# Generics of antibiotics:

# An evidence-based approach

**Paul M. Tulkens**, MD, PhD

Cellular and Molecular Pharmacology
& Center for Clinical Pharmacy
Louvain Drug Research Institute
*Université catholique de Louvain*
Brussels, Belgium

Anti-Infective Bayer Middle East Forum
Dubai, UAE, 5th November 2015

*With approval of the Belgian Common Ethical Health Platform – visa no. 14/V1/7042/063261*

# Disclosures and slides availability

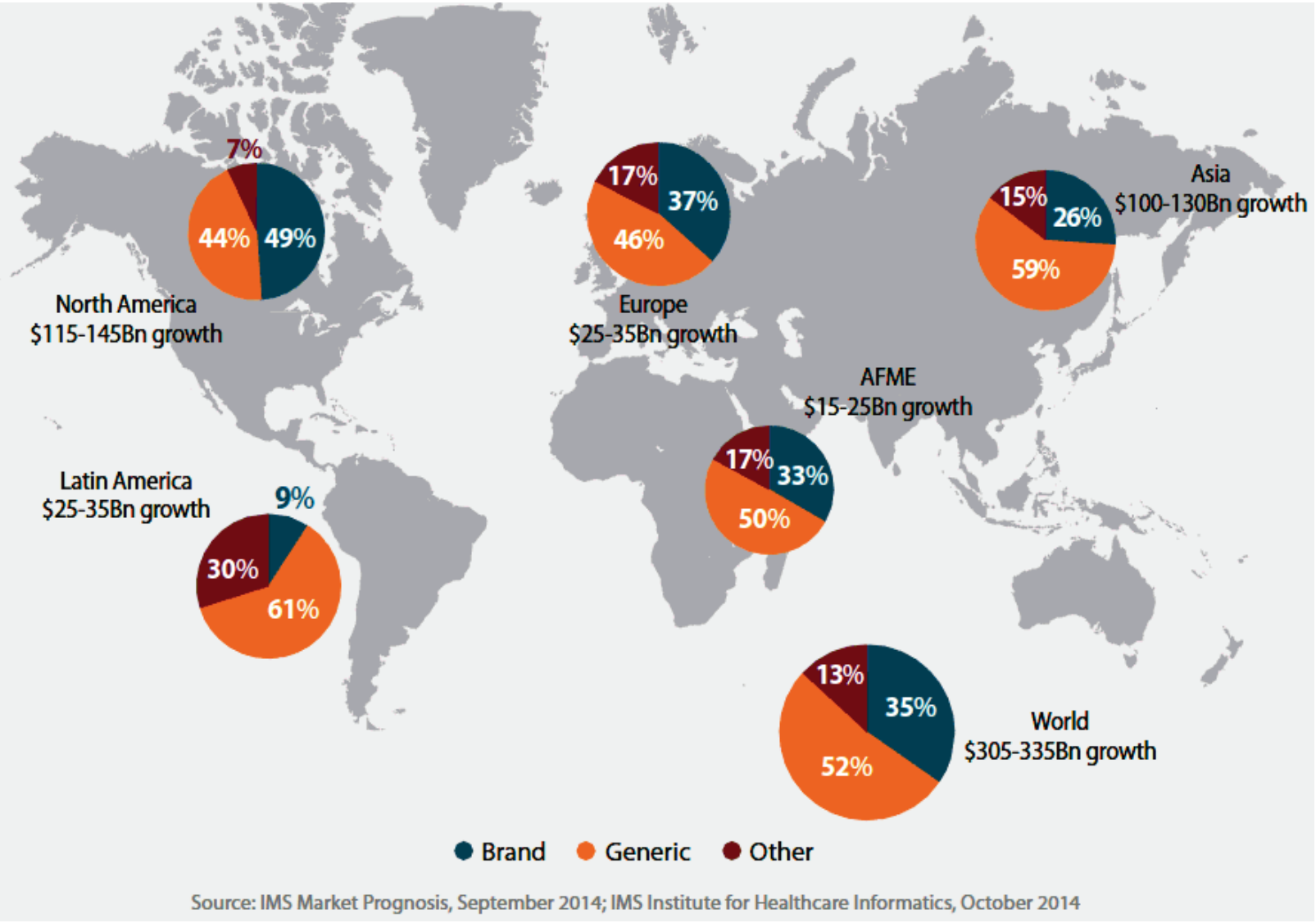
- Research grants
  - Theravance, Astellas, Targanta, Cerexa/Forest, AstraZeneca, Bayer, GSK, Trius, Rib-X, Eumedica, Debiopharm
  - Belgian Science Foundation (*F.R.S.-FNRS*), Ministry of Health (*SPF*), Walloon and Brussels Regions, European Union (*FP7 programme*)

- 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**

# 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...

# 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

# 1st 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…

# 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 !**

# 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** [1] (including for branded drugs when the mareketed form differs from the form used in development…)[2]
- Primary metrics are [1,3]
  - **AUC** (area under the plasma concentration–time profile of the active substance)

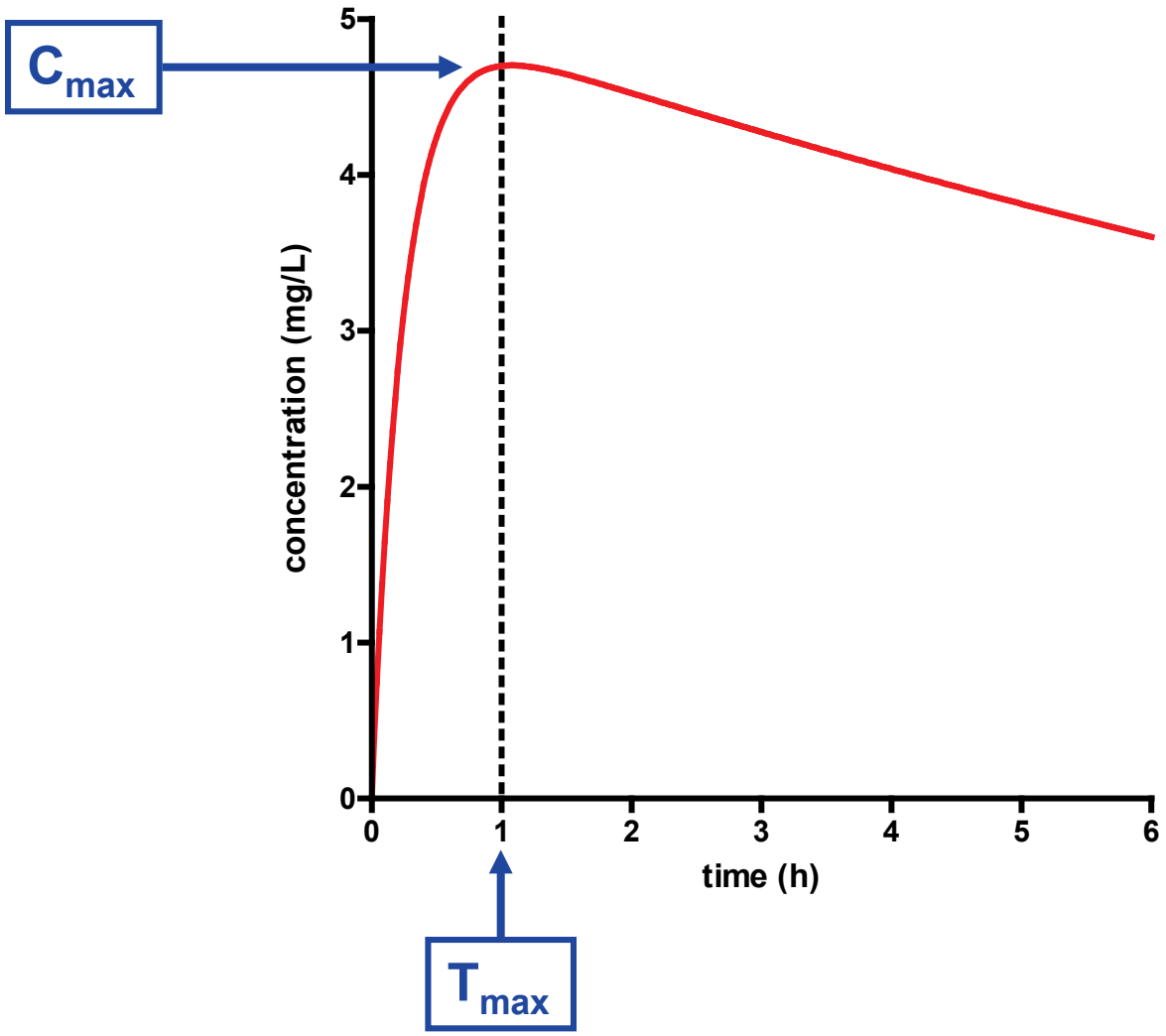
    → **extent of absorption**
  - **$C_{max}$** (the maximum plasma concentration of the active substance)

    → **extent and rate of absorption**
  - **$T_{max}$** (the time when $C_{max}$ is reached)

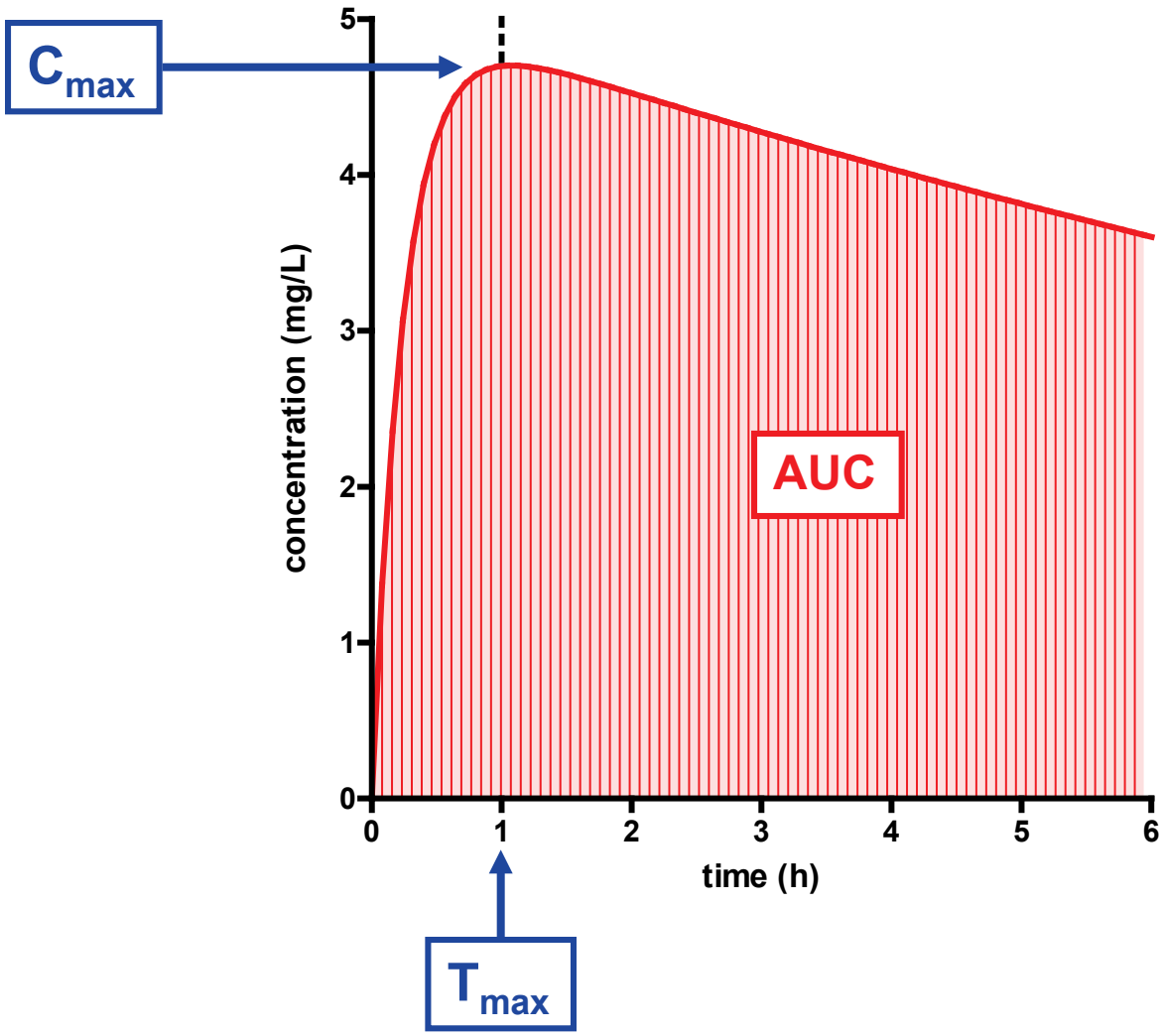
    → **rate of absorption**


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.

