Product Safety and Quality:
An act of social and ethical responsibility
(a discussion about generic antibiotics)

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

- **Speaking fees**
  - Bayer, GSK, Sanofi, Johnson & Johnson, OM-Pharma

- **Decision-making and consultation bodies**
  - General Assembly and steering committee of EUCAST
  - European Medicines Agency (external expert)
  - US National Institutes of Health (grant reviewing)

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

You said "generics":
the recent story of a well known antibiotic

Before patent expiration

Tavanic (PI-Pharma)				▲
[lévofloxacine] compr. (séc.)				
€ 10 x 500mg		Rx	b⊖	€ 21,94
(importation parallèle)				

Tavanic (Sanofi-Aventis)				▲
[lévofloxacine] compr. (séc.)				
▯▮ € 10 x 250mg		Rx	b⊖	€ 14,98
▯▮ € 10 x 500mg		Rx	b⊖	€ 21,97
flacon perf.				
▯▮ € 1 x 500mg / 100ml		U.H.		[€17]

http://www.cbip.be/GGR/Index.cfm?ggrWelk=/nIndex/GGR/Stof/IN_L.cfm

A well known antibiotic in Belgium

After …

1 Levofloxacine Actavis (Actavis) ▲

[lévofloxacine]
sac perf.
€ 5 × 500mg / 100ml   U.H.   [€85]

2 Levofloxacine EG (Eurogenerics) ▲

[lévofloxacine]
compr. (séc.)
€ 10 × 500mg   Rx   b⊖   € 21,42
€ 30 × 500mg   Rx   b⊖   € 57,66
sac perf.
€ 1 × 500mg / 100ml   U.H.   [€17]

3 Levofloxacine Fresenius Kabi (Fresenius Kabi) ▲

[lévofloxacine]
flacon perf.
€ 1 × 500mg / 100ml   U.H.   [€17]

4 Levofloxacin Hospira (Hospira) ▲

[lévofloxacine]
sac perf.
€ 1 × 500mg / 100ml   U.H.   [€17]

5 Levofloxacine Mylan (Mylan) ▲

[lévofloxacine]
compr. (séc.)
€ 10 × 250mg   Rx   b⊖   € 14,98
€ 14 × 250mg   Rx   b⊖   € 24,43
€ 10 × 500mg   Rx   b⊖   € 21,98
€ 14 × 500mg   Rx   b⊖   € 35,13
flacon perf.
€ 10 × 500mg / 100ml   U.H.   [€170]

6 Levofloxacine Sandoz (Sandoz) ▲

[lévofloxacine]
compr. (séc.)
€ 10 × 250mg   Rx   b⊖   € 14,42
€ 10 × 500mg   Rx   b⊖   € 21,09
€ 30 × 500mg   Rx   b⊖   € 58,15

7 Levofloxacine Teva (Teva) ▲

[lévofloxacine]
compr. (séc.)
€ 10 × 250mg   Rx   b⊖   € 14,42
€ 10 × 500mg   Rx   b⊖   € 21,09
€ 30 × 500mg   Rx   b⊖   € 56,66
sac perf.
€ 10 × 250mg / 50ml   U.H.   [€85]
€ 10 × 500mg / 100ml   U.H.   [€170]

Tavanic (PI-Pharma) ▲

[lévofloxacine]
compr. (séc.)
€ 10 × 500mg   Rx   b⊖   € 21,94
(importation parallèle)

Tavanic (Sanofi-Aventis) ▲

[lévofloxacine]
compr. (séc.)
€ 10 × 250mg   Rx   b⊖   € 14,98
€ 10 × 500mg   Rx   b⊖   € 21,97
flacon perf.
€ 1 × 500mg / 100ml   U.H.   [€17]

http://www.cbip.be/GGR/Index.cfm?ggrWelk=/nIndex/GGR/Stof/IN_L.cfm

And also in Vietnam for all fluoroquinolones… coming from all over the world

Đọc kỹ hướng dẫn sử dụng trước khi dùng.
Nếu cần thêm thông tin, xin hỏi ý kiến thầy thuốc.
Chỉ dùng thuốc này theo sự kê đơn của thầy thuốc.
Để xa tầm tay trẻ em.

Hướng dẫn sử dụng thuốc:

MOXFLO
(Moxifloxacin 400mg/100ml)

MARCK BIOSCIENCES LTD
876,N.H.No.8,Vill. Hariyala, Tal. Matar, Dist. Kheda-387411, Gujarat, Ấn Độ

Rx – Thuốc bán theo đơn
PROXACIN 1%
(Ciprofloxacin)
Dung dịch đậm đặc dùng pha dung dịch tiêm truyền 10 mg/ml

Nhà sản xuất:
Warsaw Pharmaceutical Works Polfa S.A.
Karolkowa 22/24, 01-207 Warsaw, Ba lan.

MOXY™ IV Infusion 400mg/250mL
(Moxifloxacin)

Manufactured by:
Getz pharma (PVT) LIMITED
www.getzpharma.com | 29-30/27, K.I.A., Karachi, Pakistan

VN01-200005959

YURiA·PHARM
Thuốc chỉ dùng theo hướng dẫn của thầy thuốc
CIPROFLOXACIN INFUSION – 2mg/ml
Nhà sản xuất: "Yuria-Pharm", Ltd..,
Địa chỉ: 108, Verbovetskogo Str., Cherkassy, Ukraine, 18030

