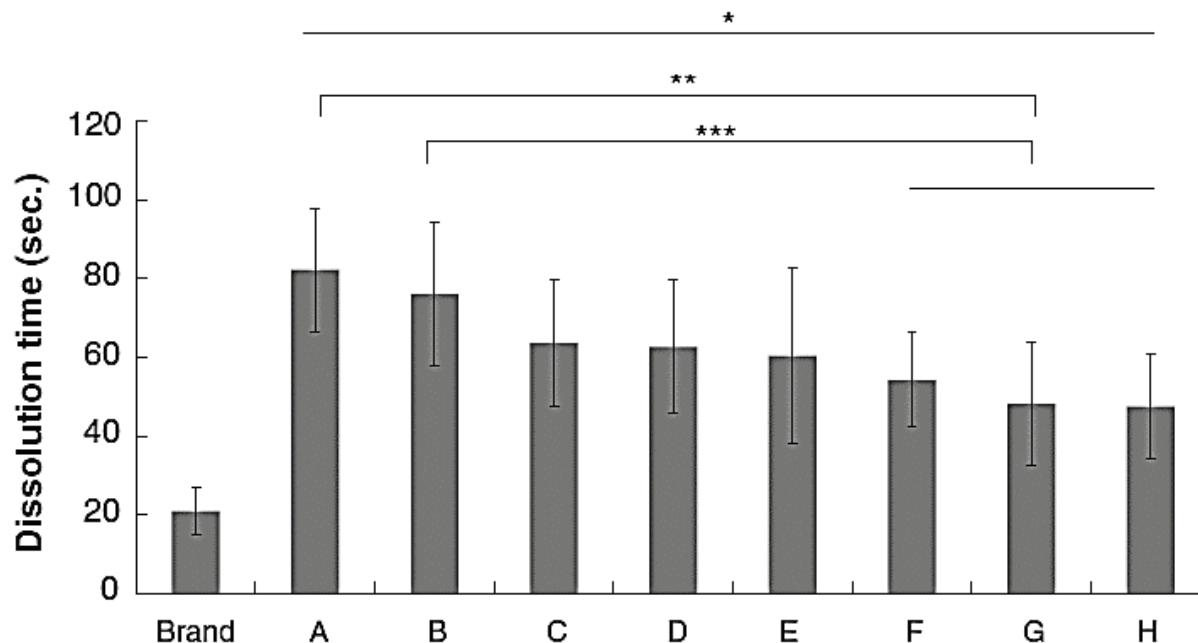
Who can we  
really trust ?

# **And this brings me to pharmaceutical quality... What is your opinion ?**

- 1. The generic must have the same solubility / dispersion properties than the original ...**
- 2. The generic cannot contain more impurities (or give rise to more degradation products) than the original ...**
- 3. I must be sure about the real content of what I prescribe ...**
- 4. All of the above is important...**
- 5. None of the above is important ...**

**Please, think about  
what YOU would choose !**

# Dissolution of meropenem in Japan



**Fig. 3** Comparison of dissolution time between brand name meropenem and eight generics. A–H Generic products of meropenem.  
\* $P < 0.001$  versus brand name drug; \*\* $P < 0.001$  versus generic A drug; \*\*\* $P < 0.001$  versus generic B drug

# Crystals size in meropenem in Japan

J Infect Chemother (2012) 18:421–427

425

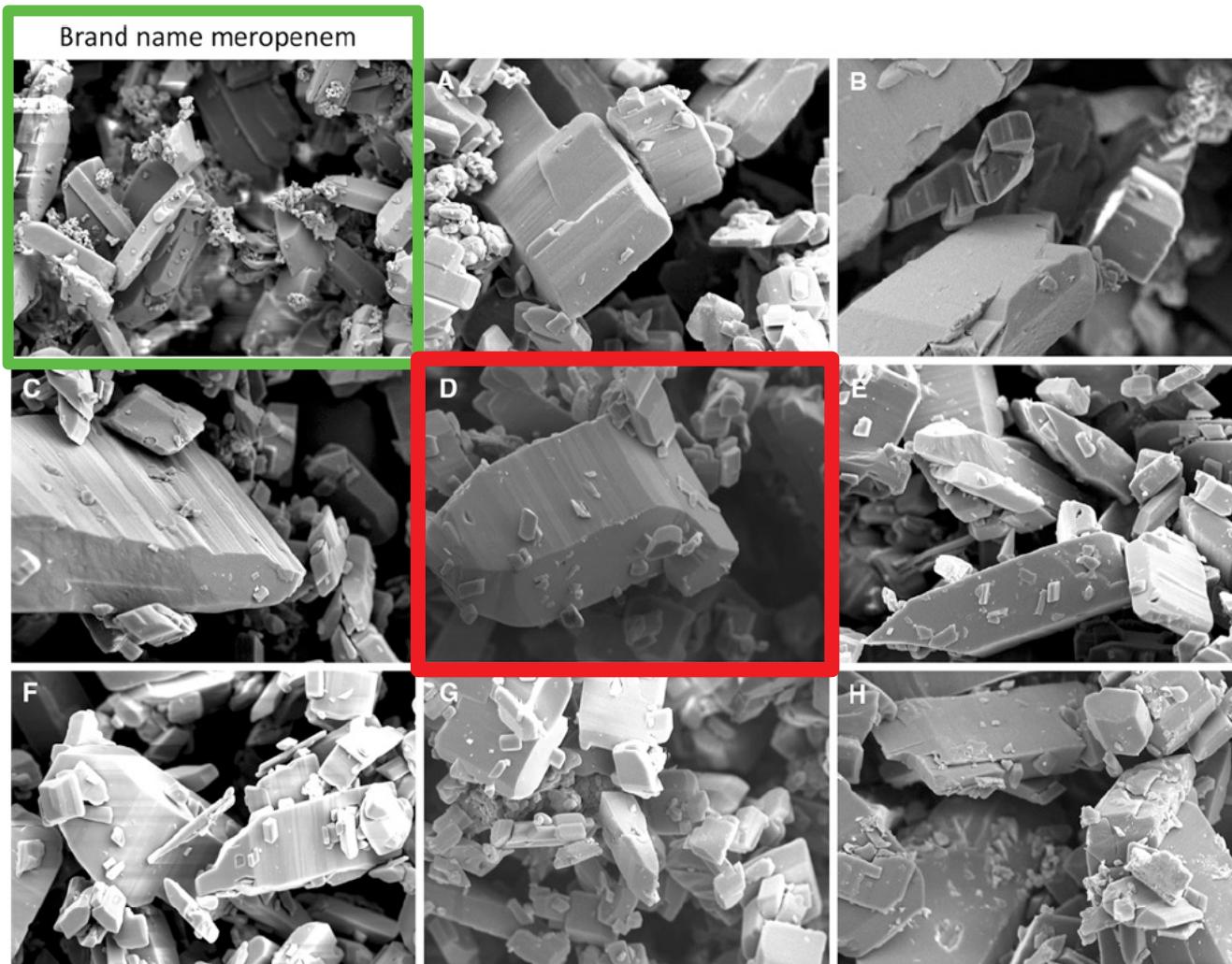
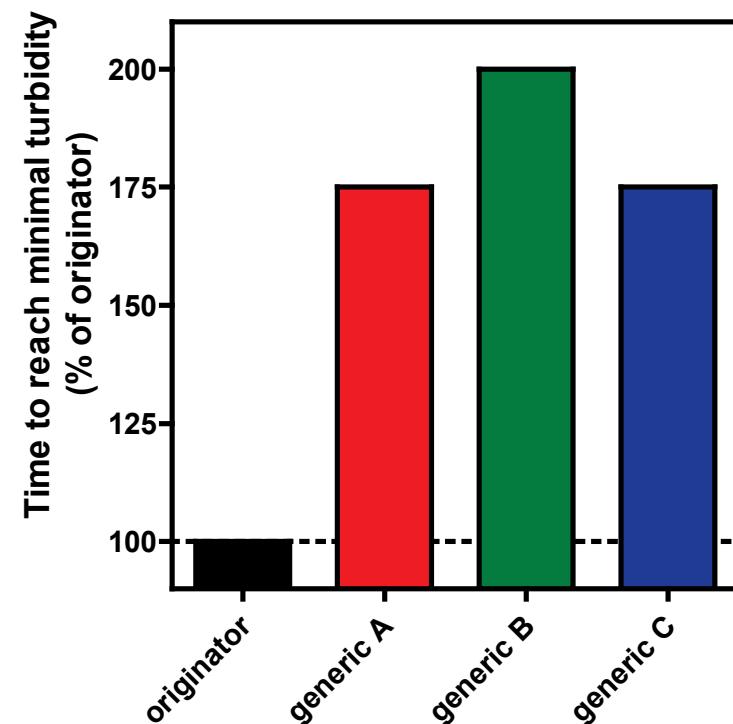
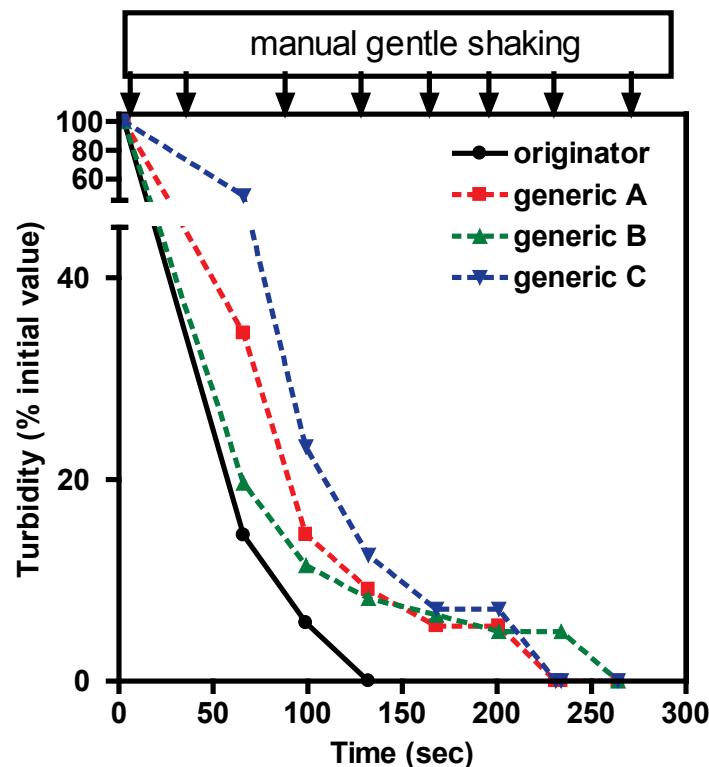