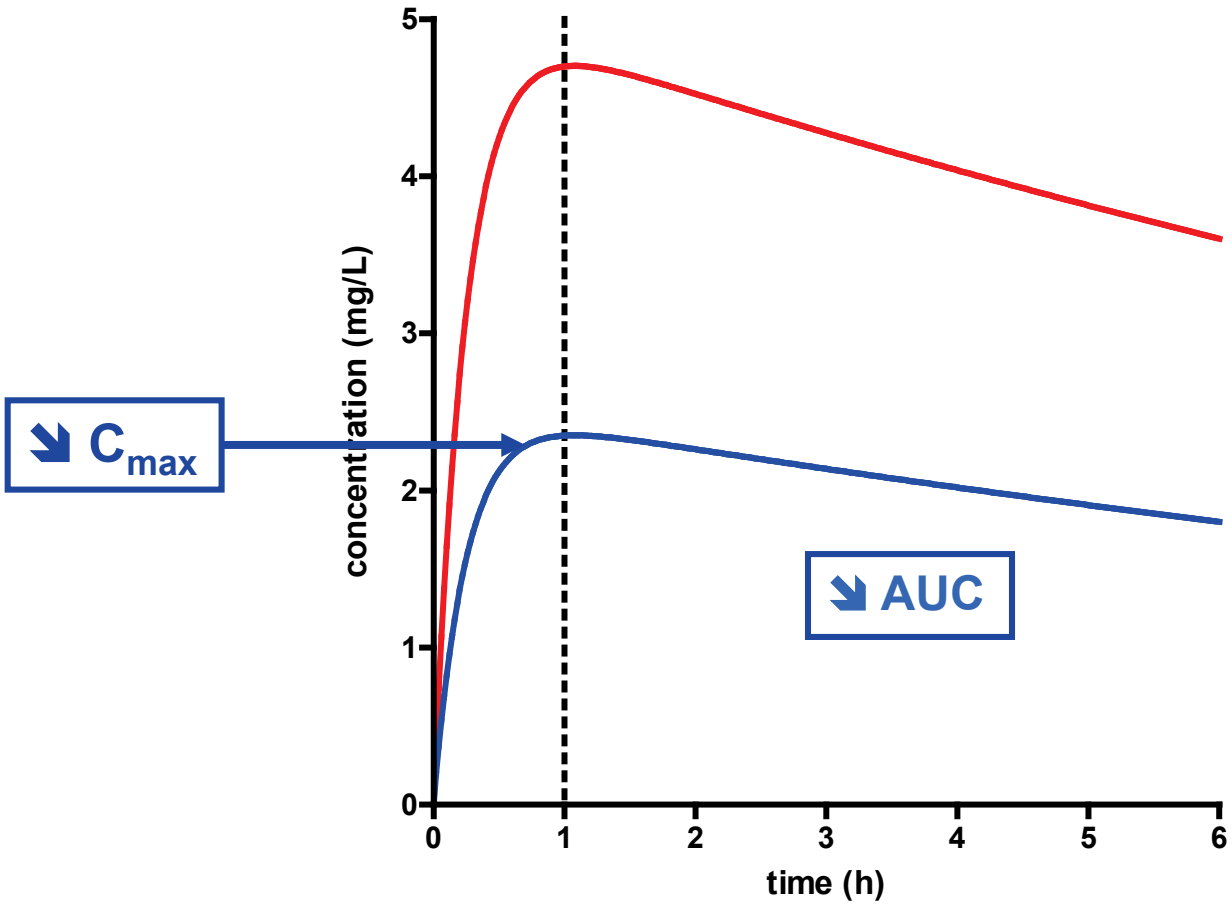
# AUC – $C_{max}$ – $T_{max}$



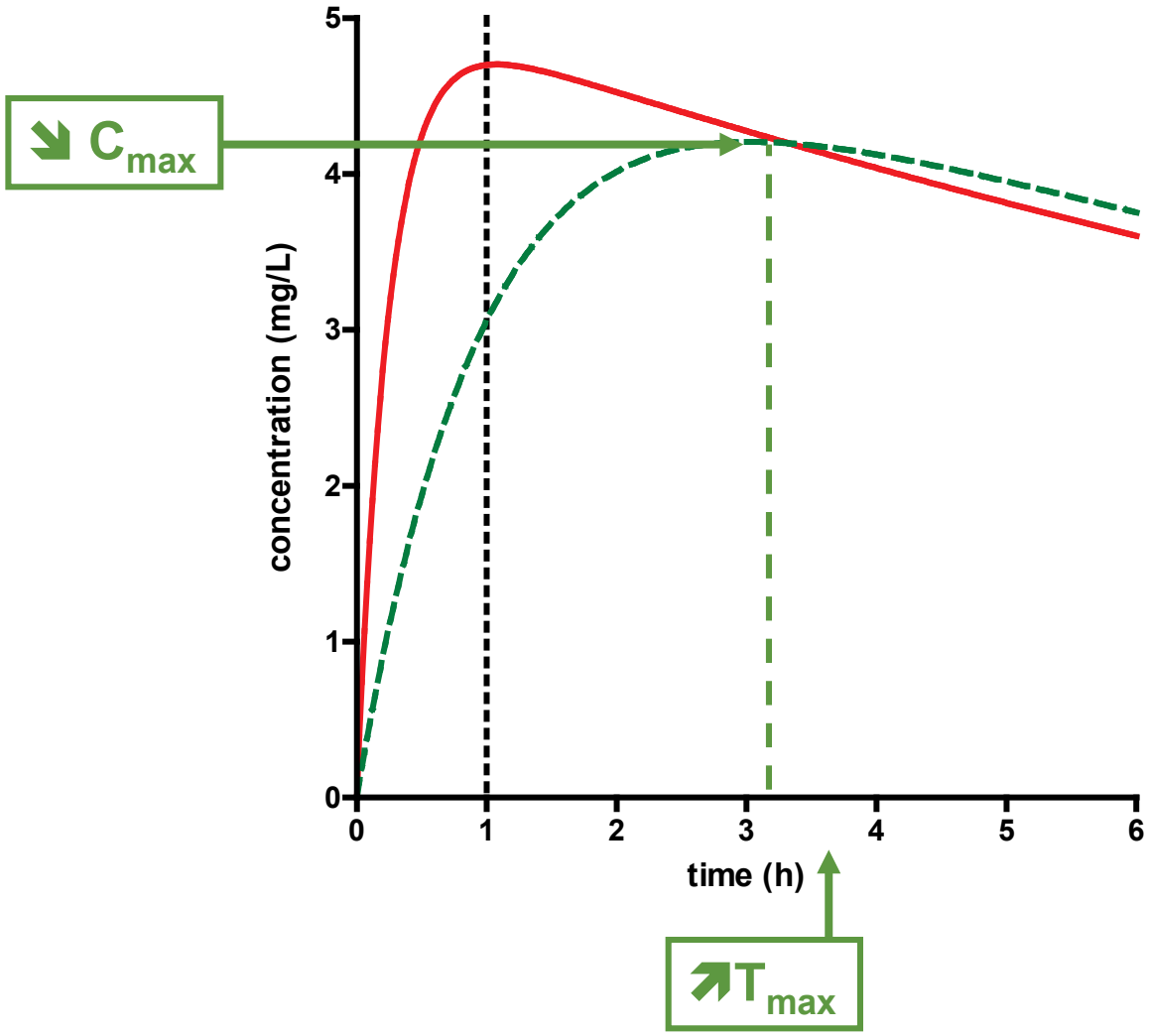
# AUC – $C_{max}$ – $T_{max}$



# What if the absorption is decreased ?

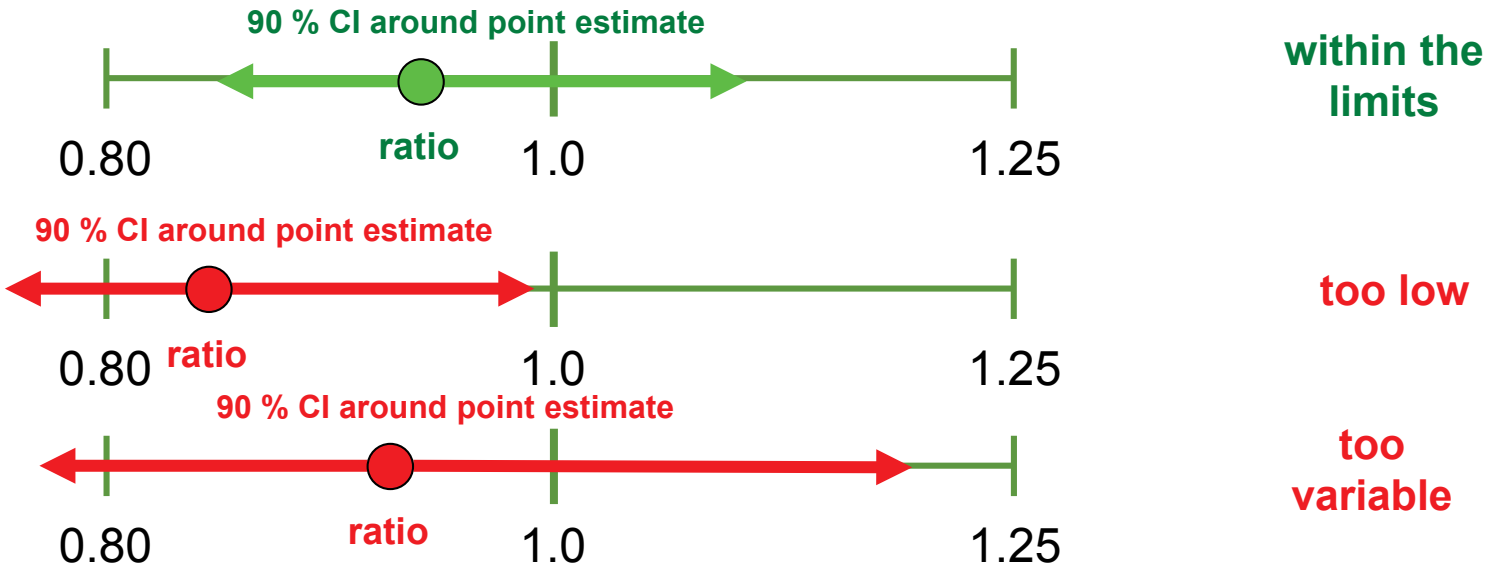


# What if absorption is delayed ?



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

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

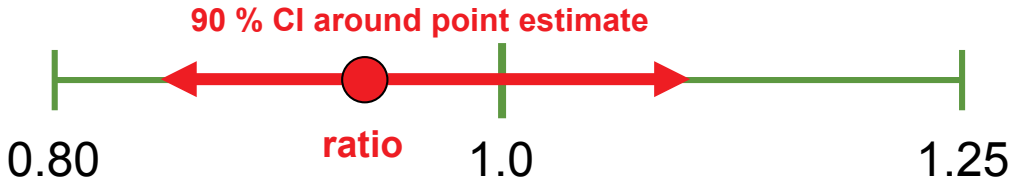



* Guideline to the Investigation of Bioequivalence, London, 20 January 2010 - Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf

** 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 $C_{max}$ 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 $C_{max}$ are within range, the generic should have the same bioavailability as the reference
2. statistical evaluation of $T_{max}$ 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 [1-3]

[1] Tothfalusi *et al.* Eur J Health Econ (2014) 15 (Suppl 1):S5–S11
[2] Ahn & Lee, Ungyong Tonggye Yongu (2011) 24(3): 495–503
[3] Lee *et al*. Nature Biotechnology (2013) 31:220-226

# Is this enough ? What do you think ?

1. The US / EU laws (or the law of my country) are sufficient and convince me to say that generics are like the original products
2. While accepting the laws, I'm not convinced and would like to have additional information from the producers
3. What is required by law is insufficient and the laws need to be changed.