Thuốc kháng khuẩn uống có phổ rộng
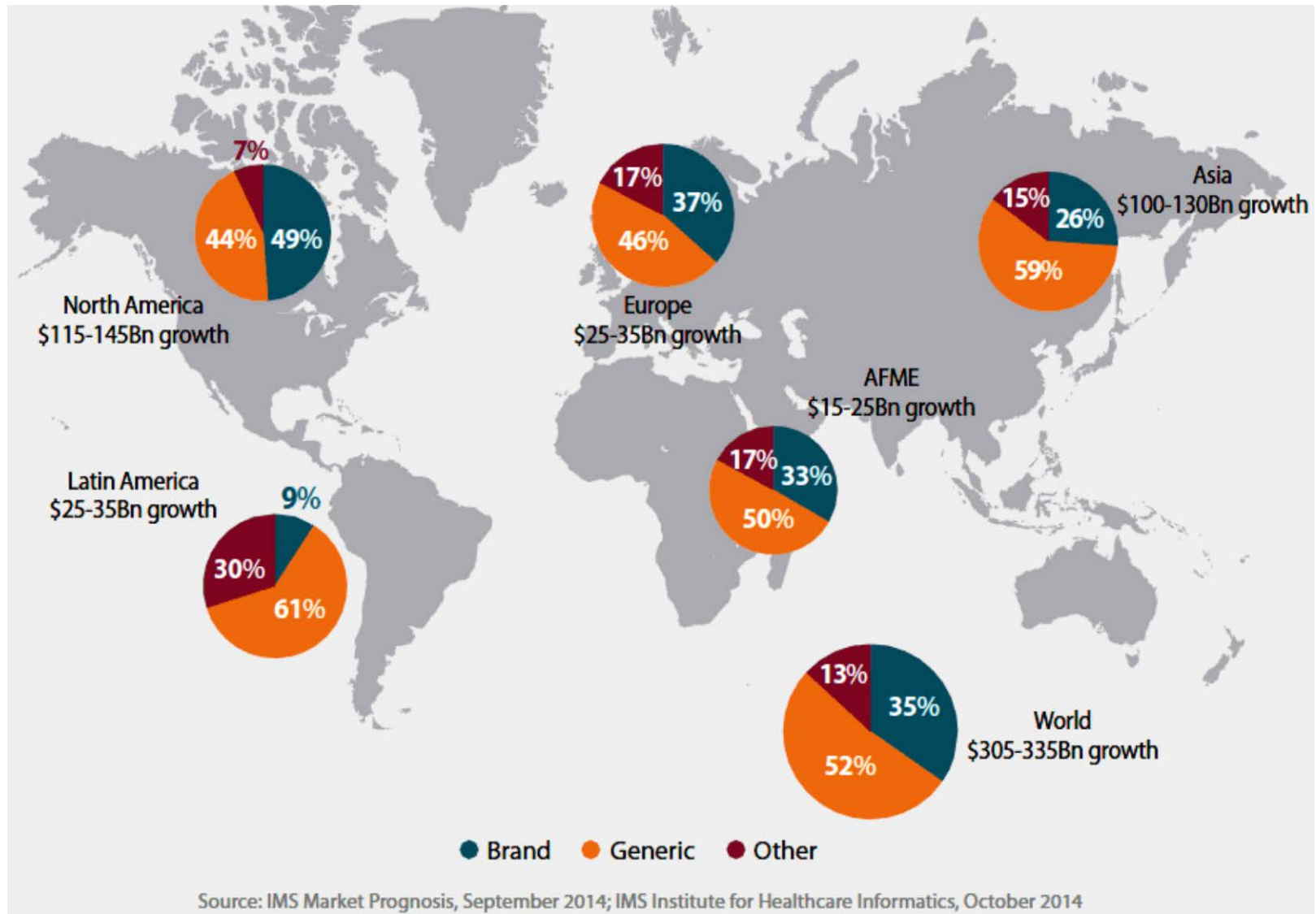Viên nén **Cravit**˚ (250mg và 500mg)
(Levofloxacin)

Mọi chi tiết xin liên hệ:
Daiichi Sankyo (Thailand) Ltd.
24th Fl. United Center Bldg., 323, Silom Rd., Silom, Bangrak, Bangkok 10500, Thailand
Tel:+66 2631-2070-9 FAX: +66 2236-2656

Daiichi (Japan) is actually the originator !

And all over the world…

North America
$115-145Bn growth
- 7% Other
- 44% Generic
- 49% Brand

Europe
$25-35Bn growth
- 17% Other
- 46% Generic
- 37% Brand

Asia
$100-130Bn growth
- 15% Other
- 59% Generic
- 26% Brand

Latin America
$25-35Bn growth
- 9% Brand
- 30% Other
- 61% Generic

AFME
$15-25Bn growth
- 17% Other
- 50% Generic
- 33% Brand

World
$305-335Bn growth
- 13% Other
- 52% Generic
- 35% Brand

● Brand   ● Generic   ● Other

Source: IMS Market Prognosis, September 2014; IMS Institute for Healthcare Informatics, October 2014

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, vote now (1 choice)

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

What shall we discuss?

1. A **political choice** (US and EU laws as an example)

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 Restora-
tion 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 <u>encouraged</u> 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 a **political** decision

- It finds its origin and basis in
  - the **limited duration of the patent protection** (usually about 20 years post patent application), which makes generics possible after about 10 years of effective commercialisation)
  - 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 main and only incentive in the promotion of the generics is, for governments, to acquire and provide drugs **more cheaply** to the population

What shall we discuss?