Fig. 4 Electron micrographs of drug particles of brand name meropenem and eight generics. a–h Generic products of meropenem.  $\times 1,000$

Fujimura & Watanabe J Infect Chemother (2012) 18:421–427

# Dissolution of meropenem in Belgium

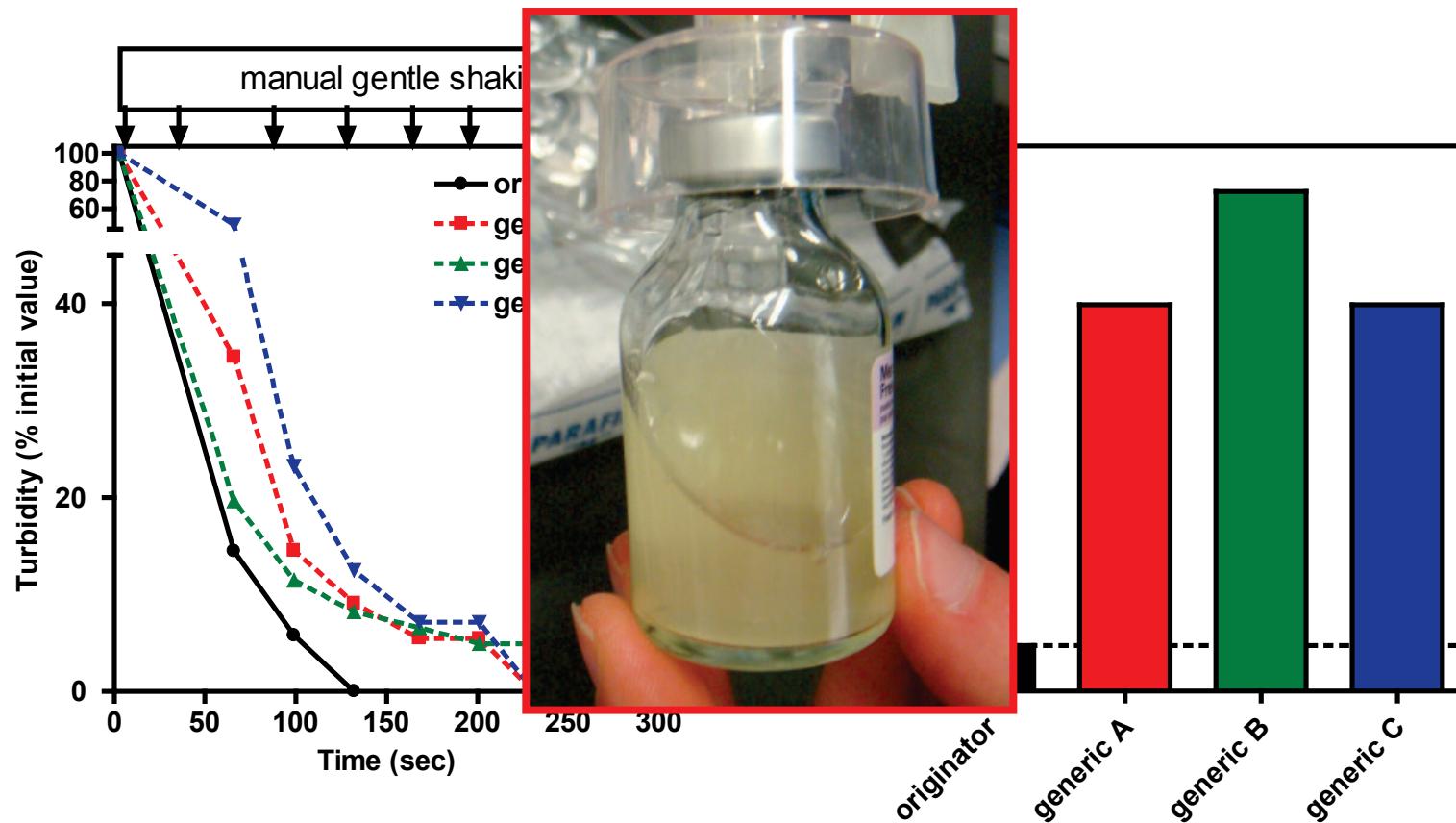
Drug concentration : 50 mg/mL (~ solution used for infusion)  
gentle manual shaking followed by turbidity measures;  
room temperature



Van Bambeke et al., in preparation

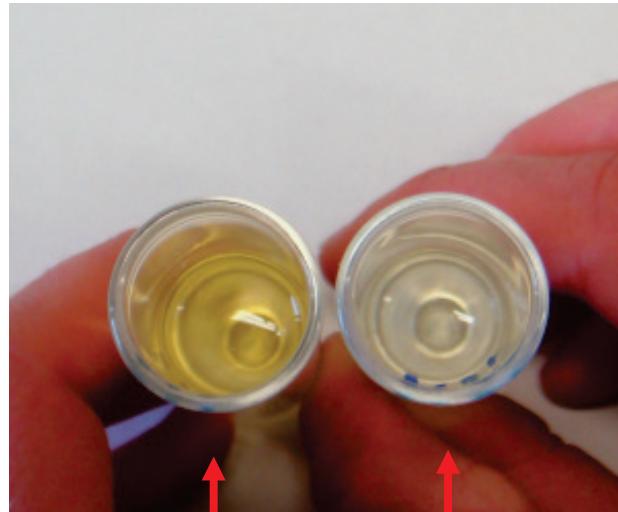
# Dissolution of meropenem in Belgium

Drug concentration : 50 mg/mL (~ solution used for infusion)  
gentle manual shaking followed by turbidity measures;  
room temperature