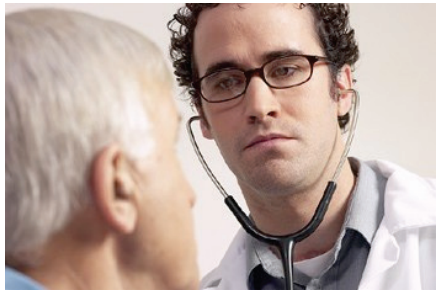
**Please, think about what YOU would choose !**

# 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).

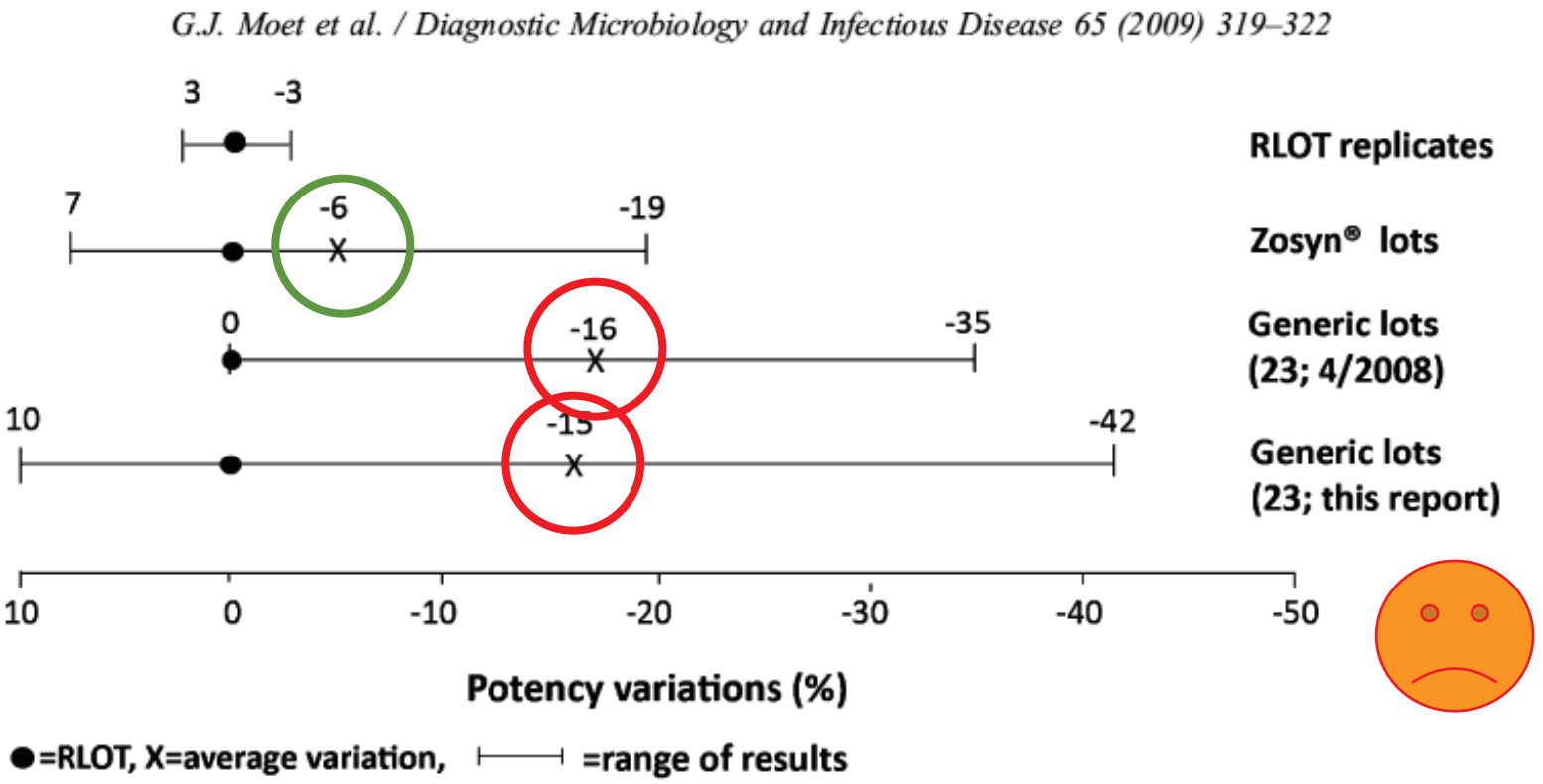



Fig. 1. Extent of potency variations among 4 groups of experiments with piperacillin/tazobactam intravenous injection lots.

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

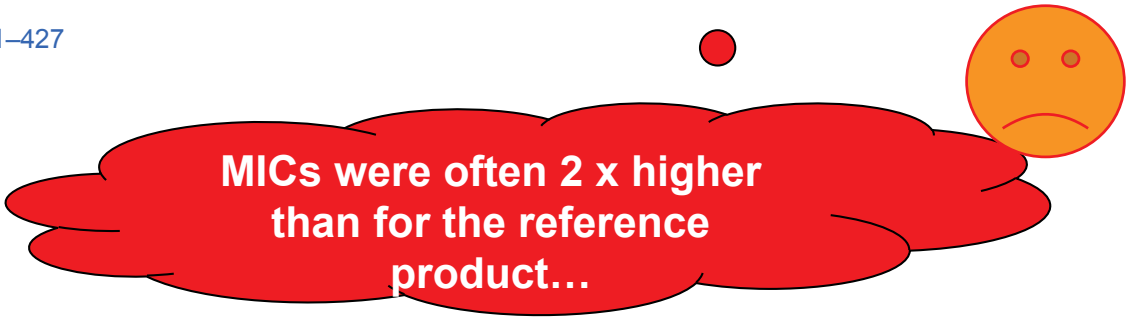
# MIC values (vancomycin)

**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 ± SD) | MIC distribution (%) of the most different generic versus brand name drug | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 1/8 | 1/4 | 1/2 | 1[a] | 2 | 4 | 8 |
| Vancomycin | MRSA (90) | 5 | 25.00 ± 15.52 | – | – | – | 54.4 | 45.6 | – | – |
| Teicoplanin | MRSA (147) | 7 | 28.09 ± 10.29 | – | – | – | 59.2 | 40.1 | 0.7 | – |
| Cefotiam | *Staphylococcus aureus* (100) | 7 | 8.71 ± 3.04 | – | – | – | 87.0 | 13.0 | – | – |
| | *Escherichia coli* (100) | 7 | 12.00 ± 5.89 | – | – | – | 77.0 | 22.0 | 1.0 | – |
| Ceftriaxone | *Streptococcus pneumoniae* (126) | 6 | 12.70 ± 4.77 | – | – | – | 81.7 | 18.3 | – | – |
| Ceftazidime | *Pseudomonas aeruginosa* (100) | 2 | 3.00 ± 2.83 | – | – | – | 95.0 | 5.0 | – | – |
| Meropenem | *P. aeruginosa* (100) | 7 | 18.57 ± 3.46 | – | – | – | 78.0 | 19.0 | 2.0 | 1.0 |
| Imipenem | *P. aeruginosa* (100) | 4 | 9.00 ± 2.58 | – | – | – | 88.0 | 11.0 | 1.0 | – |

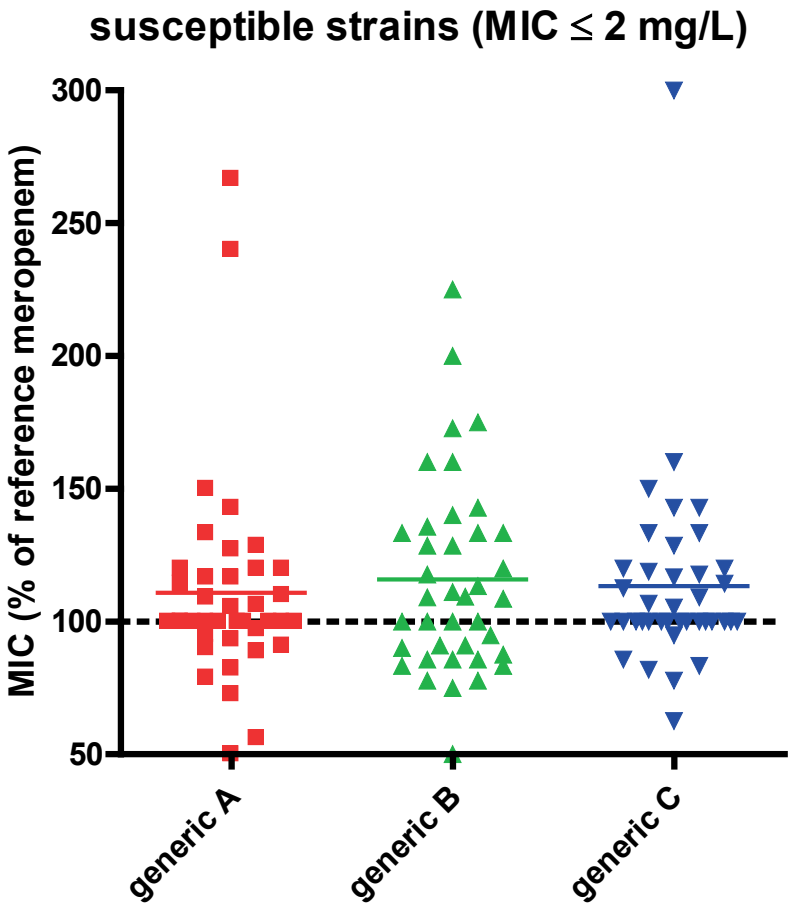
*MRSA* methicillin-resistant *Staphylococcus aureus*[a]Note that the distribution of one minimal inhibitory concentration (1 MIC) shows the identical rate with the brand drug: MIC was determined by broth micro-dilution method using powder in each drug vial

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



# 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

Neutropenic mouse thigh infection model

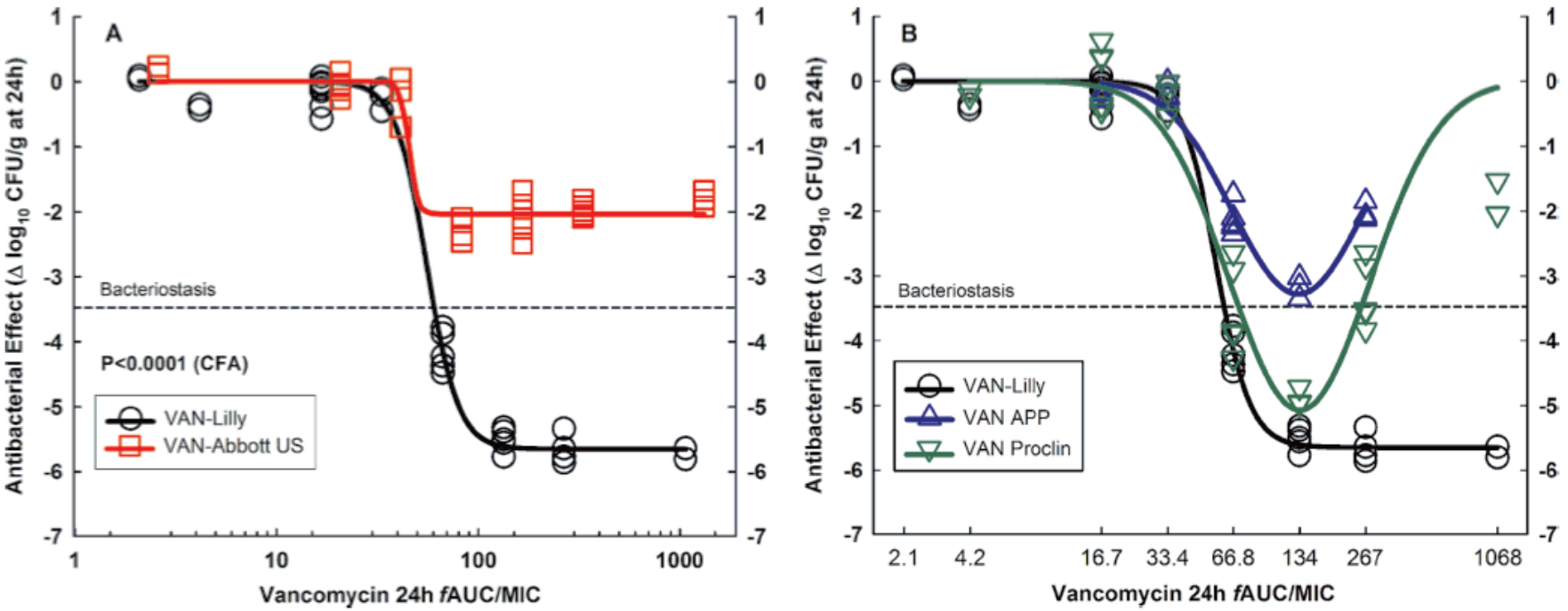



FIG. 1. *In vivo* efficacy against *S. aureus* GRP-0057 (years 2002 and 2003) at a low inoculum (4.30 ± 0.05 $\log_{10}$ CFU per thigh when subcutaneous treatment q1h started). Vancomycin generic products are compared with the innovator (VAN-Lilly) in dose-effect experiments (2.34 to 1,200 mg/kg per 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 (*f*AUC/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