1. The US and the EU laws

2. **Approach to PK bioequivalence**

http://www.choosinggenerics.ca/Bioequivalence.aspx
Last visited: 15 March 2014

Bioequivalence: principles

- 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}
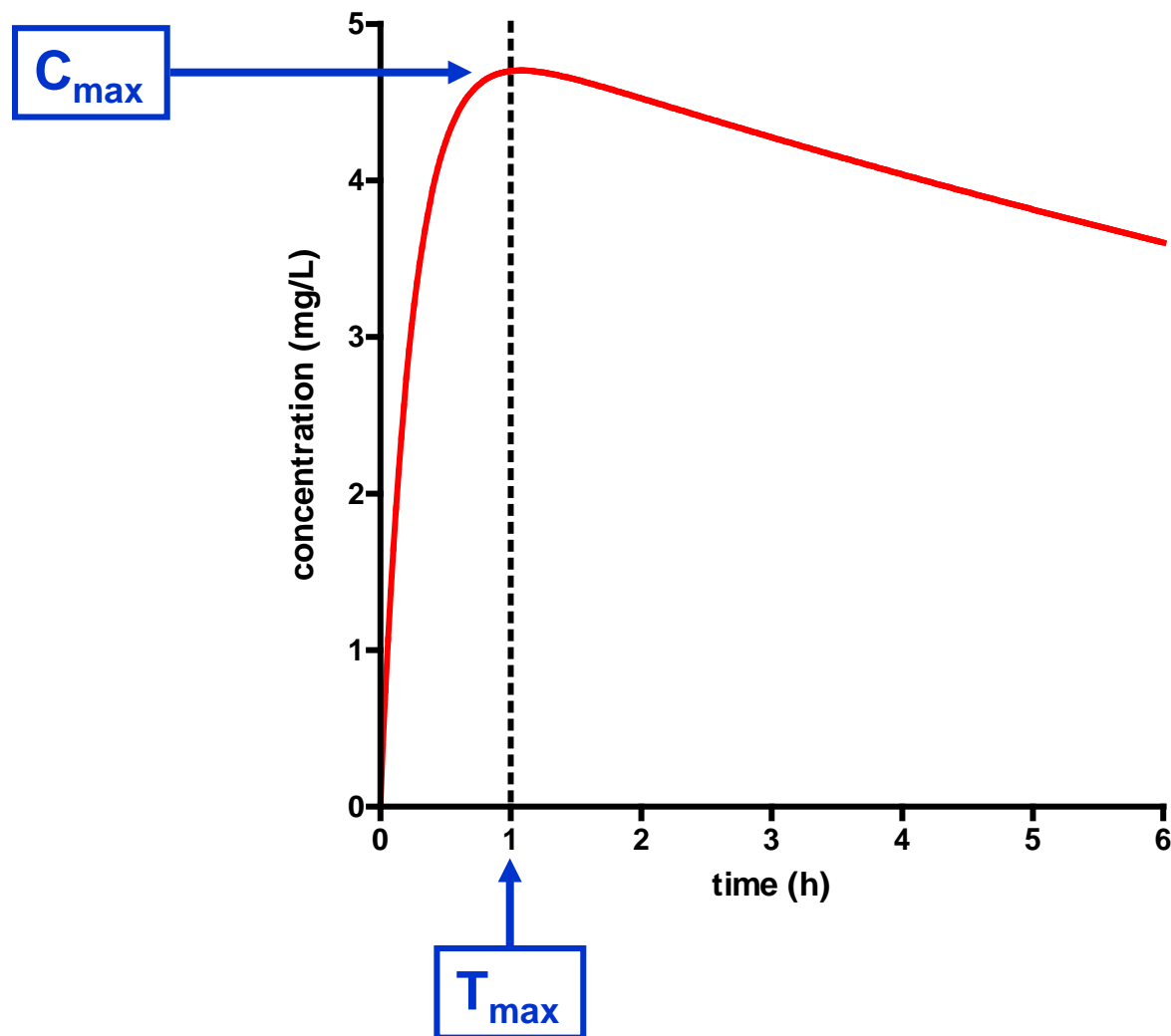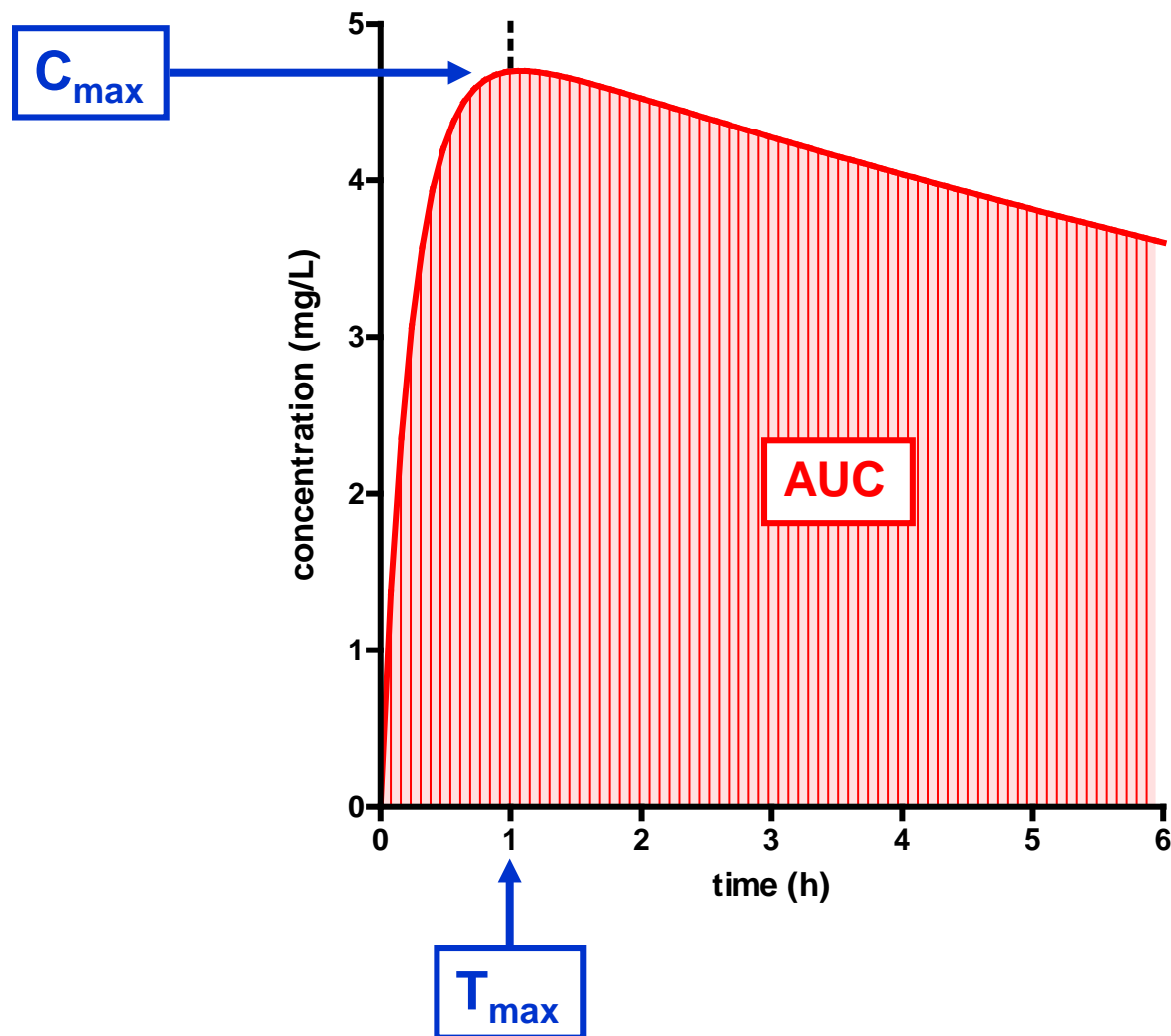
What if the absorption is decreased ?
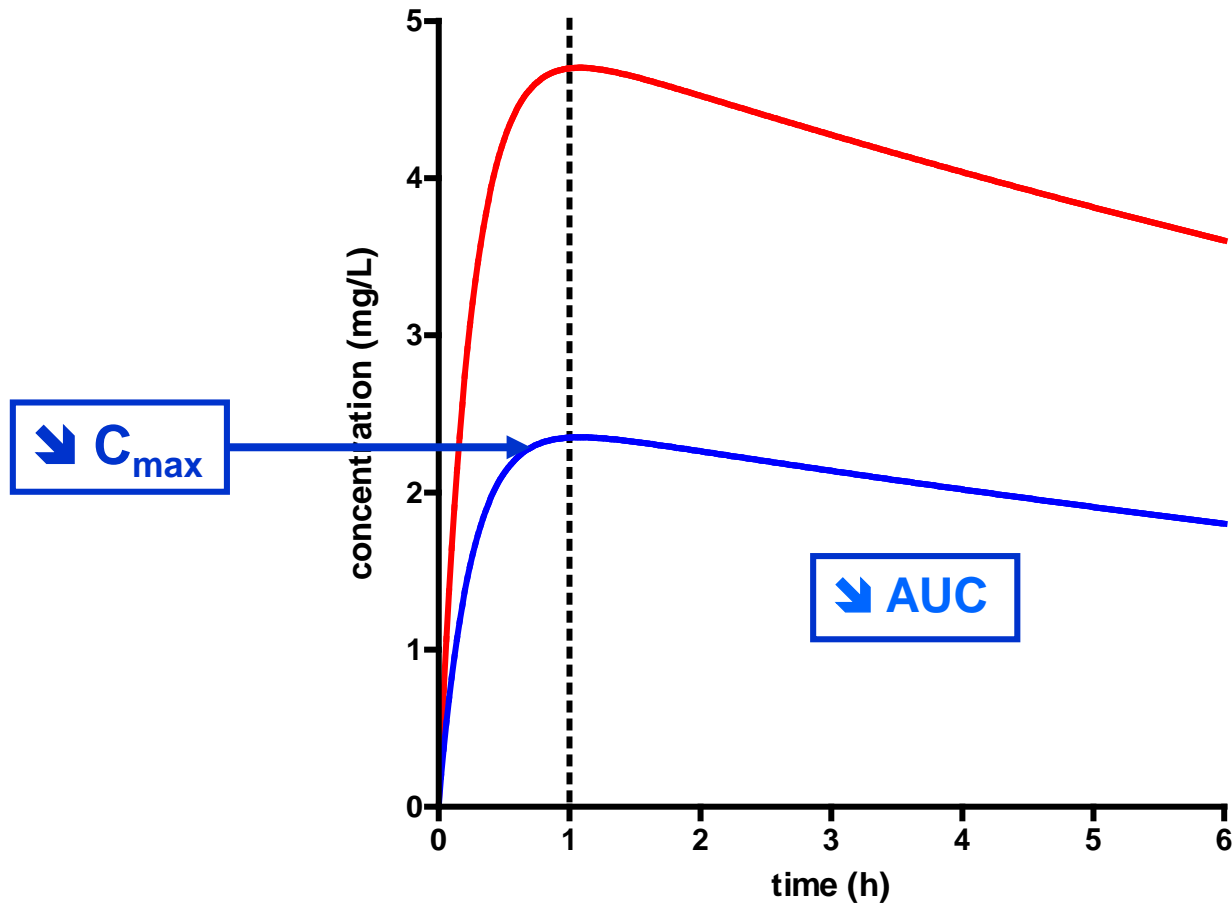
What if absorption is delayed ?
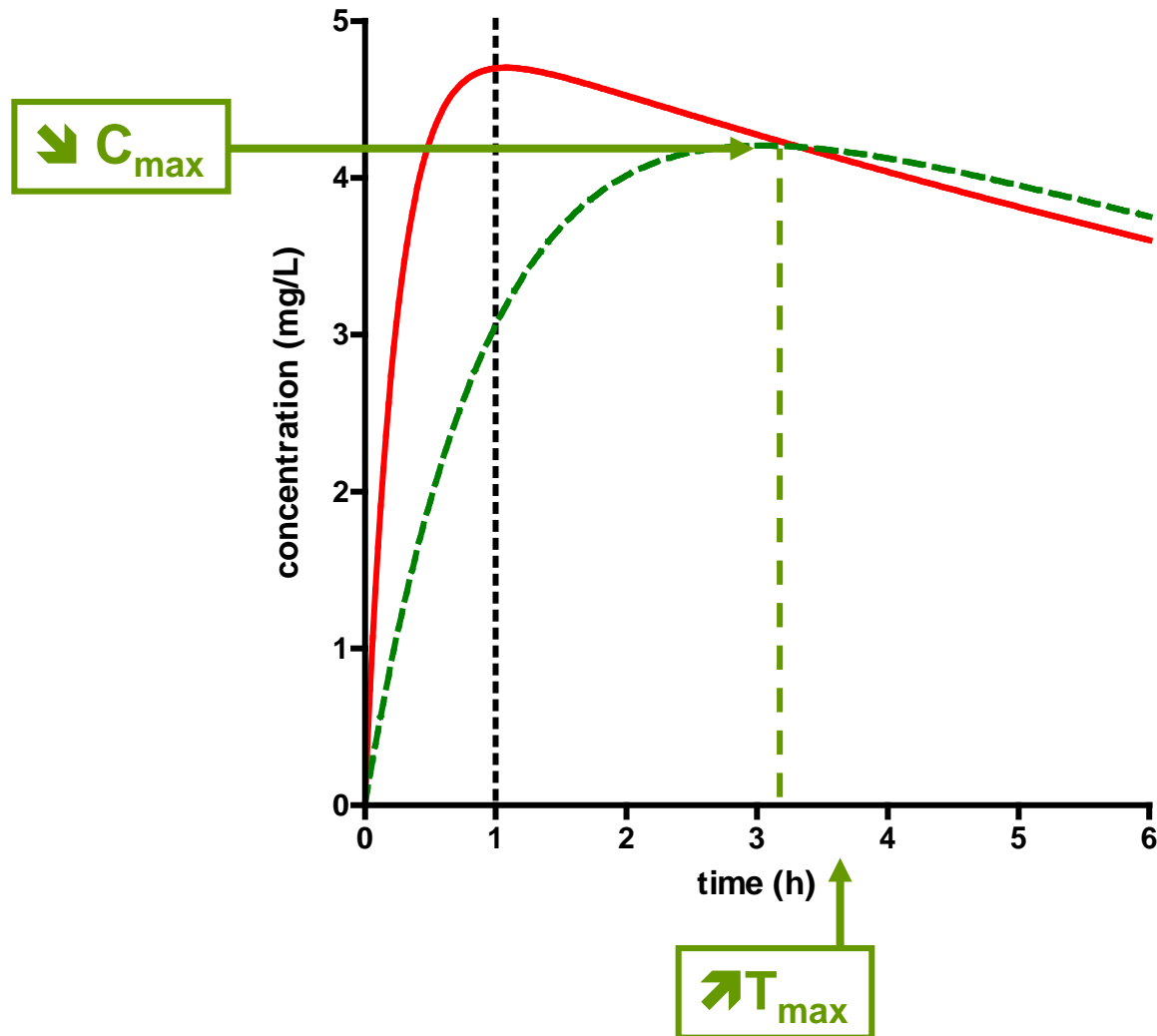
Criteria of bioequivalence (EMA* / FDA**)