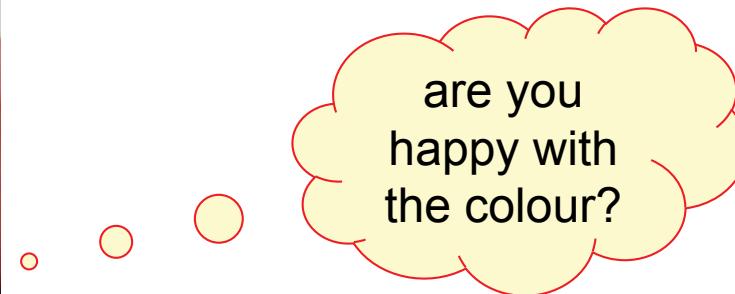
Van Bambeke et al., in preparation

# Impurities in meropenem: coloured compounds



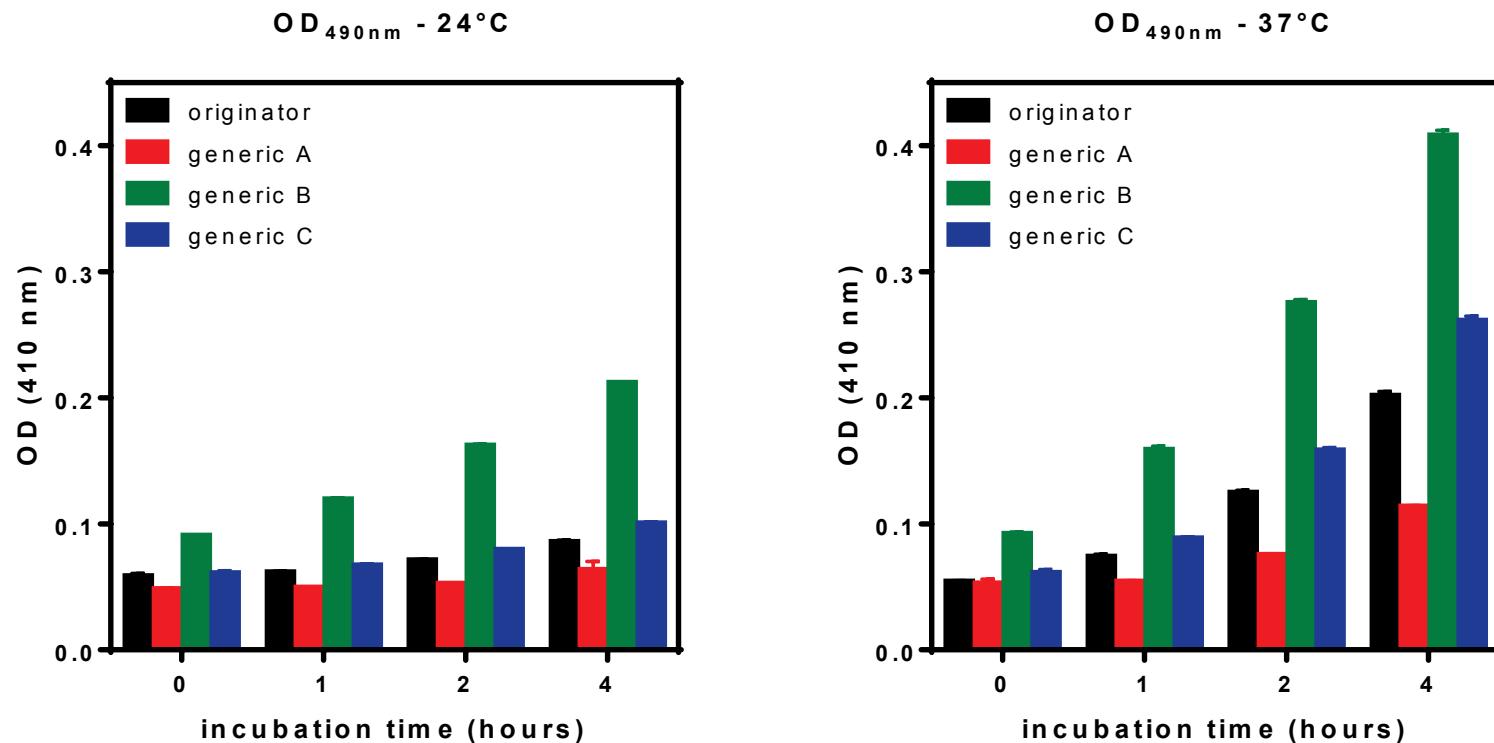
generic B

originator



Van Bambeke *et al.*, in preparation

# Impurities in meropenem: coloured compounds



Van Bambeke *et al.*, in preparation

# Impurities in ciprofloxacin...



Available online at [www.sciencedirect.com](http://www.sciencedirect.com)



Journal of Pharmaceutical and Biomedical Analysis 44 (2007) 743–754

JOURNAL OF  
PHARMACEUTICAL  
AND BIOMEDICAL  
ANALYSIS

[www.elsevier.com/locate/jpba](http://www.elsevier.com/locate/jpba)

Generic ciprofloxacin tablets contain the stated amount of drug and different impurity profiles: A  $^{19}\text{F}$ ,  $^1\text{H}$  and DOSY NMR analysis

Saleh Trefi, Véronique Gilard, Myriam Malet-Martino\*, Robert Martino

Groupe de RMN Biomédicale, Laboratoire SPCMIB (UMR CNRS 5068), Université Paul Sabatier, 118 route de Narbonne, 31062 Toulouse cedex, France

Received 29 November 2006; received in revised form 19 February 2007; accepted 19 February 2007

Available online 1 March 2007

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## Abstract

The objective of this study was to control the purity of 16 commercial formulations of ciprofloxacin tablets purchased in different countries or via the Internet using  $^{19}\text{F}$  and  $^1\text{H}$  nuclear magnetic resonance (NMR). Twelve out of the sixteen commercial formulations of ciprofloxacin measured by  $^{19}\text{F}$  NMR contain the active ingredient within  $100 \pm 5\%$  of stated concentration. Three formulations have a lower ciprofloxacin content between 90 and 95% and one shows a higher concentration superior to 105%. The impurity profile was characterised using  $^{19}\text{F}$  and  $^1\text{H}$  NMR, and is characteristic of the manufacturer. Four to twelve fluorinated impurities among them fluoride ion and two already known compounds were detected and quantified in the sixteen formulations analysed by  $^{19}\text{F}$  NMR. Two other non-fluorinated impurities were observed in the seven formulations analysed with  $^1\text{H}$  NMR. The total content of impurities as well as their individual levels are in agreement with those reported previously in the few studies devoted to ciprofloxacin purity. However, all the formulations do not comply with the limits for impurities given in the ciprofloxacin monograph of the European Pharmacopeia. Finally, a “signature” of the formulations was obtained with Diffusion-Ordered SpectroscopY (DOSY)  $^1\text{H}$  NMR which allowed the characterisation of some excipients present in the formulations studied.

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**Keywords:**  $^{19}\text{F}$  NMR;  $^1\text{H}$  NMR; DOSY  $^1\text{H}$  NMR; Ciprofloxacin; Impurities

# Impurities in ciprofloxacin

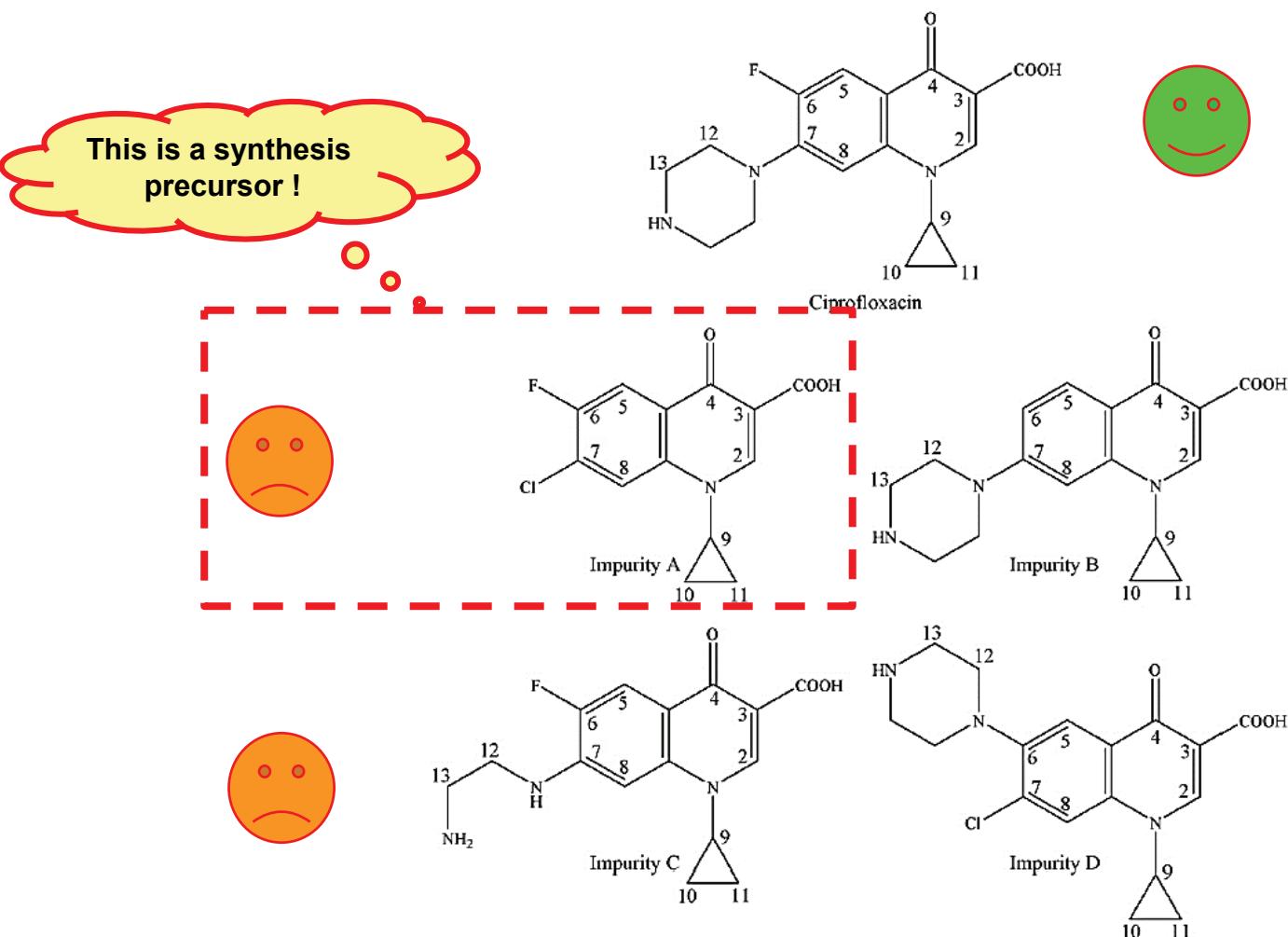


Fig. 1. Structure of ciprofloxacin and its main impurities.

Trefi *et al.* Journal of Pharmaceutical and Biomedical Analysis 44 (2007) 743–754

# Problems appearing in Europe !



Actus - E-learning - Recherches

8/12/2014



La Belgique retire 4 médicaments commercialisés par la société indienne GVK Biosciences

<http://www.mediplanet.be/fr/content/la-belgique-retire-4-m%C3%A9dicaments-commercialis%C3%A9s-par-la-soci%C3%A9t%C3%A9-indienne-gvk-biosciences>  
Last accessed: 08/02/2015



26/01/2015 - N°1519



Génériques: 8 nouveaux médicaments retirés du marché en France

Suite à la récente recommandation de l'Agence Européenne des médicaments, la France lance une procédure de suspension des AMM de 8 nouveaux médicaments qui s'ajoutent aux 25 déjà suspendus. Qu'en est-il en Belgique?