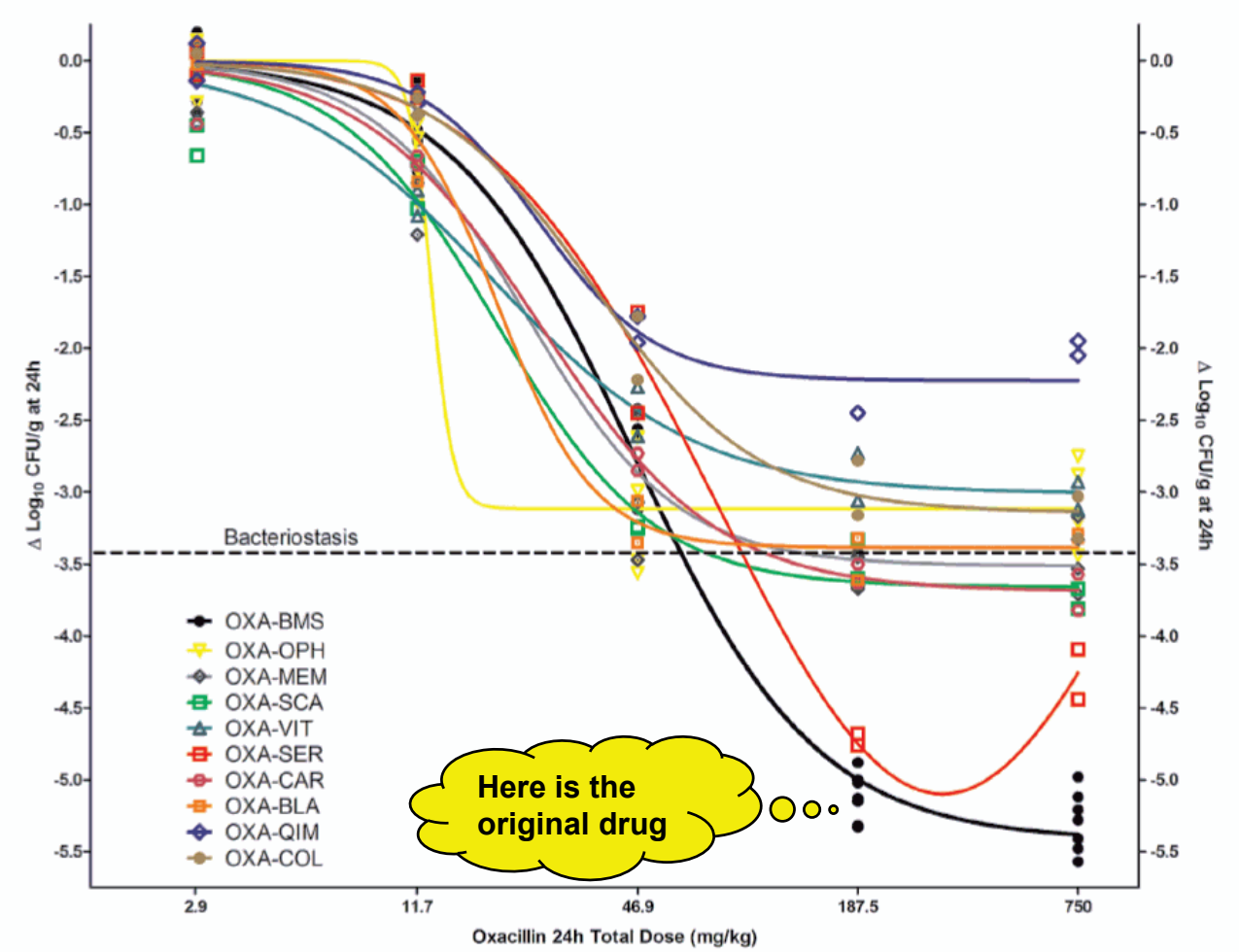



**Figure 3 Dose-response relationship of the innovator and 9 generic products of oxacillin in the neutropenic mouse thigh infection model.** OXA-BMS (innovator, black curve) and 8 generics fitted to Hill's sigmoid model, while generic product OXA-SER fitted to the Gaussian U-shaped model (red curve). 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.

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

# But pharmacodynamics equivalence can also be demonstrated

AAC Accepts, published online ahead of print on 13 October 2014
Antimicrob. Agents Chemother. doi:10.1128/AAC.03633-14


**Impact on resistance of the use of therapeutically equivalent generics: the case of ciprofloxacin.**

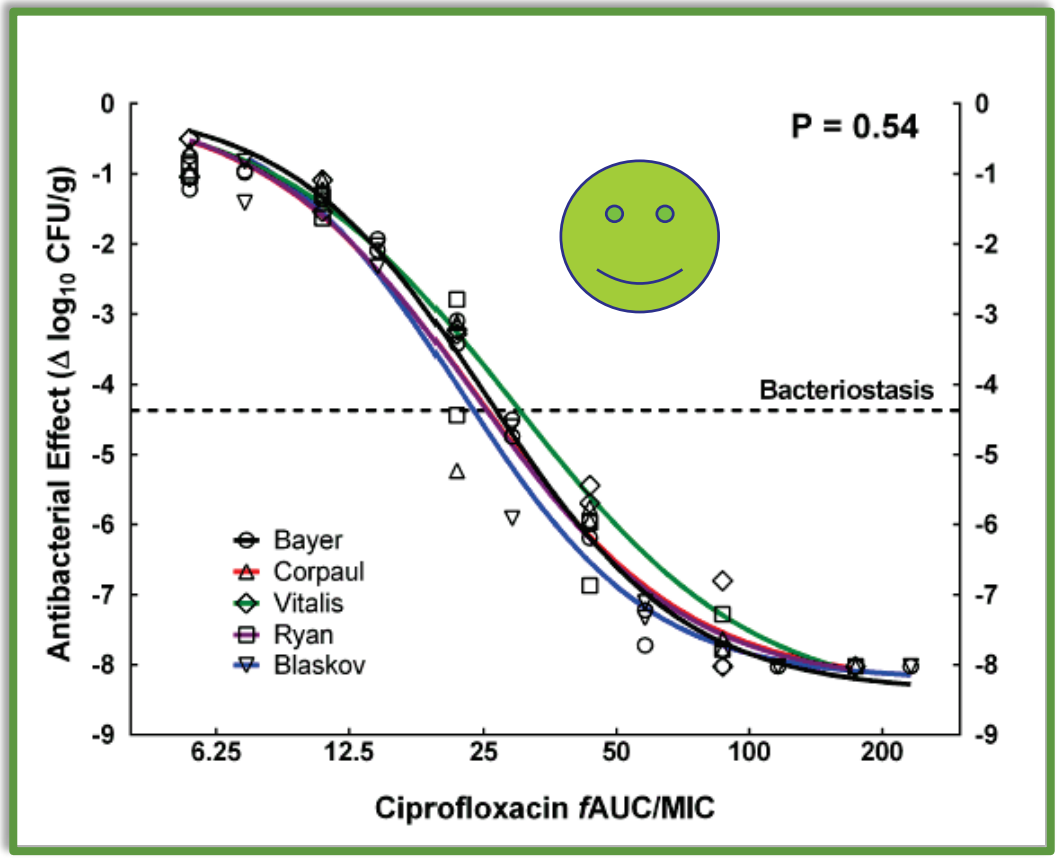
Carlos A. Rodriguez[a,b], Maria Agudelo[a,b,d], Andres F. Zuluaga[a,b], Omar Vesga[a,b,c,d#]

# But pharmacodynamics equivalence can also be demonstrated

AAC Accepts, published online ahead of print on 13 October 2014
Antimicrob. Agents Chemother. doi:10.1128/AAC.03633-14


**Impact on resistance of the use of therapeutically equivalent generics: the case of ciprofloxacin.**

Carlos A. Rodriguez[a,b], Maria Agudelo[a,b,d], Andres F. Zuluaga[a,b], Omar Vesga[a,b,c,d#]




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

# Clinical alerts (efficacy and safety) ?

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

**Luca Gallelli[1], Caterina Palleria[1], Antonio De Vuono[2], Laura Mumoli[1], Piero Vasapollo[2], Brunella Piro[3], Emilio Russo[1]**

*[1]Department of Health Science, Regional Center on drug information, Mater Domini University Hospital, Italy and Chair of Pharmacology, School of Medicine, University of Catanzaro, [2]Department of General Medicine, ASP Cosenza, [3]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 generi to brand formulation

**Luca Gallelli[1], Caterina Palleria[1], Antonio De Vuono[2], L Emilio Russo[1]**

*[1]Department of Health Science, Regional Center on drug information, Ma School of Medicine, University of Catanzaro, [2]Department of General Mec Cosenza, Italy*

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

In this case-review, we r treatment with generic f discuss the relative reas 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,[41] 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 <u>really</u> 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

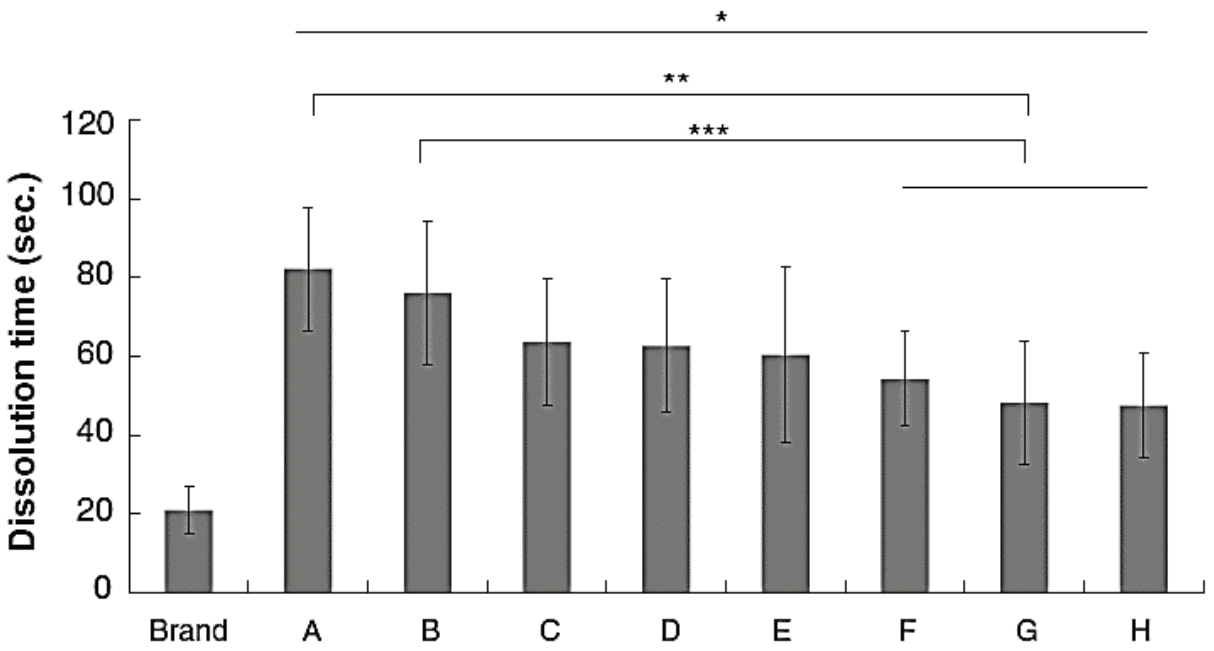



**Fig. 3** Comparison of dissolution time between brand name meropenem and eight generics. *A–H* Generic products of meropenem. $*P < 0.001$ versus brand name drug; $**P < 0.001$ versus generic A drug; $***P < 0.001$ versus generic B drug