- 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**.

90 % CI around point estimate

0.80   **ratio**   1.0   1.25
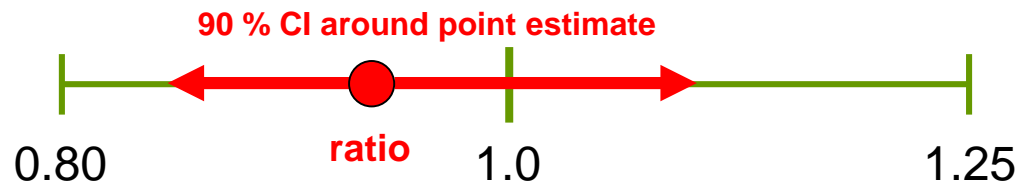
Notes:
1. if both **AUC** and **C_{max}** are within range, the generic should have the same bioavailability as the reference
2. statistical evaluation of **T_{max}** only makes sense if there is a clinically relevant claim for rapid release or action or signs related to adverse effects (see next slide)
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 <u>intravenous route</u> ! (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, vote now (1 choice)

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).

G.J. Moet et al. / Diagnostic Microbiology and Infectious Disease 65 (2009) 319–322
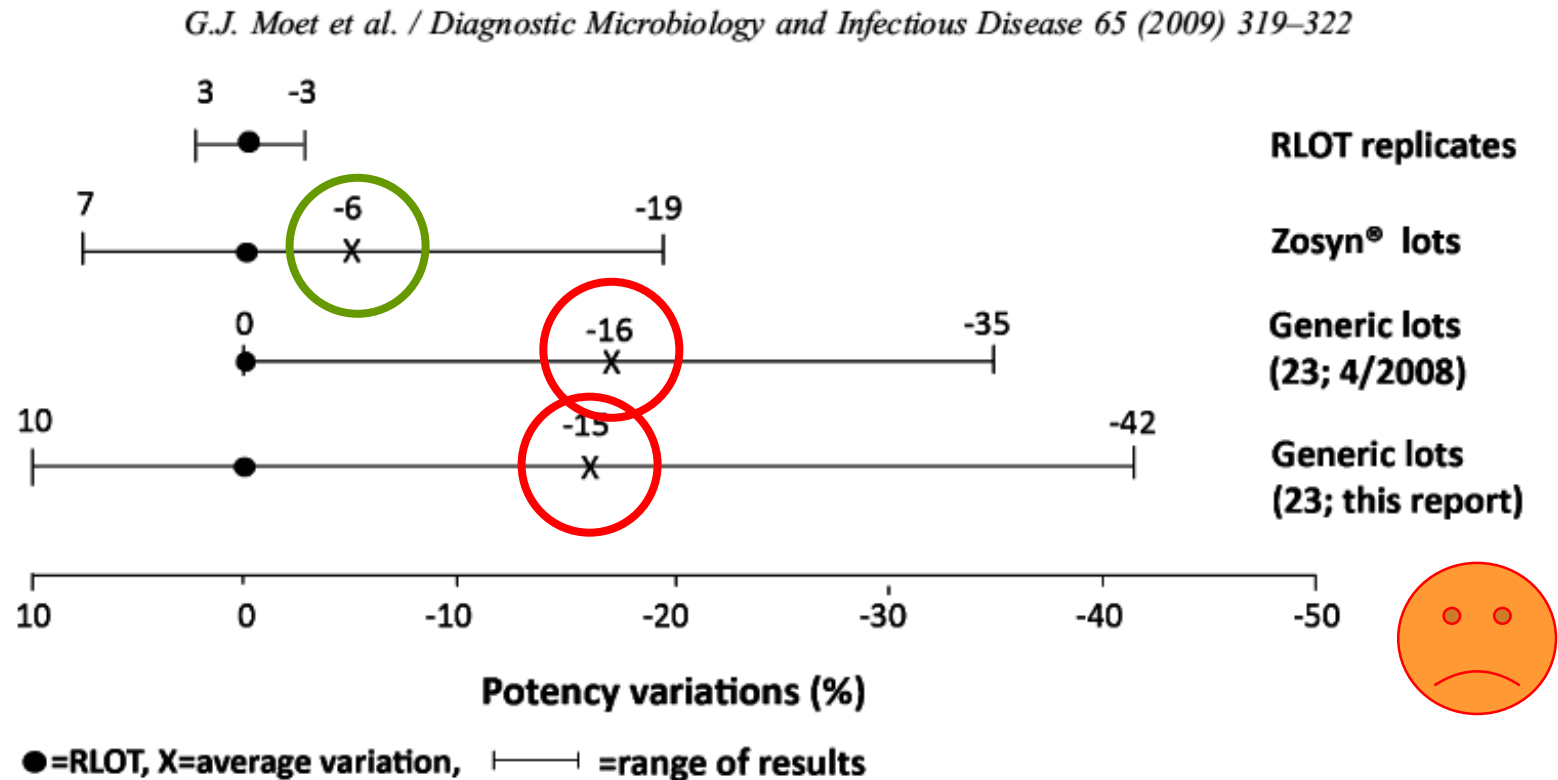
Fig. 1. Extent of potency variations among 4 groups of experiments with piperacillin/tazobactam intravenous injection lots.