<http://www.mediplanet.be/fr/content/g%C3%A9n%C3%A9riques-8-nouveaux-m%C3%A9dicaments-retir%C3%A9s-du-march%C3%A9-en-france>  
Last accessed: 08/02/2015



# ansm

Agence nationale de sécurité du médicament  
et des produits de santé



L'ANSM lance une procédure de suspension, à compter du 18 décembre, de 25 médicaments commercialisés en France - Point d'Information

05/12/2014

<http://ansm.sante.fr/S-informer/Actualite/L-ANSM-lance-une-procedure-de-suspension-a-compter-du-18-decembre-de-25-medicaments-commercialises-en-France-Point-d-Information>  
Last accessed: 07/12/2014 (no longer available on 08/02/2015)

# Problems appearing in Europe !



Actus - E-learning - Recherches

8/12/2014

La Belgique retire 4 médicaments commerciaux par la société indienne G BioSciences

<http://www.mediplanet.be/fr/content/la-belgique-retire-4-medicaments-commerciaux%C3%A9s-par-la-soci%C3%A9t%C3%A9-indienne-G-Biosciences>

Last accessed: 08/02/2015



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

23 January 2015  
EMA/52196/2015  
Procedure Management and Business Support

## Products for which the marketing authorisations are recommended for suspension by the CHMP on 22 January 2015

Some of these medicinal products may be considered critical by the individual EU Member States. The suspension of the concerned marketing authorisation(s) may be deferred by the period for which the medicinal product is considered critical.

Article 31 of Directive 2001/83/EC Procedure number: EMEA/H/A-31/1408

[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Other/2015/01/WC500180894.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/01/WC500180894.pdf)

Last accessed: 08/02/2015

Génériques: 8 nouveaux médicaments retirés du marché en France

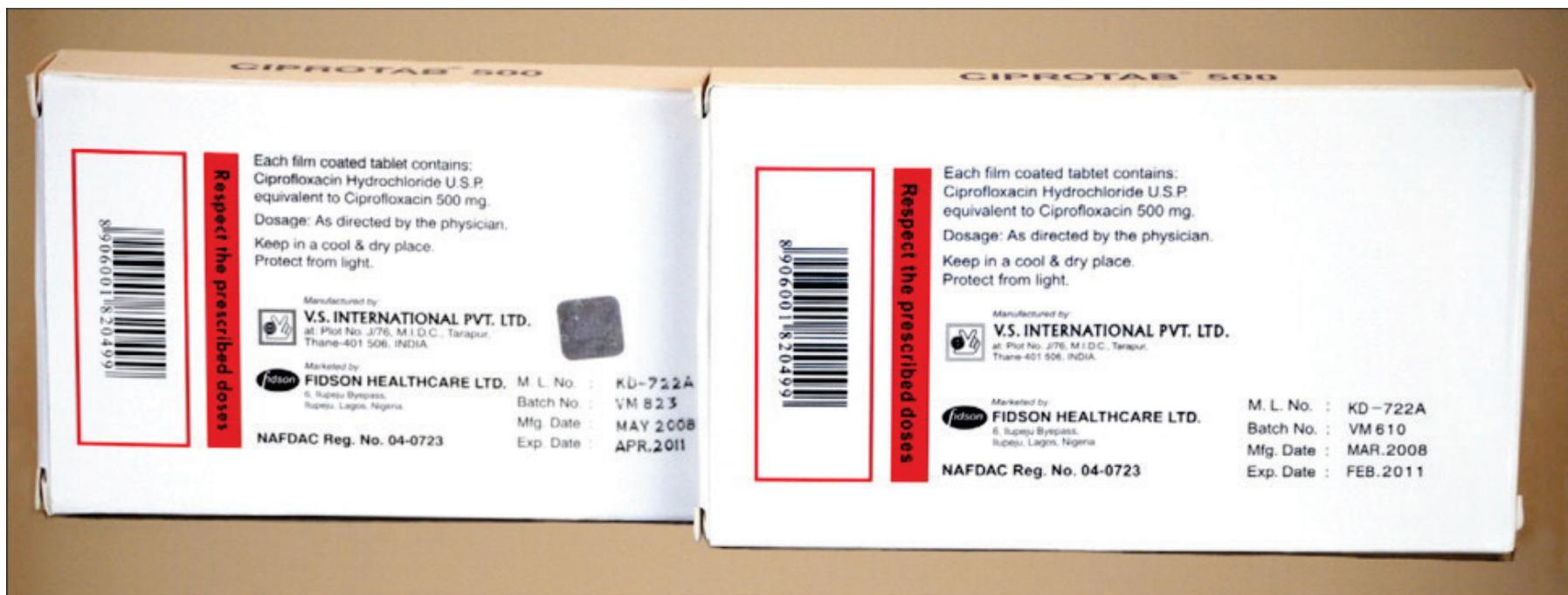
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Last accessed: 08/02/2015

The list makes  
135 pages

# We should also address the problem of counterfeited drugs



Packs bought at pharmacies in Lagos, Nigeria both sold as "CIPROTAB 500 ®"

The only noticeable difference is that the real package has a hologram on the back (left). **The fake was two-thirds talcum powder and contained no ciprofloxacin.** Even holograms can be faked.

- 25% of drugs sold worldwide are substandard and 50% in some Countries...
- It hurts low and middle income countries the most...

Slide kindly communicated by S. Opal

Bate et al. Lancet. 2010; 376(9751):1446-8.

# 3rd round of conclusions and discussion

- Generic drugs **may or may not** be of the same pharmaceutical quality as the original products
- The reasons for lower quality are
  - difficulties in **correctly reproducing the manufacturing and purifications procedures** of the originator  
(often more a “know how” than patentable matters)
  - the **race to low prices**
  - the fact that **controls may be insufficient** (after first registration)
- Only **stringent and continuous controls by public authorities** can help avoiding the flood of low quality products  
(but this may be difficult in face of the number of producers)



We have 9 levofloxacinS in Belgium

# What shall we discuss?

1. The EU and US laws
2. Approach to PK bioequivalence
3. Approach to microbiological and therapeutic equivalence
  1. MIC, MPC, heteroresistance ...
  2. Approach to pharmacodynamic equivalence
  3. PK/PD animal models and clinical data
4. Dissolution, stability, impurities
5. **The hidden risks of "low cost" drugs**
  1. **overconsumption (and wrong publicity)**
  2. **lack of innovative research ... unless the government (=you) pay !**
  3. **Drug shortages**

# We are facing contradictory situations ...

J Antimicrob Chemother 2014; **69**: 2886–2888  
doi:10.1093/jac/dku350 Advance Access publication 11 September 2014

**Journal of  
Antimicrobial  
Chemotherapy**

## Developing the first national antimicrobial prescribing and stewardship competences

D. Ashiru-Oredope<sup>1\*</sup>, B. Cookson<sup>2</sup> and C. Fry<sup>3</sup> on behalf of the Advisory Committee on Antimicrobial Resistance  
and Healthcare Associated Infection Professional Education Subgroup

<sup>1</sup>Antimicrobial Resistance, Stewardship and Healthcare Associated Infection (AMRS & HCAI) Programme, Public Health England, London, UK; <sup>2</sup>Division of Infection and Immunity, University College London, London, UK; <sup>3</sup>Department of Health, London, UK

\*Corresponding author. Tel: +44-(0)20-832-76689; E-mail: diane.ashiru-oredope@phe.gov.uk

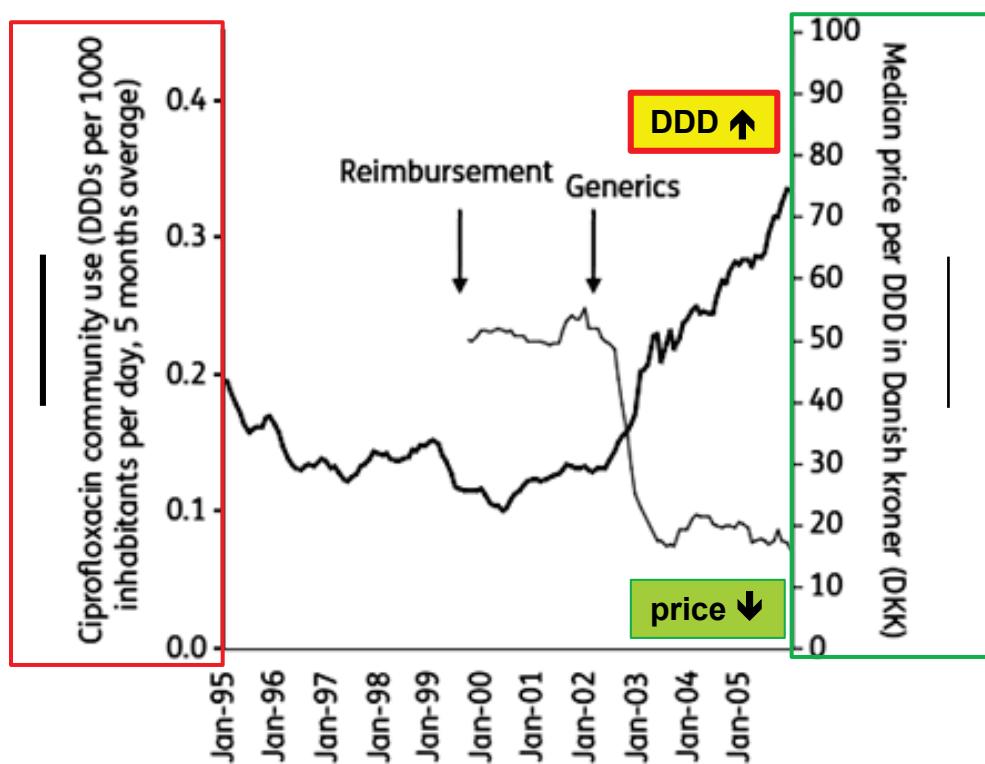
†Members are listed in the Acknowledgements section.