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

# Crystals size in meropenem in Japan



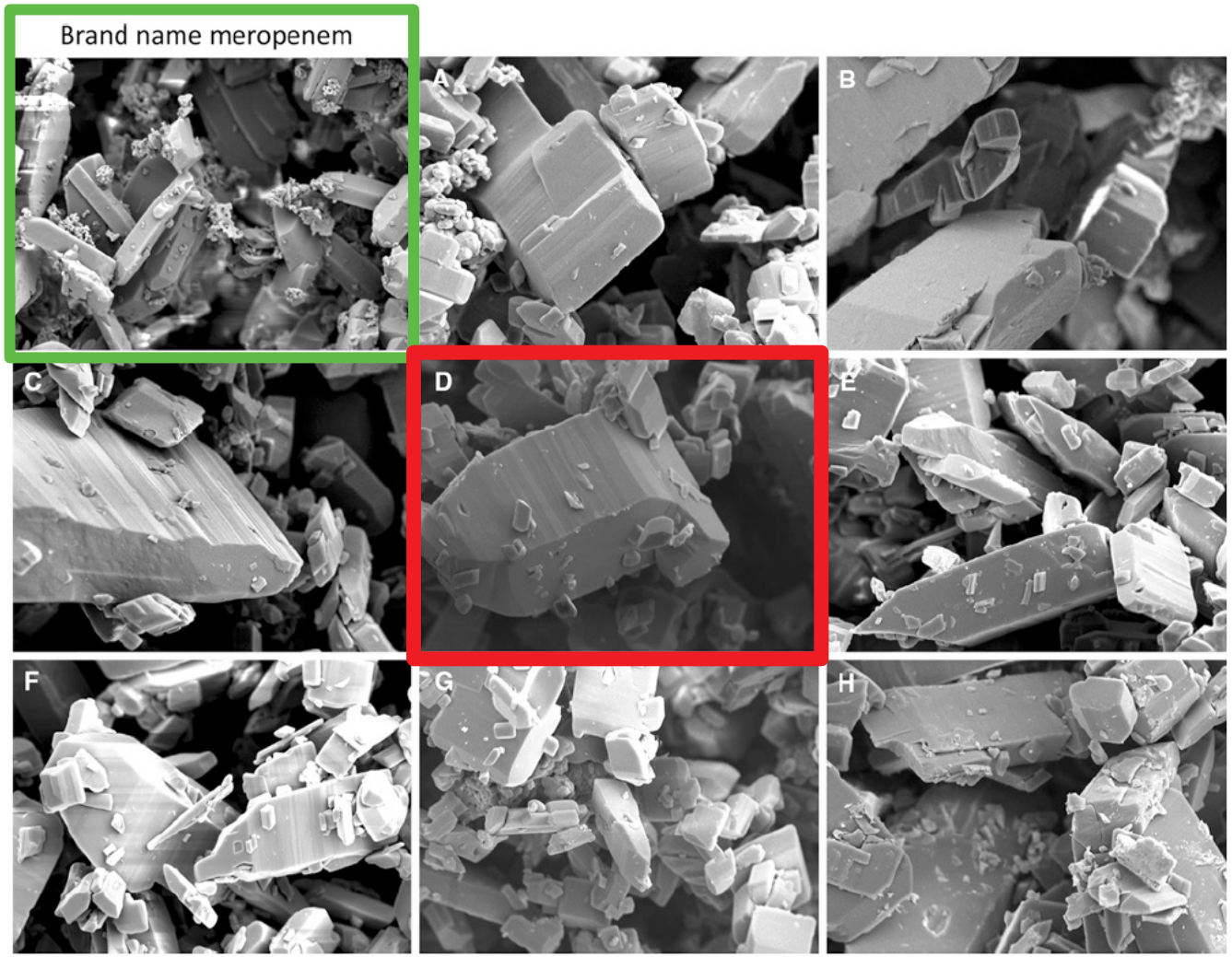
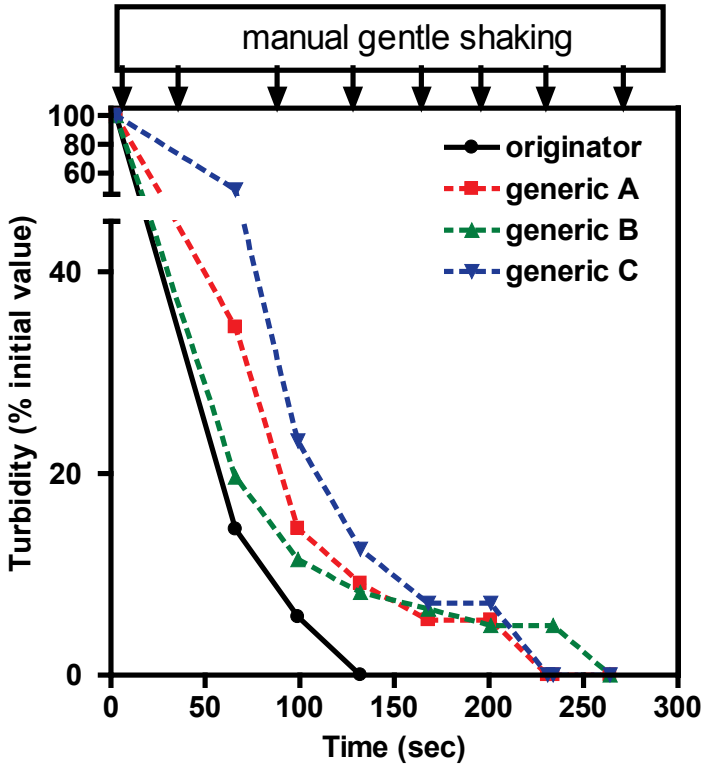


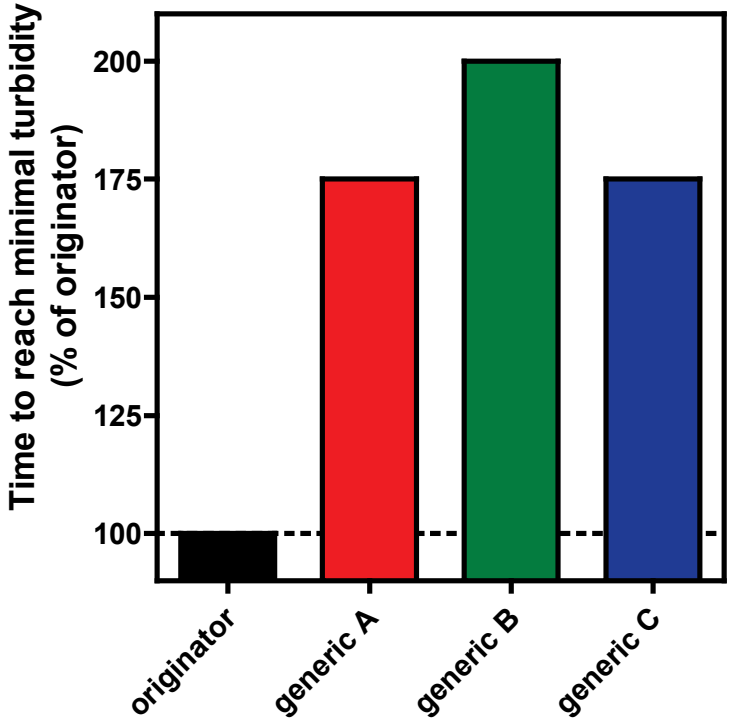

Fig. 4 Electron micrographs of drug particles of brand name meropenem and eight generics. a–h Generic products of meropenem. ×1,000