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

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®

susceptible strains (MIC ≤ 2 mg/L)
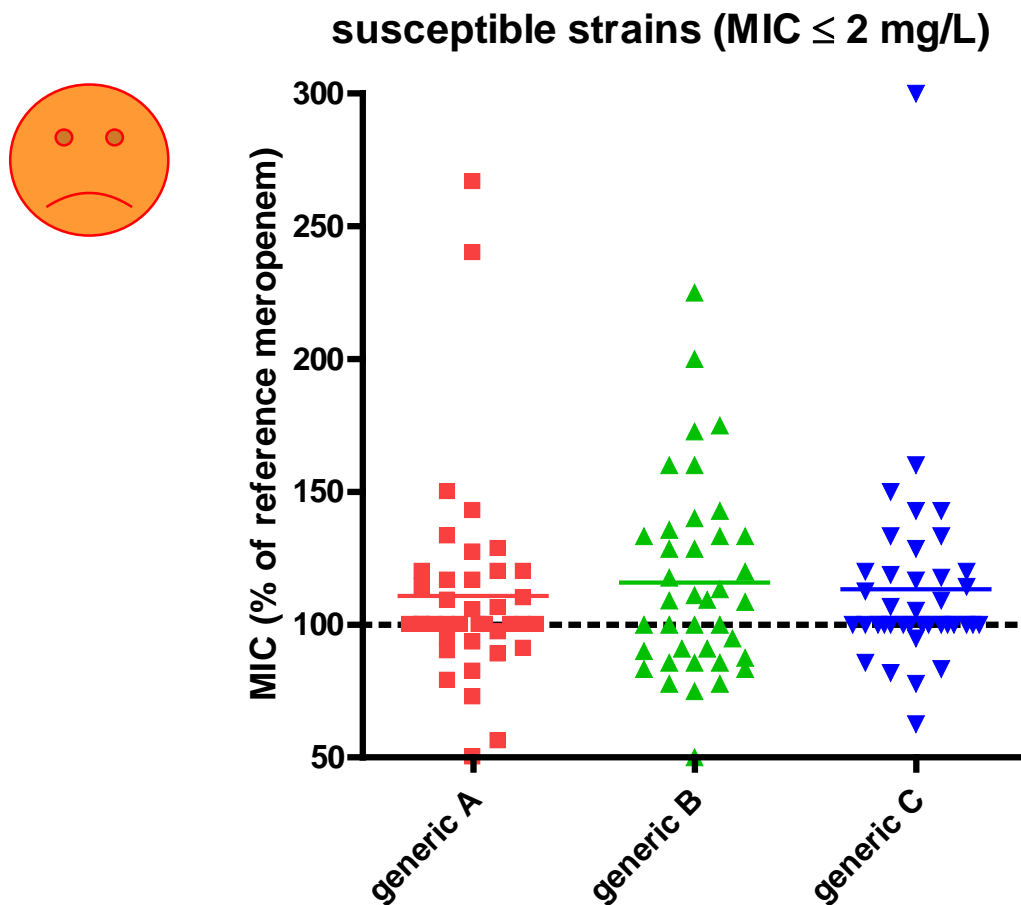
Van Bambeke *et al.*, in preparation