According to Doron and Davidson (2011) (6) three major goals for antimicrobial stewardship are to:

- optimise therapy for individual patients
- prevent overuse, misuse and abuse
- minimise development of resistance at patient and community levels

[https://www.gov.uk/government/uploads/system/uploads/attachment\\_data/file/253094/ARHAIpresrccompetencies\\_\\_2\\_.pdf](https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/253094/ARHAIpresrccompetencies__2_.pdf)

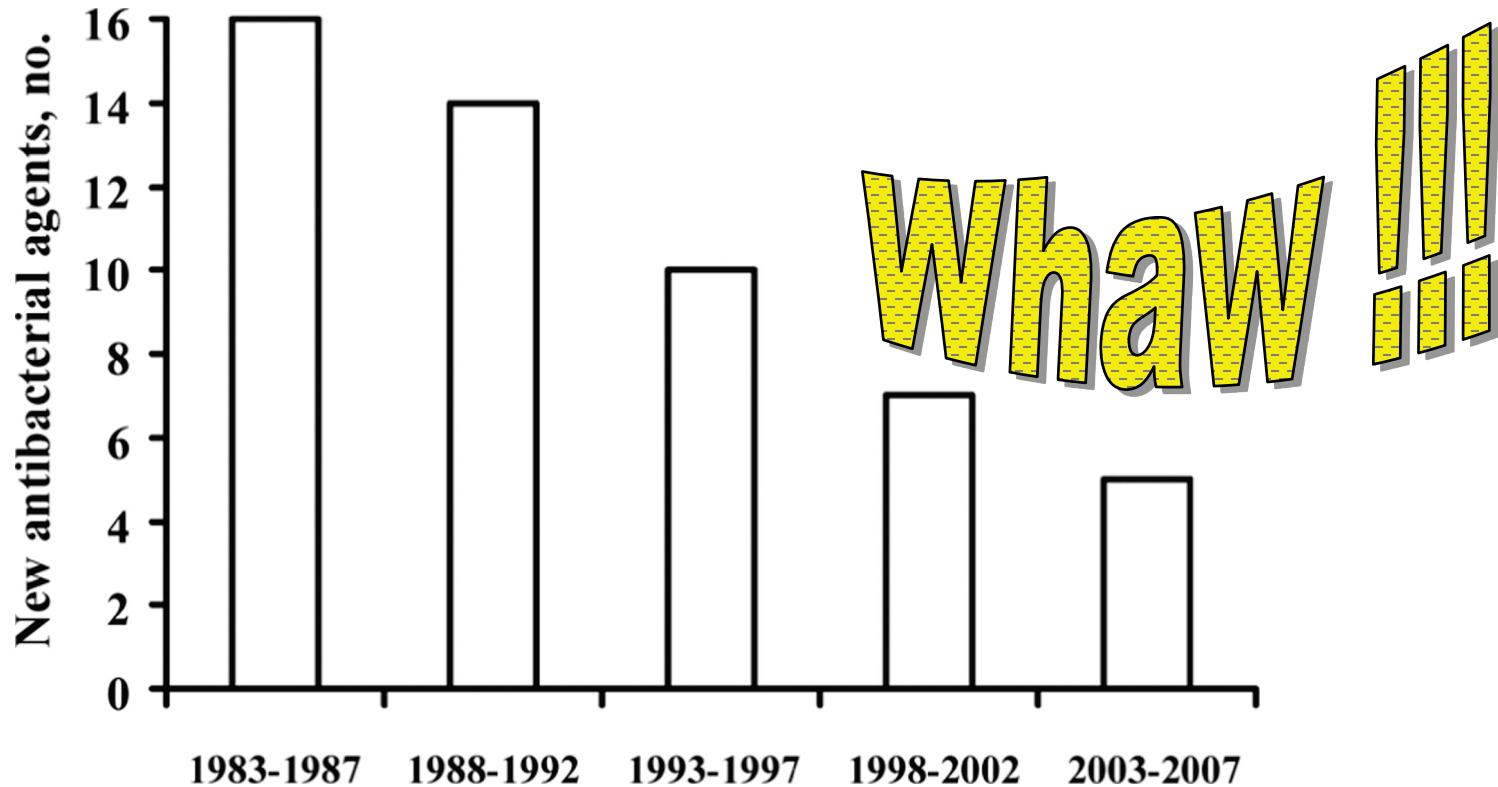
# But see what happens with “Low cost antibiotics”... *The sour Danish Experience*



**Figure 1.**  
influence of removal of 50% reimbursement  
and of the introduction of generics on the total  
use of ciprofloxacin and median price per DDD  
per 1000 inhabitants per day.

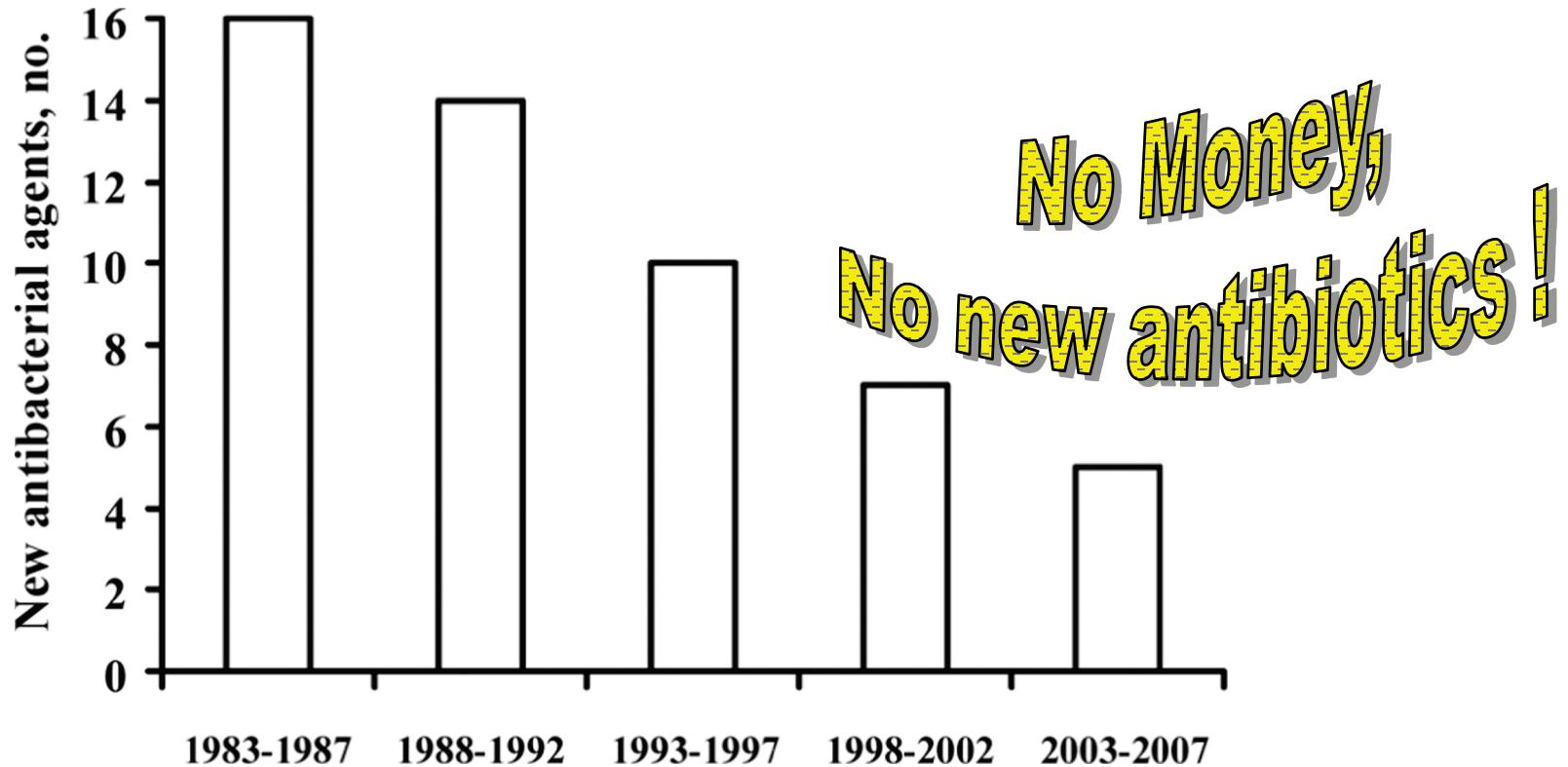
Jensen et al. J Antimicrob Chemother 2010; 65:1286–1291

# Innovative antibiotic development is abandoned by Industry



Boucher H W et al. Clin Infect Dis. 2009;48:1-12

# Why do they abandon it ?



Boucher H W et al. Clin Infect Dis. 2009;48:1-12

# Public actions ...



Dear Colleague:

The American Society for Microbiology (ASM) applauds the Administration's January 27 announcement that its FY 2016 budget would nearly double funding for combating and preventing antibiotic resistance among microbial pathogens. Fighting the emergence and spread of these resistant infections requires the highest levels of scientific innovation and economic investment. The \$1.2 billion earmarked for biomedical research and public health surveillance against antibiotic resistant bacteria would significantly reinforce the nation's campaign to stop a major threat to public health.