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

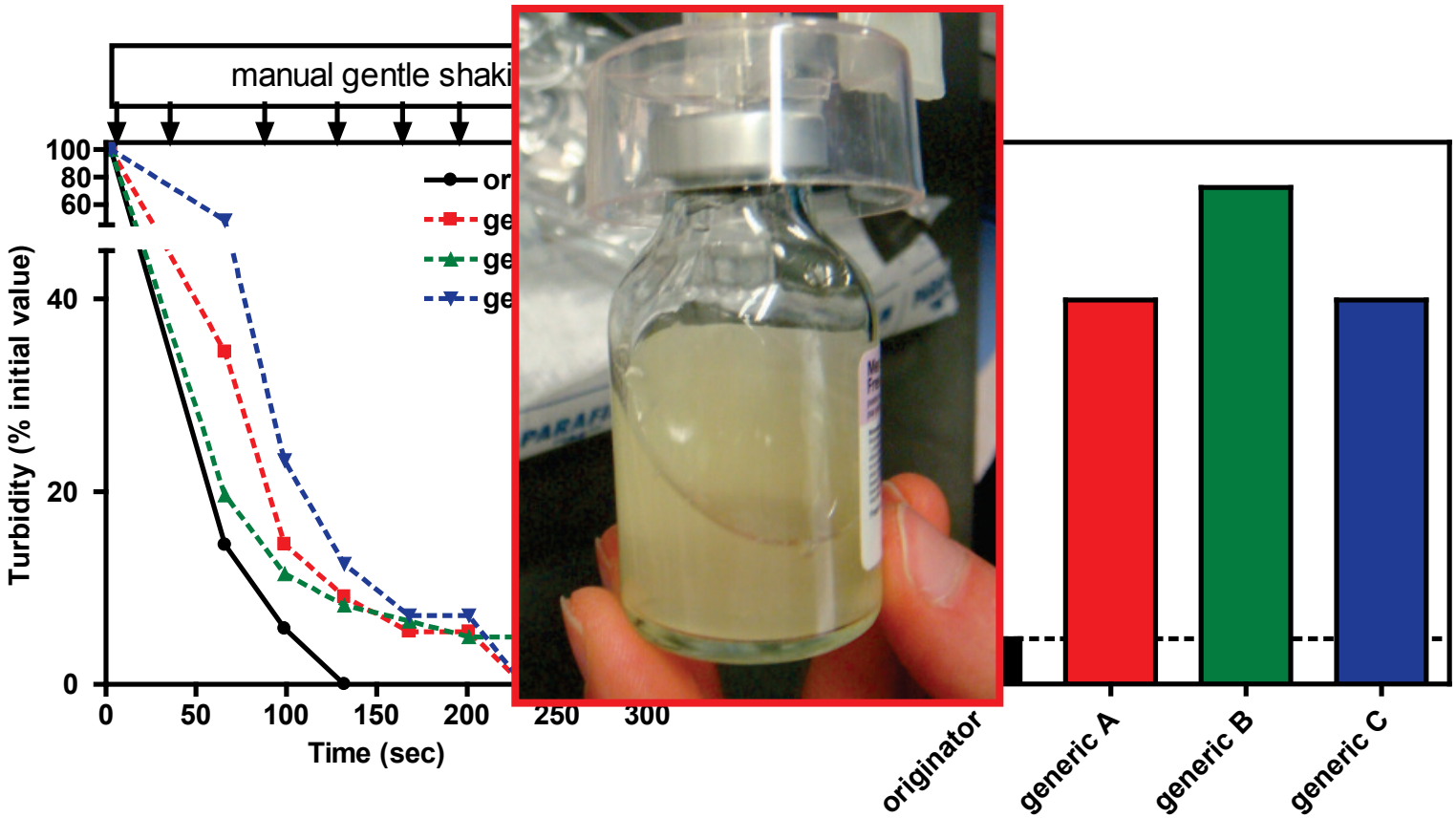



Van Bambeke *et al*., in preparation

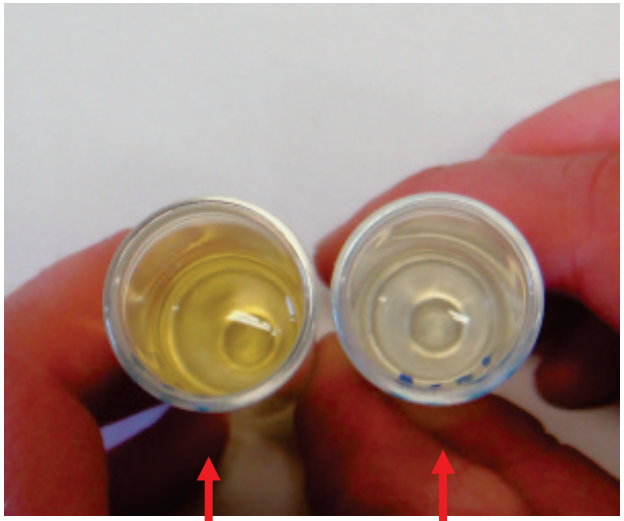
# Dissolution of meropenem in Belgium

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

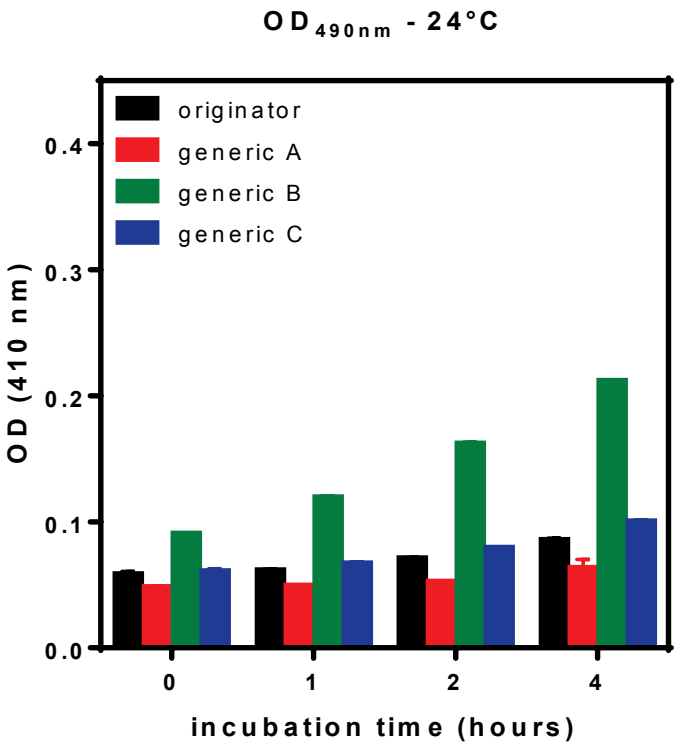


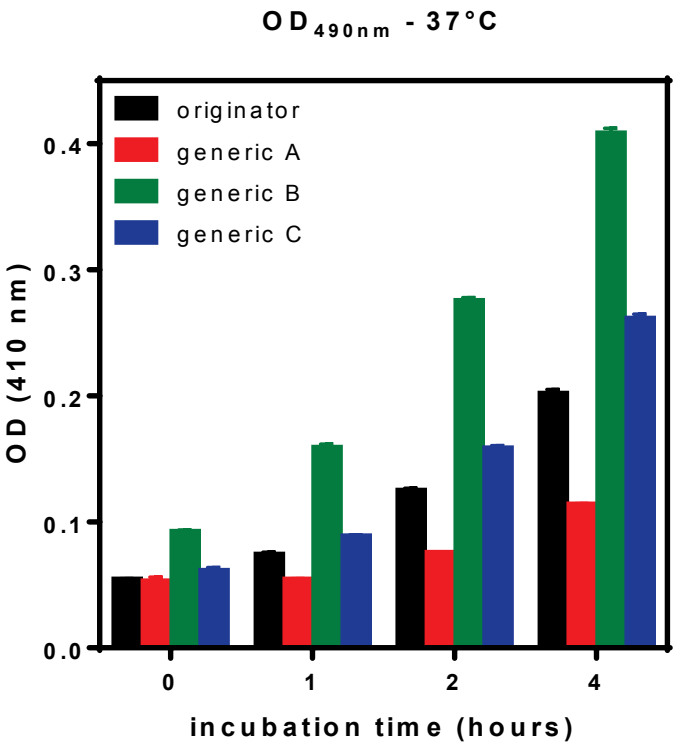
generic B originator

are you happy with the colour?

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
ScienceDirect
Journal of Pharmaceutical and Biomedical Analysis 44 (2007) 743–754
JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL ANALYSIS
www.elsevier.com/locate/jpba

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

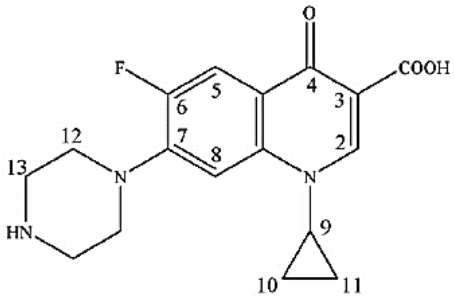
**Abstract**

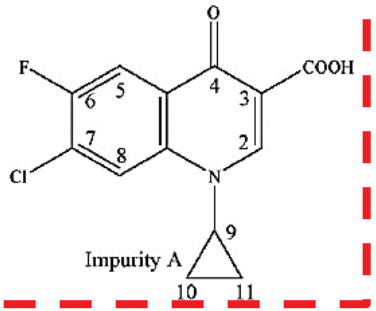
The objective of this study was to control the purity of 16 commercial formulations of ciprofloxacin tablets purchased in different countries or via the Internet using $^{19}F$ and $^{1}H$ nuclear magnetic resonance (NMR). Twelve out of the sixteen commercial formulations of ciprofloxacin measured by $^{19}F$ 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 $^{19}F$ and $^{1}H$ 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 $^{19}F$ NMR. Two other non-fluorinated impurities were observed in the seven formulations analysed with $^{1}H$ 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) $^{1}H$ NMR which allowed the characterisation of some excipients present in the formulations studied.

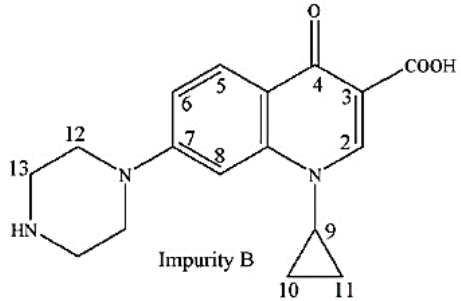

*Keywords:* $^{19}F$ NMR; $^{1}H$ NMR; DOSY $^{1}H$ NMR; Ciprofloxacin; Impurities

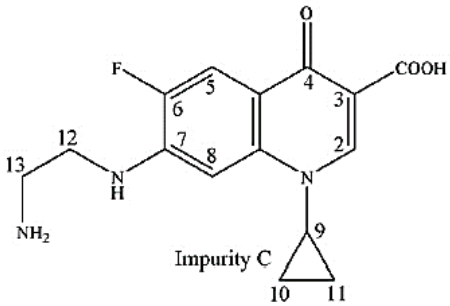
# Impurities in ciprofloxacin

This is a synthesis precursor !



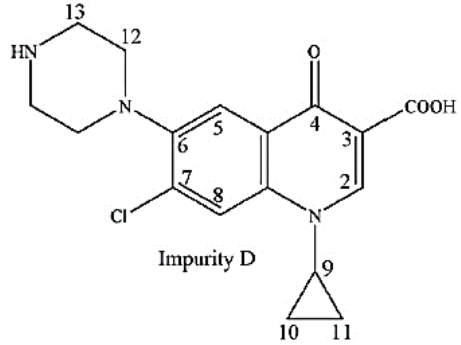




Fig. 1. Structure of ciprofloxacin and its main impurities.

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

# Substandard (wrong) drugs in the world ?

BJCP British Journal of Clinical Pharmacology

## Substandard drugs: a potential crisis for public health

Atholl Johnston[1] & David W. Holt[2]

[1]Clinical Pharmacology, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK and [2]St George's – University of London, London, UK

**Correspondence**
Professor Atholl Johnston, Clinical Pharmacology, Barts and The London, Charterhouse Square, London EC1M 6BQ, UK.
Tel.: +44 20 7882 6055
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.

# Problems appearing in Europe !

MEDIPLANET.be
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


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 !

MEDIPLANET.be
Actus - E-learning - Recherches
8/12/2014

La Belgique retire 4 médicaments commerci
par la société indienne
Biosciences

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

MEDIPLANET

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

**The lists makes 135 pages**

# We should also address the problem of counterfeited drugs


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

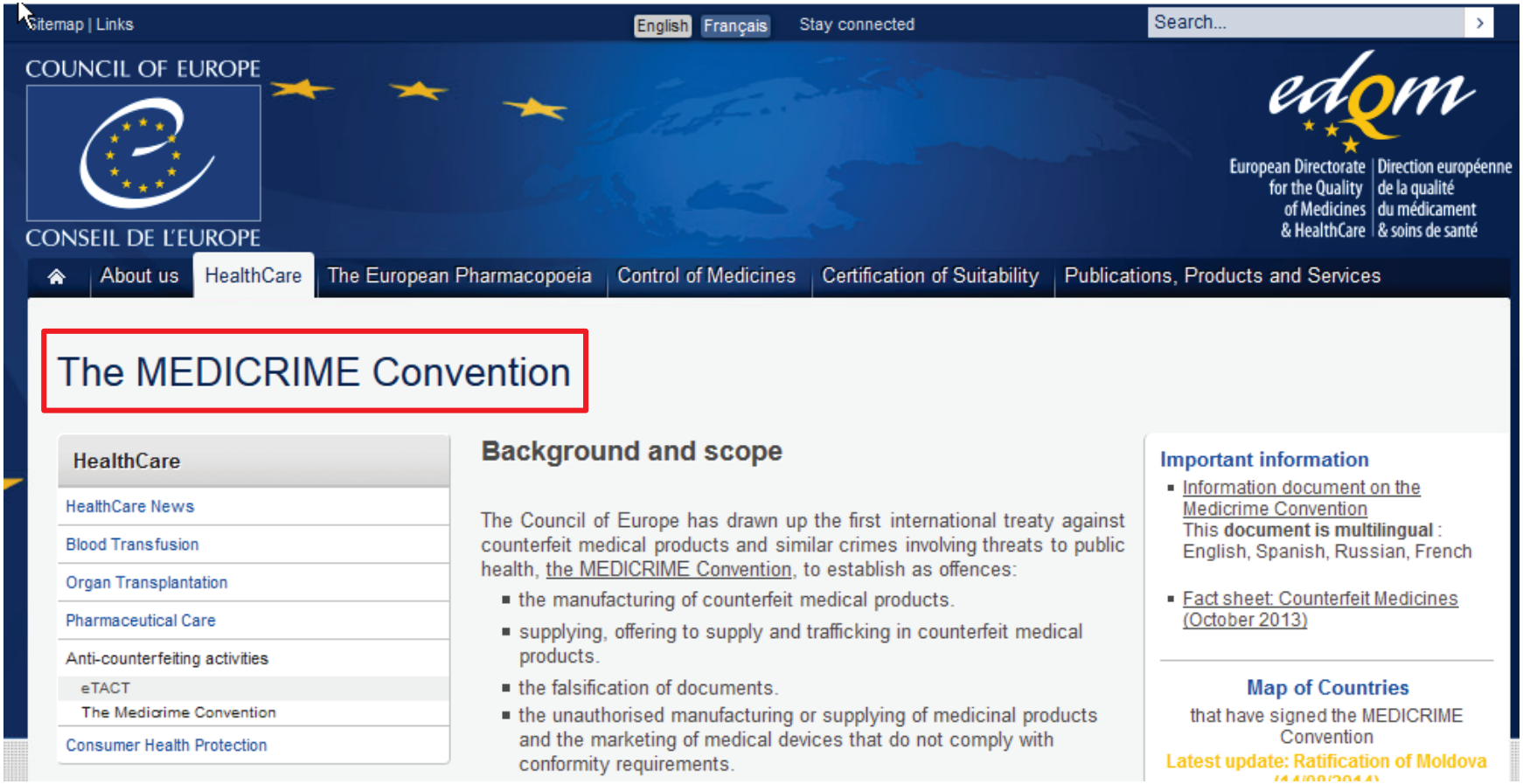
The only noticeable difference is that the real package has a hologram on the back (left). **The fake was two-thirds talcum powder and contained no ciprofloxacin**. Even holograms can be faked.

- **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.

# An European action is ongoing … but is costly




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

# An European action is ongoing … but is costly


## 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.

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

# MEDICRIME: which countries ?





https://www.edqm.eu/medias/images/medicrime_world_map_with_list_english.jpg
Last accessed: 20/02/2015

# 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[1]*, B. Cookson[2] and C. Fry[3] on behalf of the Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection Professional Education Subgroup†**

*[1]Antimicrobial Resistance, Stewardship and Healthcare Associated Infection (AMRS & HCAI) Programme, Public Health England, London, UK; [2]Division of Infection and Immunity, University College London, London, UK; [3]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/ARHAIprescrcompetencies__2_.pdf