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

Neutropenic mouse thigh infection model
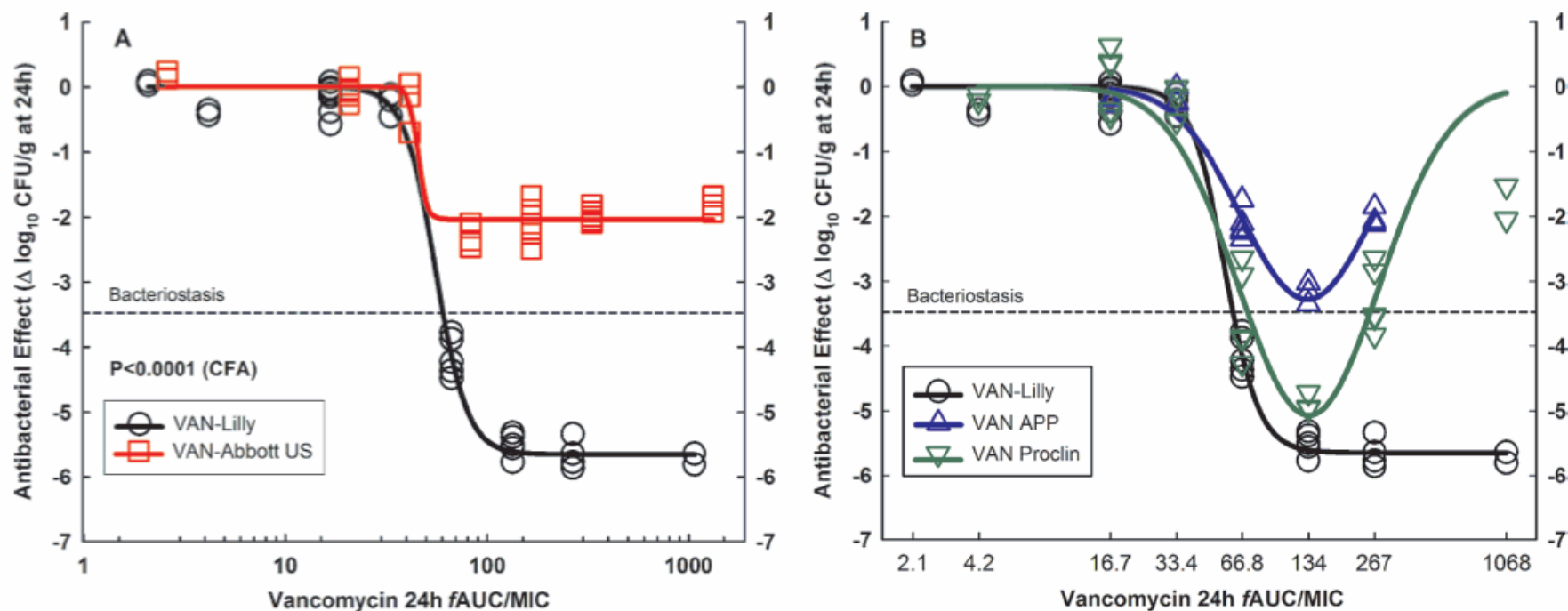
FIG. 1. *In vivo* efficacy against *S. aureus* GRP-0057 (years 2002 and 2003) at a low inoculum (4.30 ± 0.05 log$_{10}$ CFU per thigh when subcutaneous treatment q1h started). Vancomycin generic products are compared with the innovator (VAN-Lilly) in dose-effect experiments (2.34 to 1,200 mg/kg per day) 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
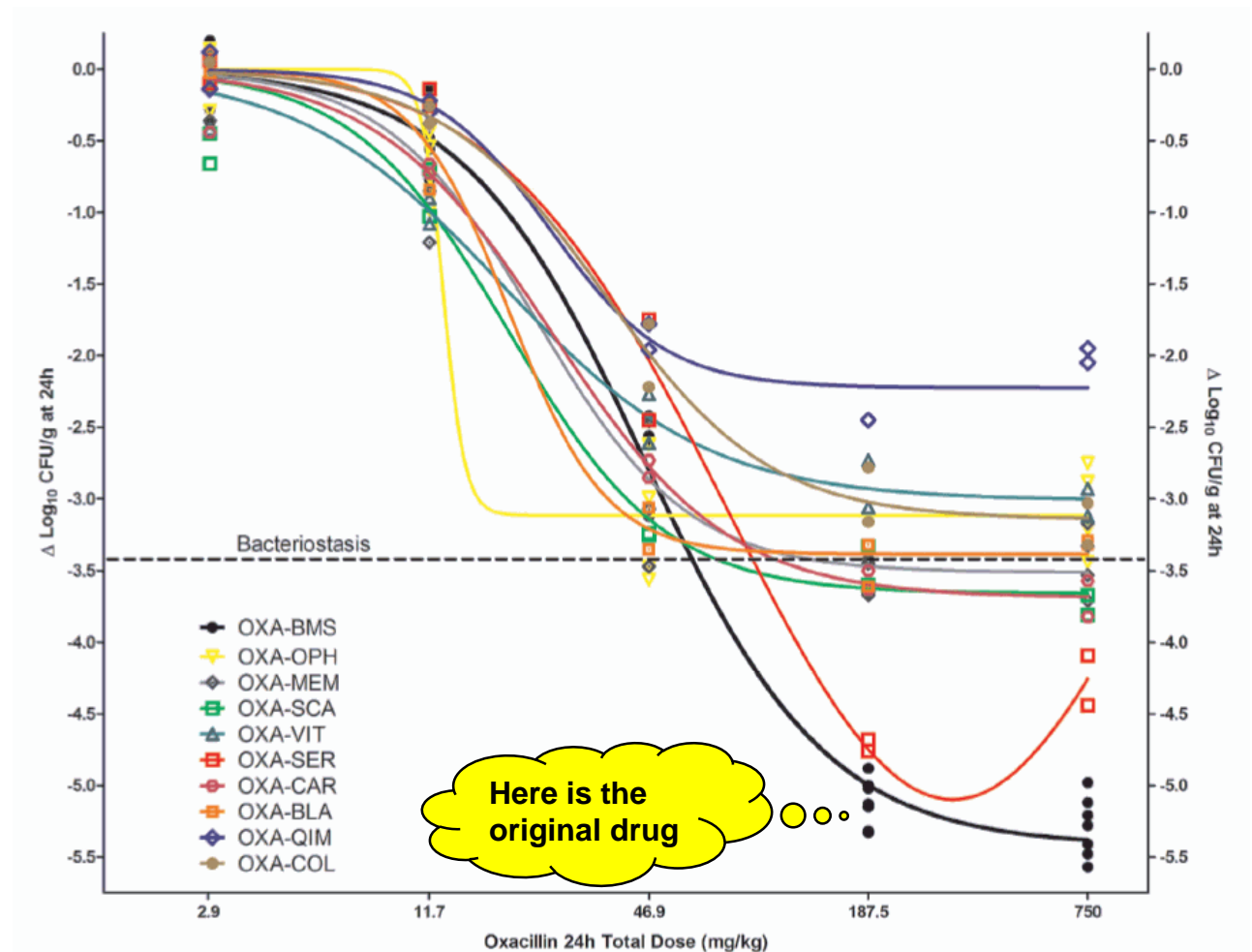
Figure 3 Dose-response relationship of the innovator and 9 generic products of oxacillin in the neutropenic mouse thigh infection model. OXA-BMS (innovator, black curve) and 8 generics fitted to Hill's sigmoid model, while generic product OXA-SER fitted to the Gaussian U-shaped model (red curve). Regardless 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

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

"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 Me[...] Cosenza, Italy

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

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 !
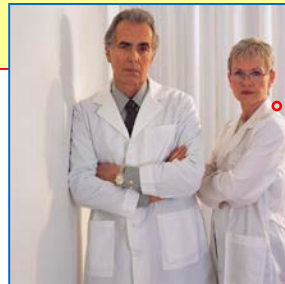
Who can we really trust ?

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, vote now (1 choice)

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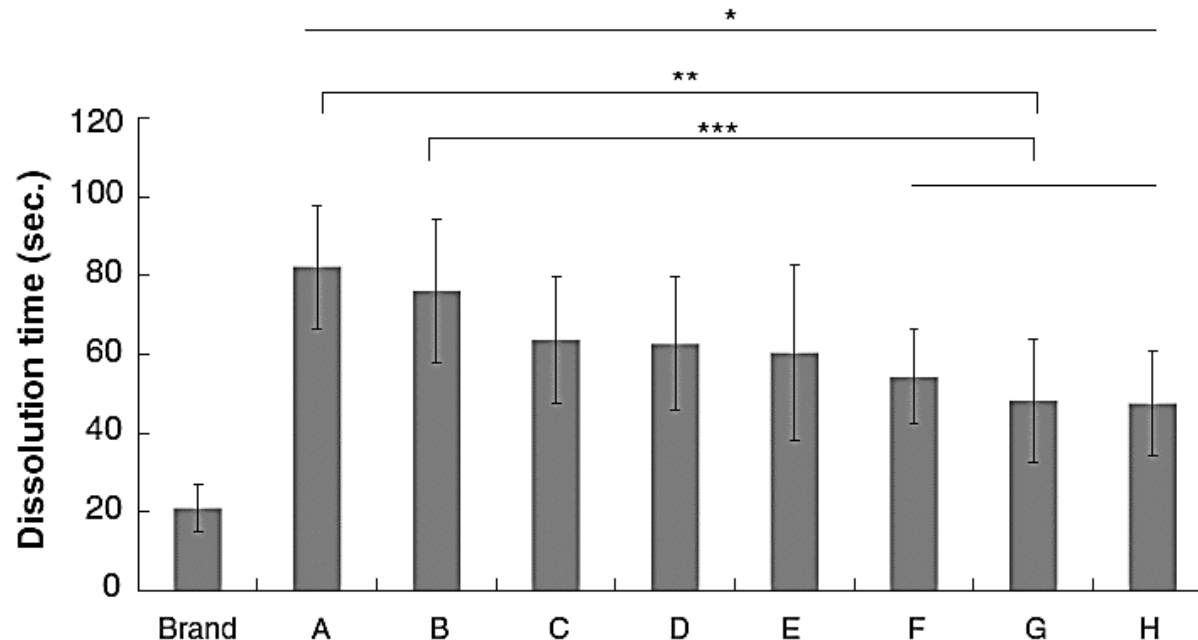
Fig. 3 Comparison of dissolution time between brand name meropenem and eight generics. *A–H* Generic products of meropenem. *P < 0.001 versus brand name drug; **P < 0.001 versus generic A drug; ***P < 0.001 versus generic B drug