<https://www.asm.org/index.php/public-policy/137-policy/documents/statements-and-testimony/93355-ar-2015>  
Last accessed: 08/02/2015

&lt;/div

# Public actions ...



Dear Colleague:

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<https://www.asm.org/index.cfm>

Last accessed: 08/02/2015

## The tax-payer will pay for this !



- **€2 billions euros budget...**
- collaborative research projects and networks Industry-Academia...
- establish Europe as **the most attractive place for pharmaceutical R&D**

<http://www.imi.europa.eu/> -- Last accessed: 8/2/2015

# Drug shortages ...



RESEARCH ARTICLE

## Insights into European Drug Shortages: A Survey of Hospital Pharmacists

**Kim Pauwels\*, Steven Simoens, Minne Casteels, Isabelle Huys**

KU Leuven Department of Pharmaceutical and Pharmacological Sciences, 3000, Leuven, Belgium

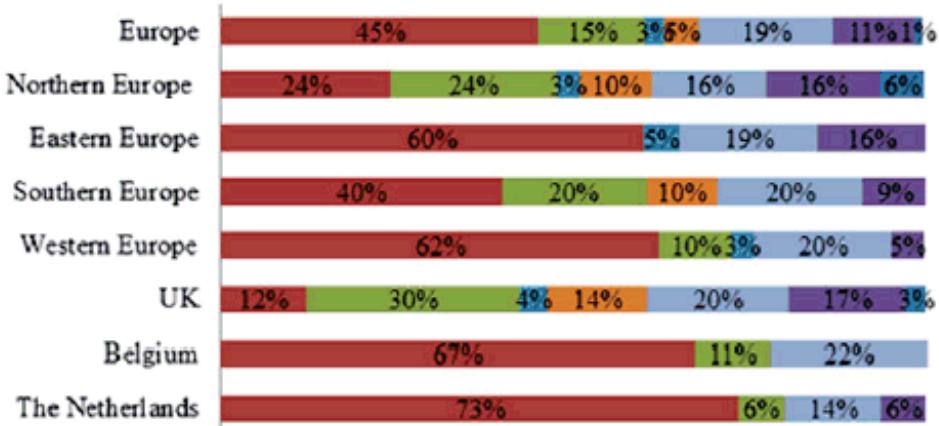
PLoS ONE 2015 - 10(3): e0119322. doi:10.1371/journal.pone.0119322

a recent paper ...  
(2015...)

## RESEARCH ARTICLE

# Insights into European Drug Shortages: A Survey of Hospital Pharmacists

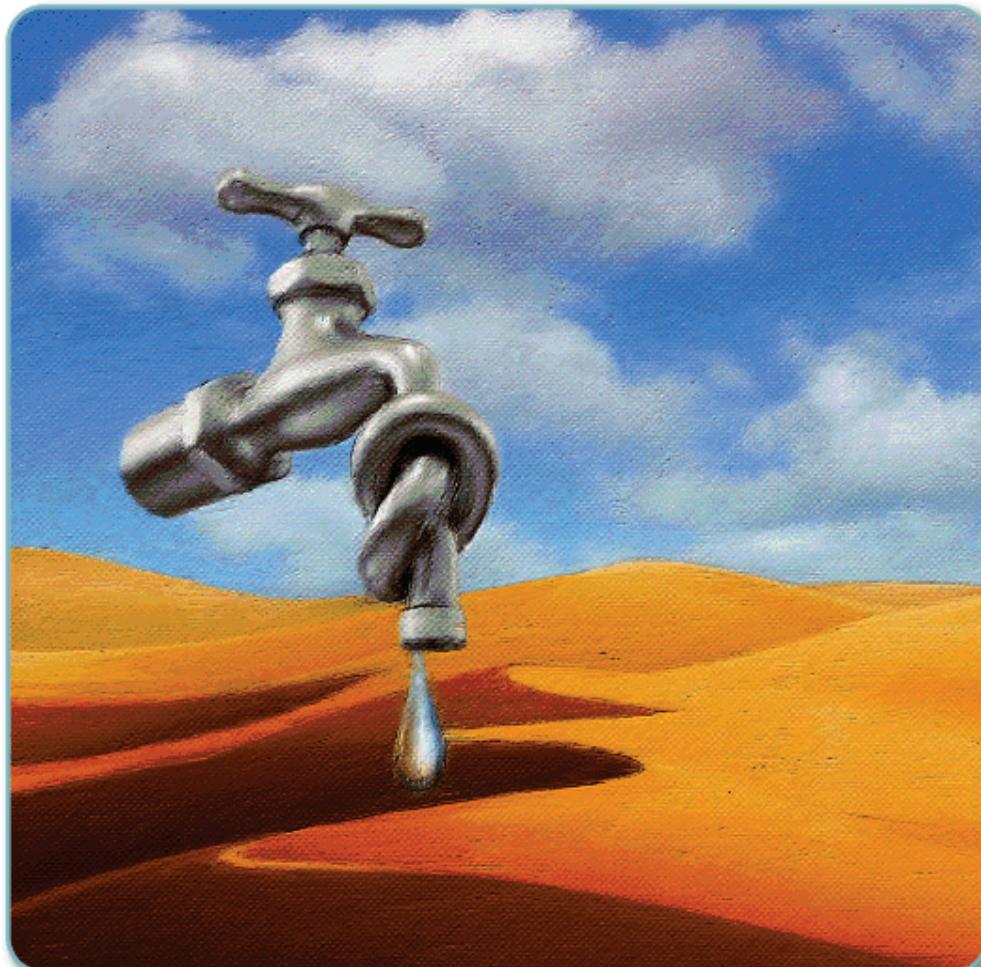
a recent paper ...  
(2015...)



- Life sustaining or life preserving (eg. oncology drugs)
- Management of a long-term or chronic health issue but not life sustaining (eg. a drug for managing hypertension or depression)
- Preventive (eg. an inoculation or birth control product)
- Quality of life (eg. painkiller or antidepressant)
- Treatment of an acute but short-term illness (eg. an antibiotic)
- Other
- No answer

**Fig 1. Drug types affected by drug shortages according to the respondents.** Respondents who indicated that particular types of medicines suffered more from shortages than others were considered. The relative number of respondents per answer was shown for Europe (n = 128), Northern Europe (n = 8), Eastern Europe (n = 20), Southern Europe (n = 30), Western Europe (n = 16), the UK (n = 29), Belgium (n = 9) and the Netherlands (n = 15).

# But the situation was known years ago ...



Report by the IMS Institute for Healthcare Informatics

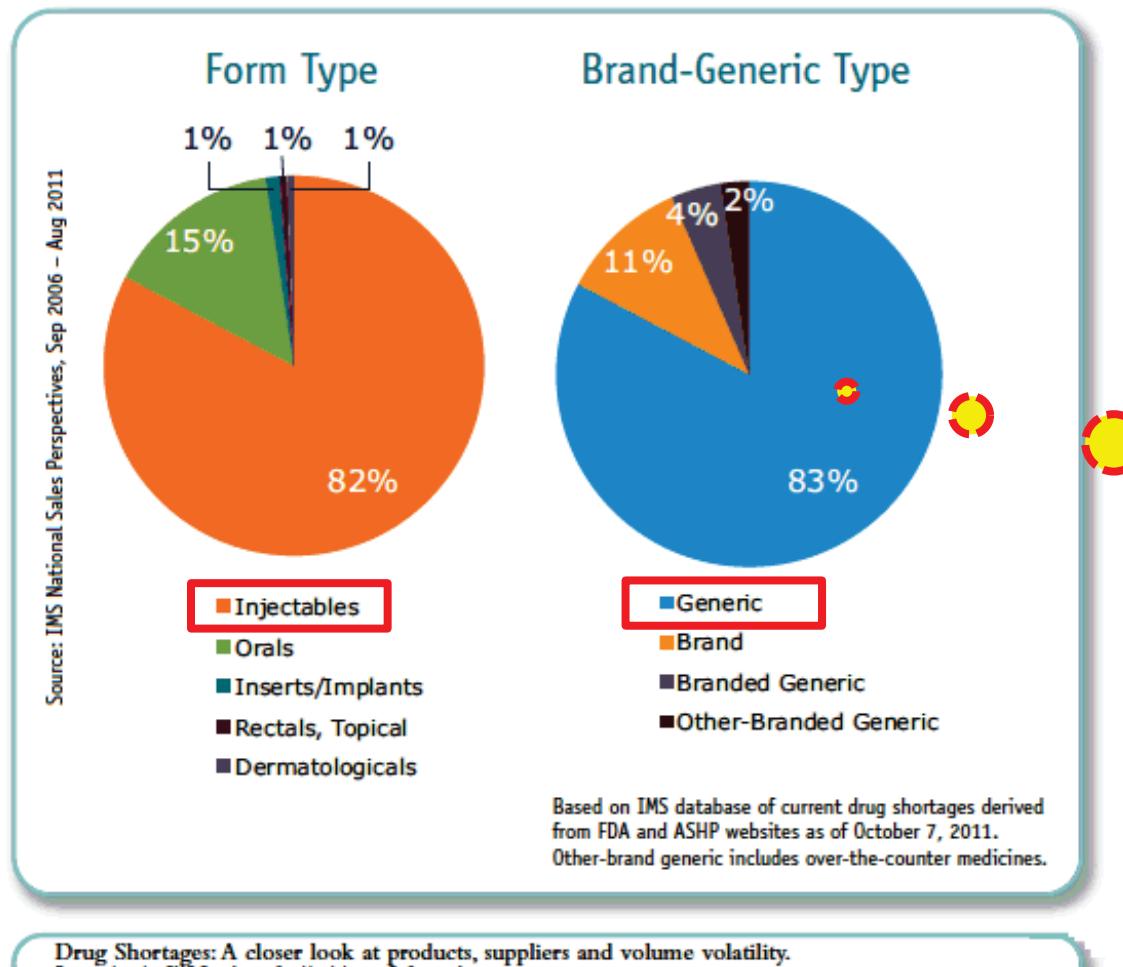
IMS INSTITUTE  
FOR  
HEALTHCARE INFORMATICS

Drug Shortages:  
A closer look  
at products,  
suppliers and  
volume volatility.