# But see what happens with "Low cost antibiotics"…
## *The sour Danish Experience*

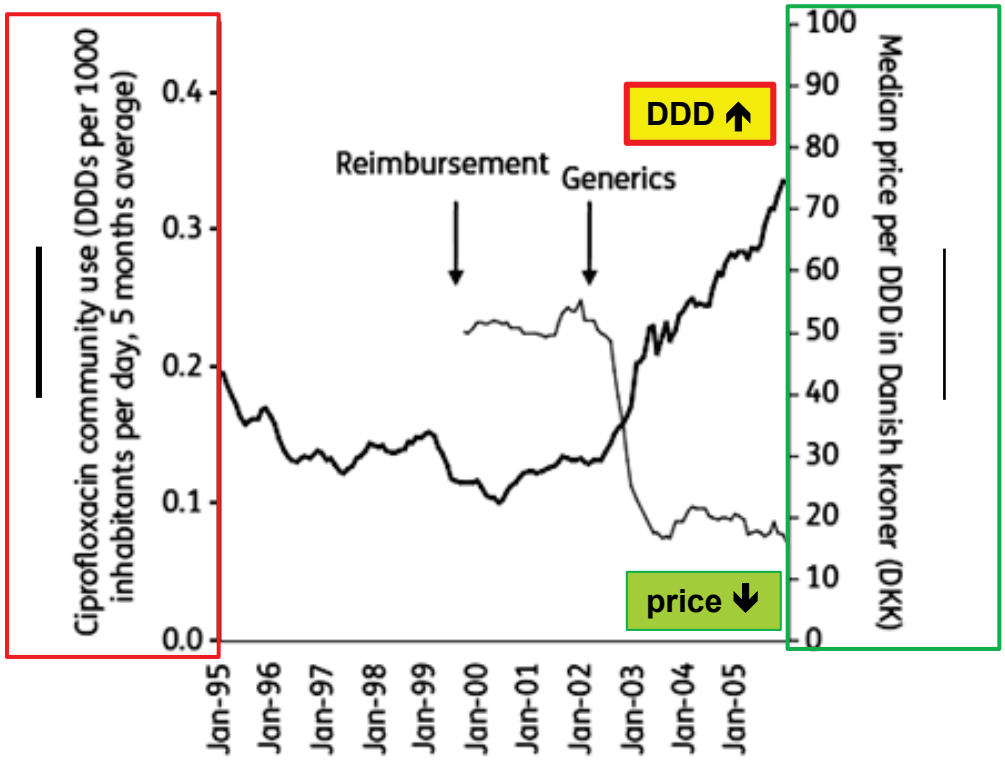


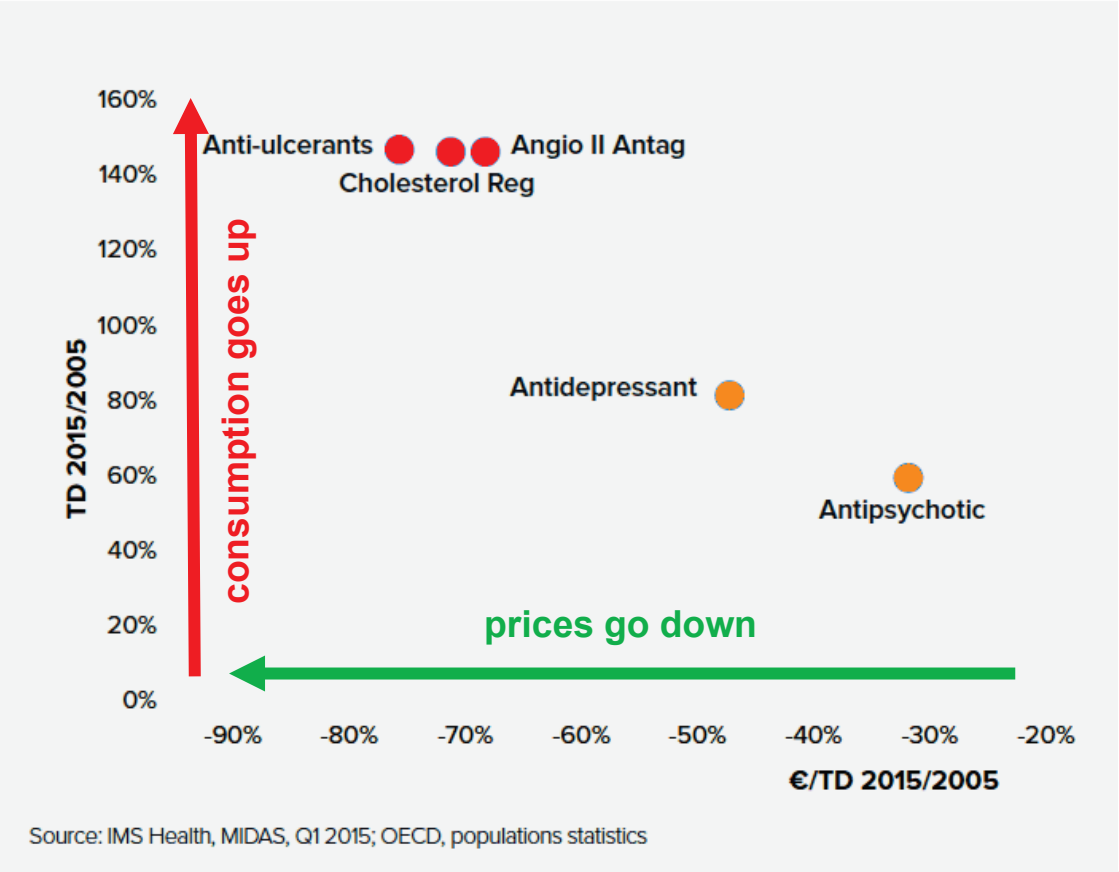

**Figure 1.**

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

# But this is not specific to antibiotics…

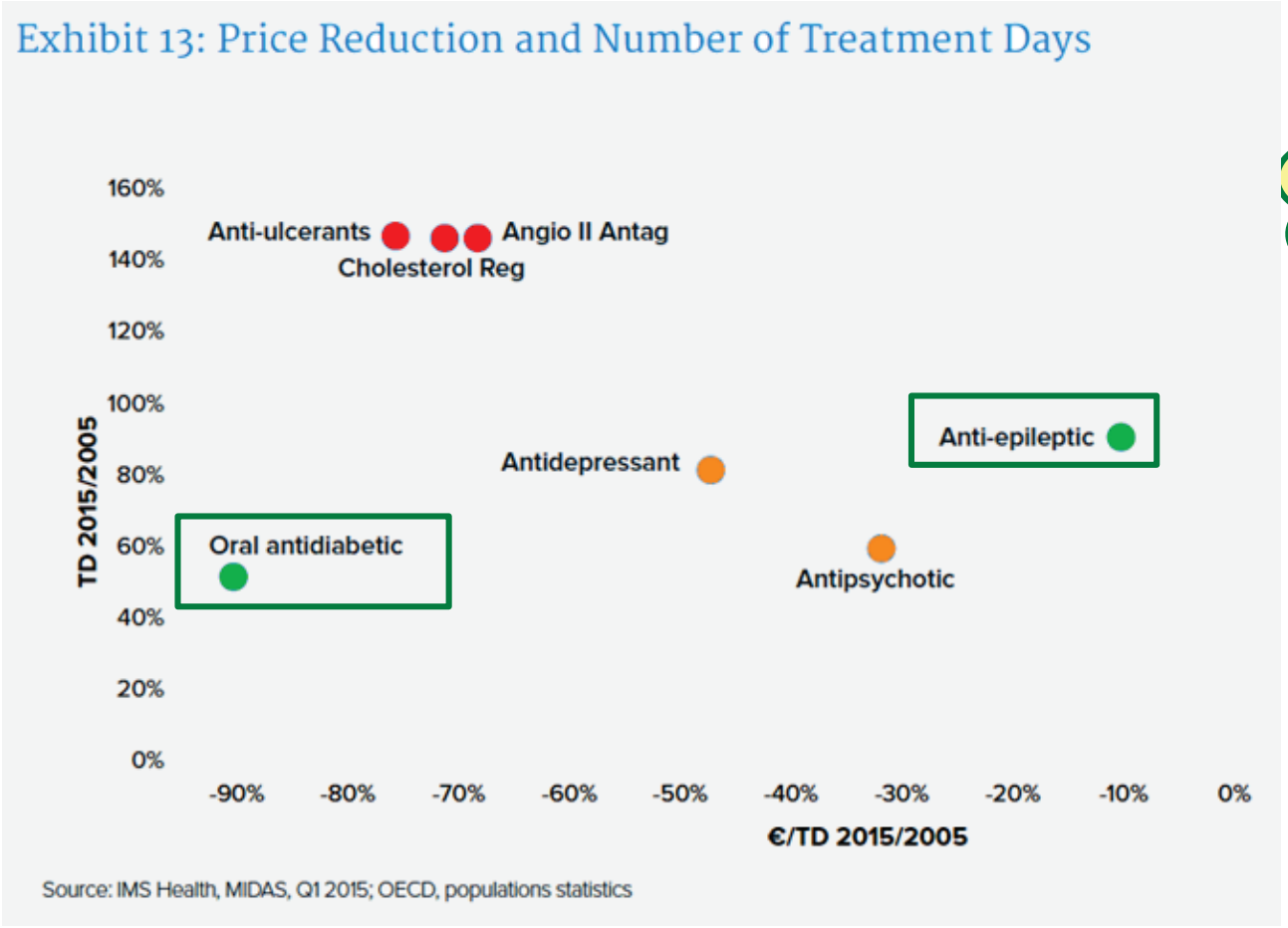
Exhibit 13: Price Reduction and Number of Treatment Days




Source: IMS Health, MIDAS, Q1 2015; OECD, populations statistics

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#

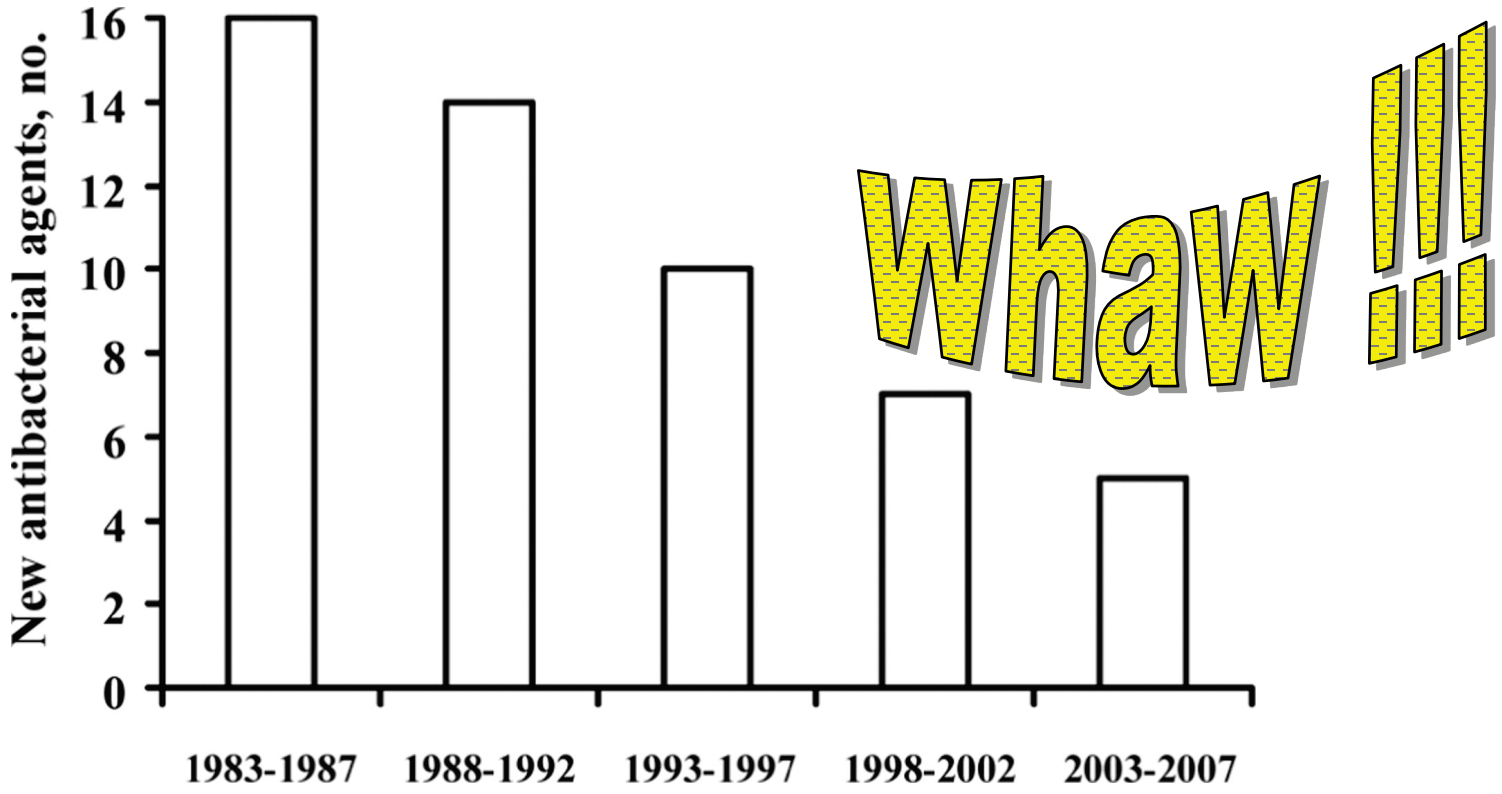
# There are specific exceptions…




but not for drugs with "clear" indications and contraindications

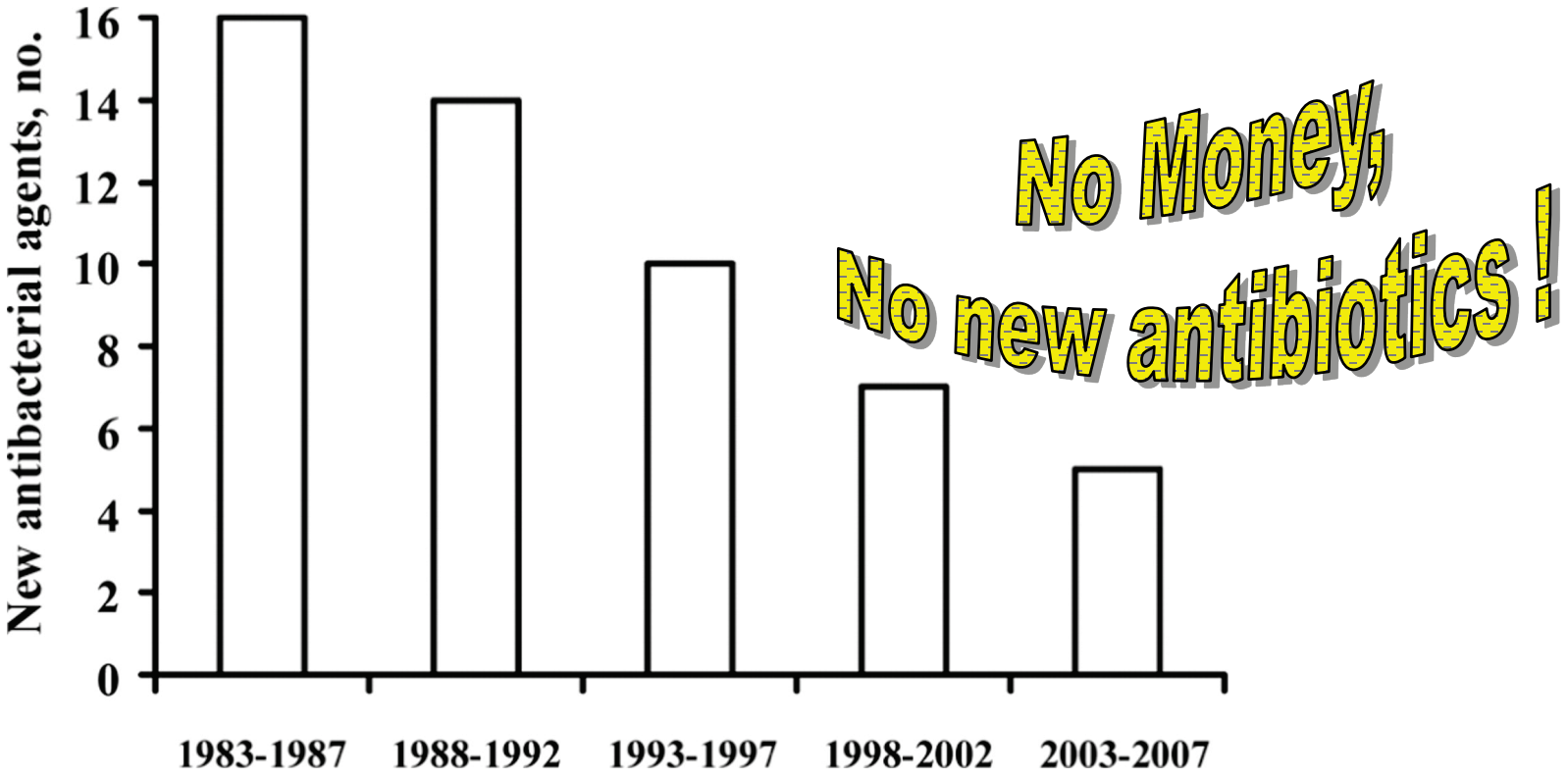
Source: The Role of Generic Medicines in Sustaining Healthcare Systems: A European Perspective
IMS Institute for Healthcare Informatics – June 2015
http://www.imshealth.com/vgn-ext-templating/v/index.jsp?vgnextoid=a64de5fda6370410VgnVCM10000076192ca2RCRD&vgnextfmt=default#

# 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


56

# Public actions …

ASM society

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 healt 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

imi

Innovative Medicines Initiative

- **€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

# Public actions …

OCIETY FOR MICROBIOLOGY

ASM society

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 healt surveillance agains tibiotic resistant bacteria would significantly reinforce the nation's campaign to stop Health

https://www.asm.org/i ...ency/93355-ar-2015
Last accessed: 08/0

**The citizens will 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 …

PLOS ONE

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…)**

# Drug shortages …

PLOS ONE

RESEARCH ARTICLE

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

a recent paper … (2015…)

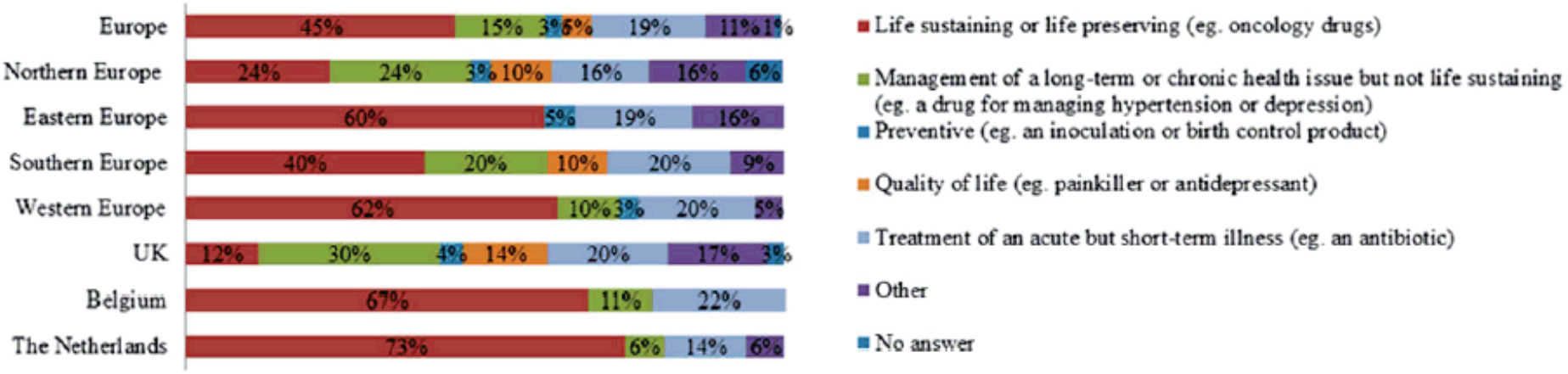



**Fig 1. Drug types affected by drug shortages according to the respondents.** Respondents who indicated that particular types of medicines suffered more from shortages than others were considered. The relative number of respondents per answer was shown for Europe (n = 128), Northern Europe (n = 8), 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 …

IMS INSTITUTE FOR HEALTHCARE INFORMATICS

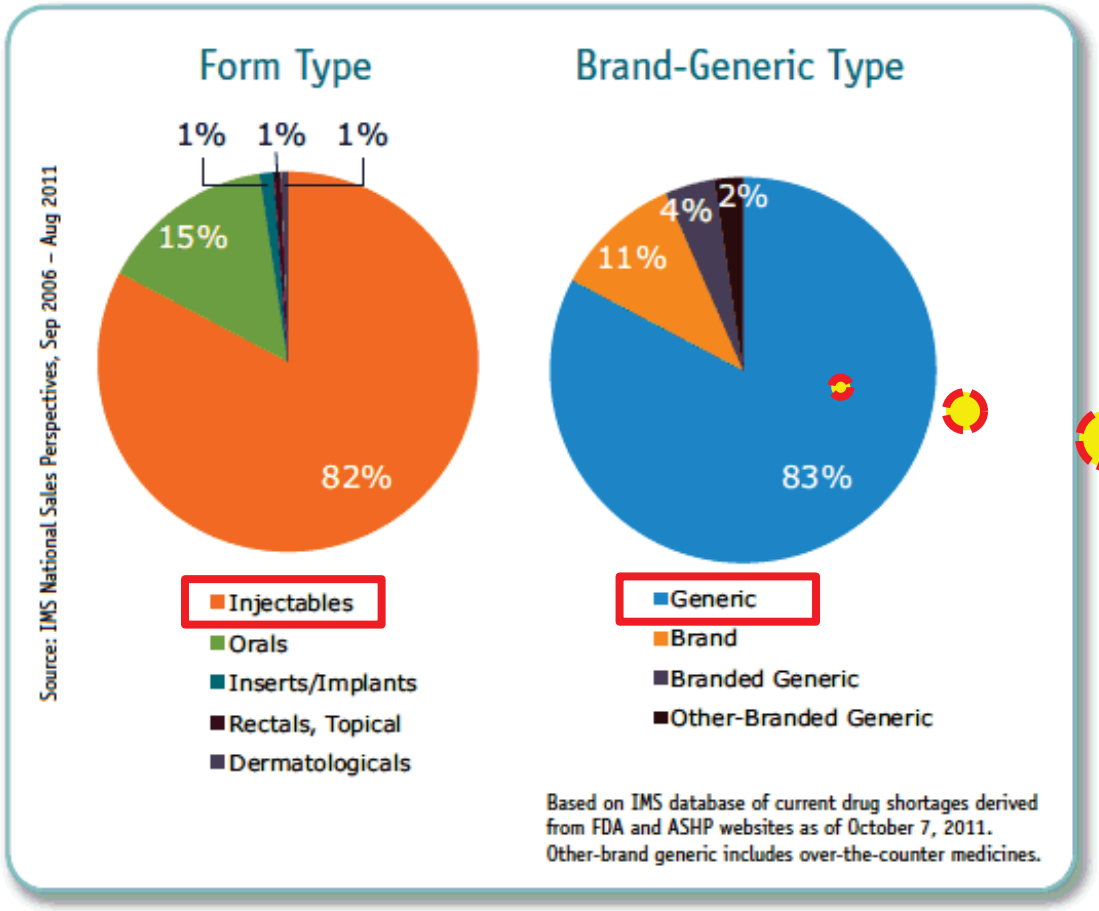
Drug Shortages:
A closer look
at products,
suppliers and
volume volatility.

November 2011

Report by the IMS Institute for Healthcare Informatics

# … and the main affected products were known

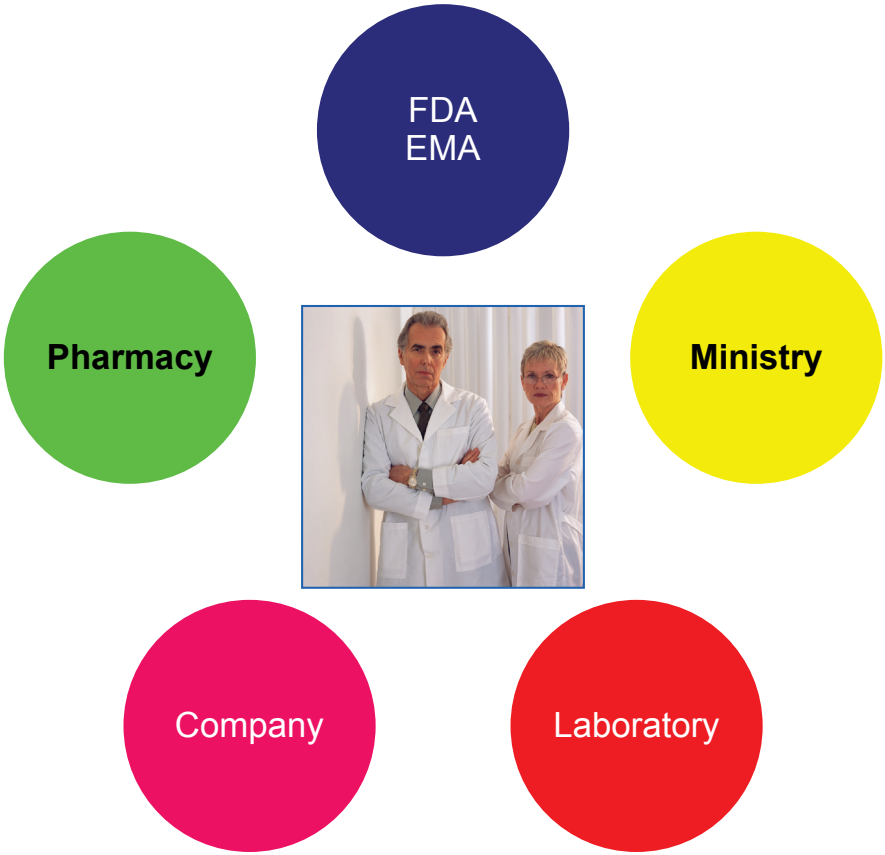
## Most products are injectables and generics




Drug Shortages: A closer look at products, suppliers and volume volatility.
Report by the IMS Institute for Healthcare Informatics

**and the main reason is "market volatility"**

# Now, what can you do as clinicians ?



# 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…** [1]

[1] already calculated at … O'Neill report

# Thank you for your attention!

## And ask questions