November 2011

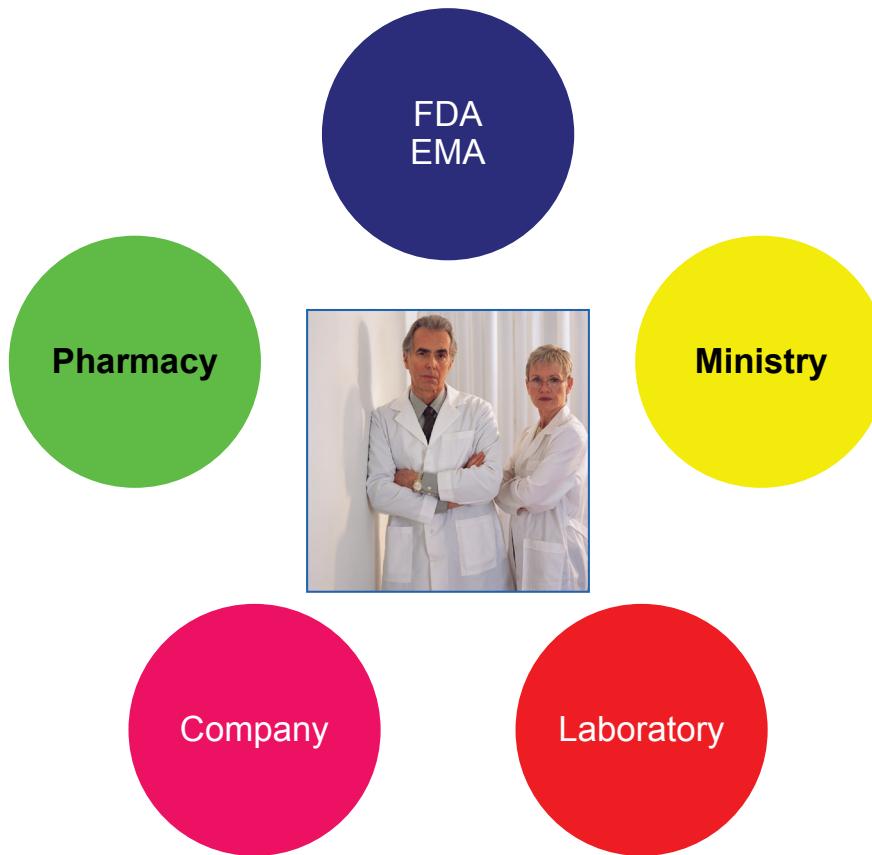
# ... and the main affected products were known

Most products are injectables and generics



and the main reason is "market volatility"

# Now, what can I do as a clinician ?



# Summary / Suggestions

- The decision to "go for generics" is a political one that may need revision (at political level) to avoid over-use of antibiotics
- **Pharmacokinetic criteria** are, so far, the (nearly) only ones adopted and accepted by the Regulatory Authorities (EMA / FDA / others...)
- **Improved criteria** for **anti-infective drugs** (MIC, MPC, animal PK/PD, ...) are probably necessary (but are not yet implemented)
- The **control of the quality of the generics** (and of all antibiotics in general), of their **availability**, and of their **responsible use** are all critical and should go beyond declarations and initial lot analysis...
- **Antibiotics are a precious commodity** that should not be lost. Misuse may cause **HUGE expenses in the future...**

**Thank you for your attention!**

*And ask questions*



# **What I did not show ... and questions...**

# **Are you happy about the law(s) ?**

- 1. The US and EU laws are enough and we only need to follow them...**
- 2. An "Middle East" regulation is essential and should be developed...**
- 3. I need a law specific to my country ...**
- 4. We do not need any law (Industry will autoregulate it-self)...**
- 5. I cannot decide because I'm not an expert (I'm a doctor)...**

**Please, think about  
what YOU would choose !**

# Substandard (wrong) drugs in the world ?

**BJCP** British Journal of Clinical Pharmacology

## Substandard drugs: a potential crisis for public health

Atholl Johnston<sup>1</sup> & David W. Holt<sup>2</sup>

<sup>1</sup>Clinical Pharmacology, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK and <sup>2</sup>St George's – University of London, London, UK

### Correspondence

Professor Atholl Johnston, Clinical Pharmacology, Barts and The London, Charterhouse Square, London EC1M 6BQ, UK.

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Fax: +44 20 7882 3408

E-mail: a.johnston@qmul.ac.uk

### Keywords

drug quality, falsification, inspection, regulation, substandard

### Received

13 August 2013

### Accepted

1 November 2013

### Accepted Article

### Published Online

29 November 2013

Poor-quality medicines present a serious public health problem, particularly in emerging economies and developing countries, and may have a significant impact on the national clinical and economic burden. Attention has largely focused on the increasing availability of deliberately falsified drugs, but substandard medicines are also reaching patients because of poor manufacturing and quality-control practices in the production of genuine drugs (either branded or generic). Substandard medicines are widespread and represent a threat to health because they can inadvertently lead to healthcare failures, such as antibiotic resistance and the spread of disease within a community, as well as death or additional illness in individuals. This article reviews the different aspects of

A concerted effort is required on the part of governments, drug manufacturers, charities and healthcare providers to ensure that only drugs of acceptable quality reach the patient.

# An European action is ongoing ... but is costly

The screenshot shows the homepage of the European Directorate for the Quality of Medicines & HealthCare (edQM). The top navigation bar includes links for Sitemap, English, Français, Stay connected, and a search bar. The main header features the Council of Europe logo and the text "edQM European Directorate for the Quality of Medicines & HealthCare". Below the header, a menu bar offers links to About us, HealthCare, The European Pharmacopoeia, Control of Medicines, Certification of Suitability, and Publications, Products and Services. A red box highlights the title "The MEDICRIME Convention". The left sidebar under "HealthCare" lists various topics: HealthCare News, Blood Transfusion, Organ Transplantation, Pharmaceutical Care, Anti-counterfeiting activities, eTACT, The Medicrime Convention, and Consumer Health Protection. The main content area discusses the MEDICRIME Convention, detailing its purpose and scope, which includes manufacturing, supplying, falsification, and unauthorized manufacturing of counterfeit medical products. An "Important information" section provides links to an information document and a fact sheet about counterfeit medicines. A "Map of Countries" section indicates that Moldova has ratified the convention.

## The MEDICRIME Convention

### Background and scope

The Council of Europe has drawn up the first international treaty against counterfeit medical products and similar crimes involving threats to public health, [the MEDICRIME Convention](#), to establish as offences:

- the manufacturing of counterfeit medical products.
- supplying, offering to supply and trafficking in counterfeit medical products.
- the falsification of documents.
- the unauthorised manufacturing or supplying of medicinal products and the marketing of medical devices that do not comply with conformity requirements.

### Important information

- [Information document on the Medicrime Convention](#)  
This document is multilingual : English, Spanish, Russian, French
- [Fact sheet: Counterfeit Medicines \(October 2013\)](#)

### Map of Countries

that have signed the MEDICRIME Convention

Latest update: Ratification of Moldova

<https://www.edqm.eu/en/the-medicrime-convention-1470.html>  
Last accessed: 20/02/2015

# An European action is ongoing ... but is costly

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## The MEDICRIME Convention

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- the falsification of documents.
- the unauthorised manufacturing or supplying of medicinal products and the marketing of medical devices that do not comply with conformity requirements.

# MEDICRIME: which countries ?

## Signatures & Ratifications of the Medicrime Convention

### Signatures

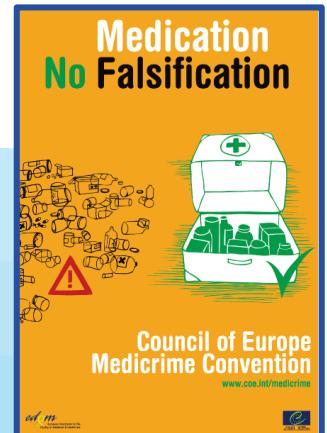
- Armenia ..... 20/09/2012
- Austria ..... 28/10/2011
- Belgium ..... 24/07/2012
- Cyprus ..... 28/10/2011
- Denmark ..... 12/01/2012
- Finland ..... 28/10/2011
- France ..... 28/10/2011
- Germany ..... 28/10/2011
- Hungary ..... 26/09/2013
- Iceland ..... 28/10/2011
- Italy ..... 28/10/2011
- Liechtenstein ..... 01/11/2011
- Luxembourg ..... 22/12/2011
- Moldova ..... 20/09/2012
- Portugal ..... 28/10/2011
- Russia ..... 28/10/2011
- Spain ..... 08/10/2012
- Switzerland ..... 28/10/2011
- Turkey ..... 29/06/2012
- Ukraine ..... 28/10/2011
- Guinea ..... 10/12/2012
- Israel ..... 28/10/2011
- Morocco ..... 13/12/2012

### Ratifications

- Moldova ..... 14/08/2014
- Hungary ..... 09/01/2014
- Spain ..... 05/08/2013
- Ukraine ..... 20/08/2012

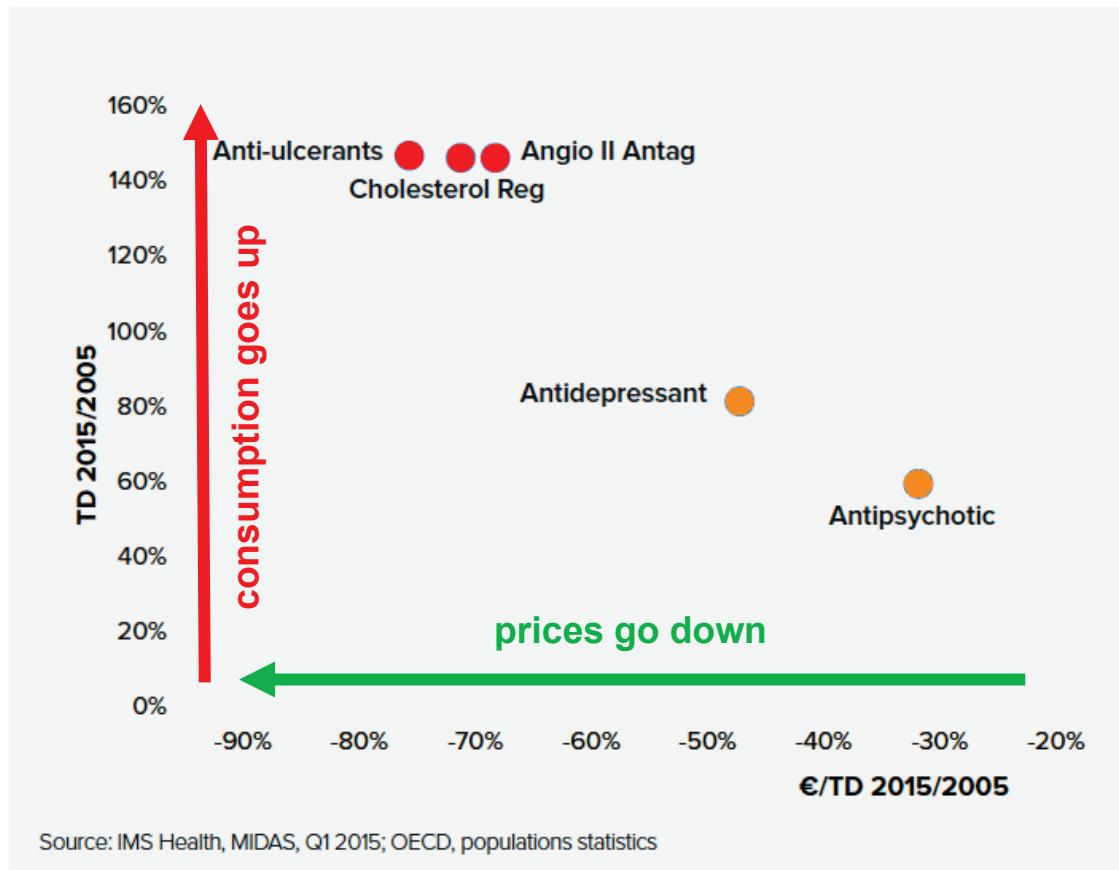


[https://www.edqm.eu/medias/images/medicrime\\_world\\_map\\_with\\_list\\_english.jpg](https://www.edqm.eu/medias/images/medicrime_world_map_with_list_english.jpg)  
Last accessed: 20/02/2015



# But this is not specific to antibiotics...

Exhibit 13: Price Reduction and Number of Treatment Days



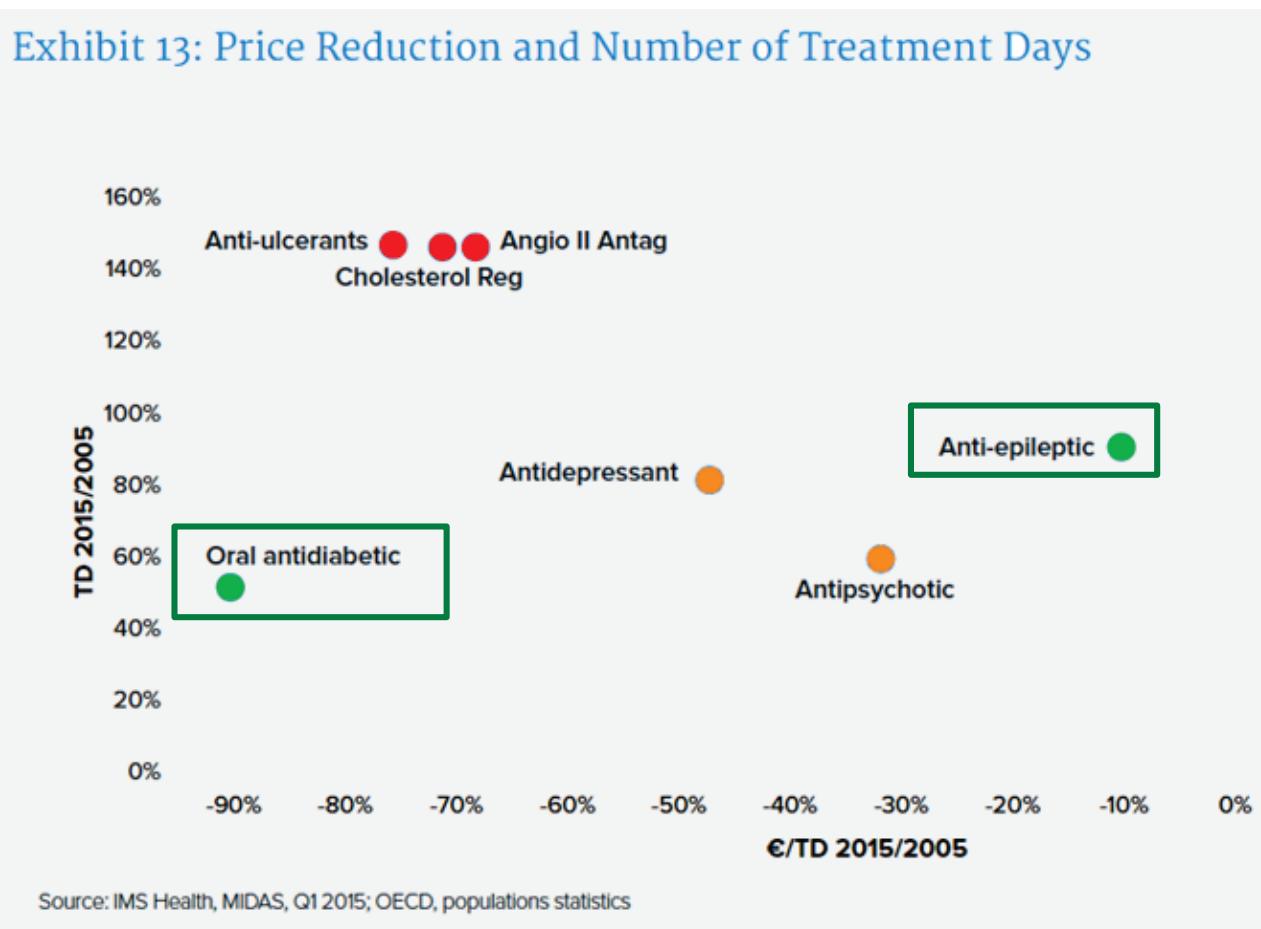
Source: The Role of Generic Medicines in Sustaining Healthcare Systems: A European Perspective

IMS Institute for Healthcare Informatics – June 2015

<http://www.imshealth.com/vgn-ext-templating/v/index.jsp?vgnextoid=a64de5fda6370410VgnVCM10000076192ca2RCRD&vgnextfmt=default#>

# There are specific exceptions...

Exhibit 13: Price Reduction and Number of Treatment Days



but not for drugs with "clear" indications and contraindications

Source: The Role of Generic Medicines in Sustaining Healthcare Systems: A European Perspective  
IMS Institute for Healthcare Informatics – June 2015  
<http://www.imshealth.com/vgn-ext-templating/v/index.jsp?vgnextoid=a64de5fda6370410VgnVCM10000076192ca2RCRD&vgnextfmt=default#>

## **Pharmaceutical quality... What is your opinion ?**

- 1. The generic must have the same solubility / dispersion properties than the original ...**
- 2. The generic cannot contain more impurities (or give rise to more degradation products) than the original ...**
- 3. I must be sure about the real content of what I prescribe ...**
- 4. All of the above is important...**
- 5. None of the above is important ...**

**Please, think about  
what YOU would choose !**