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

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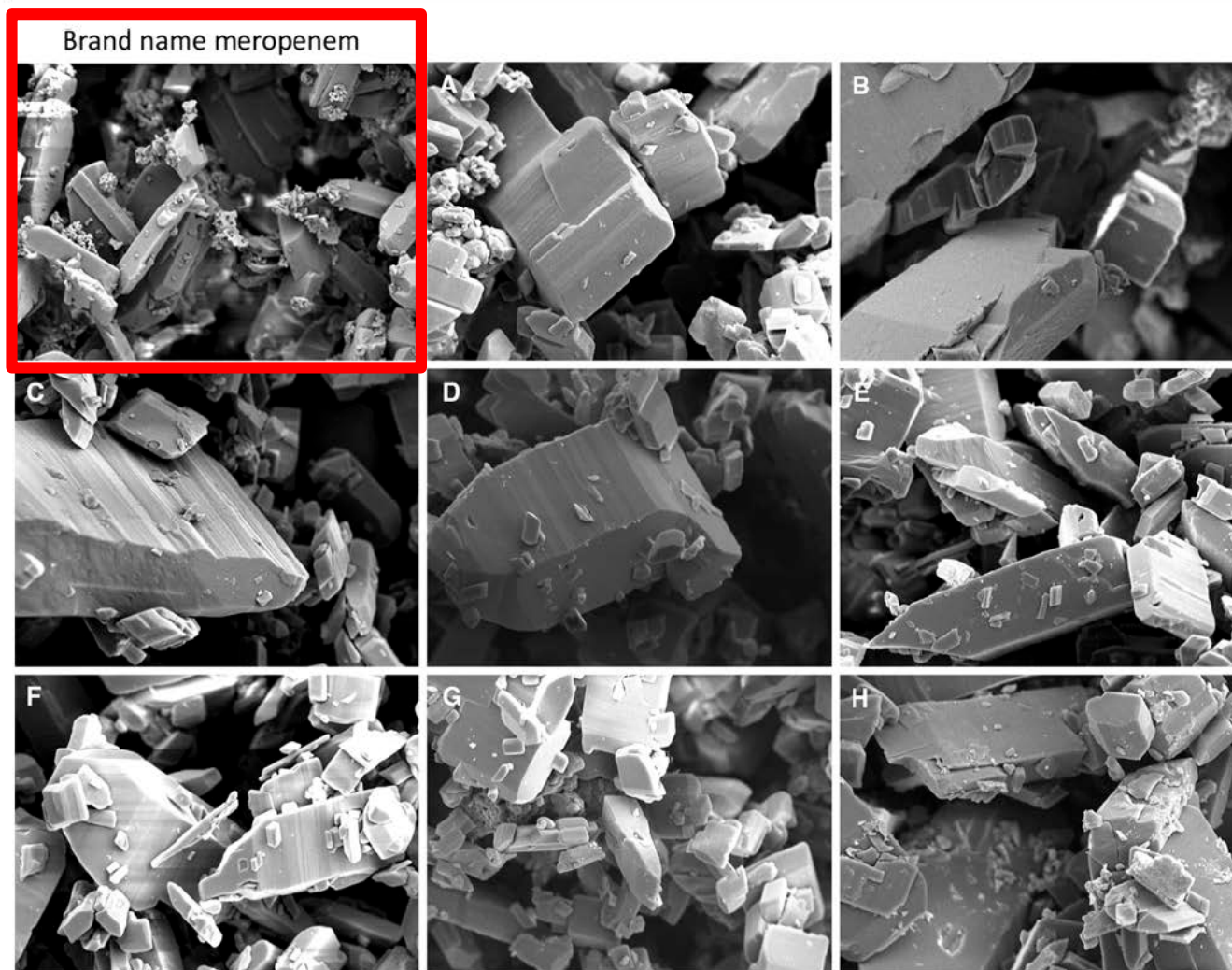
Fig. 4 Electron micrographs of drug particles of brand name meropenem and eight generics. **a–h** Generic products of meropenem. ×1,000

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
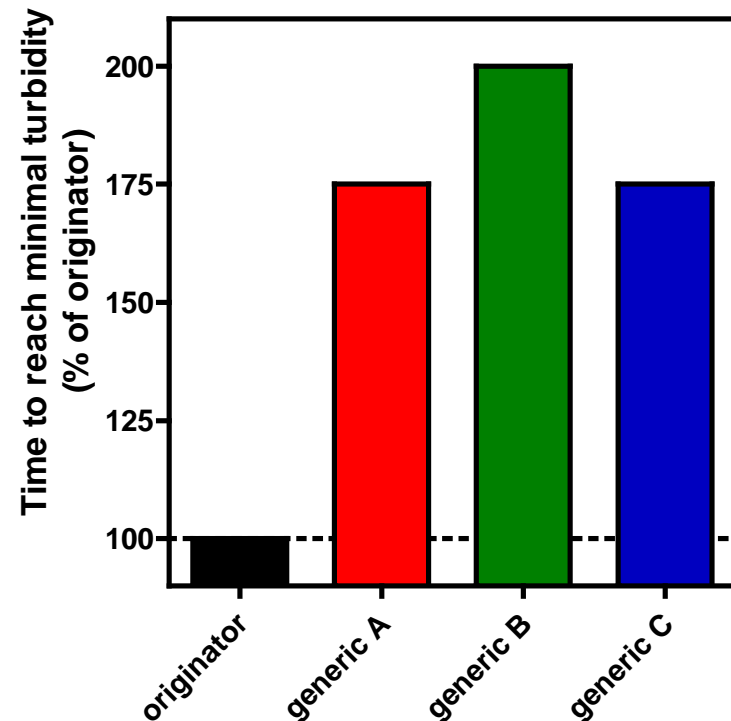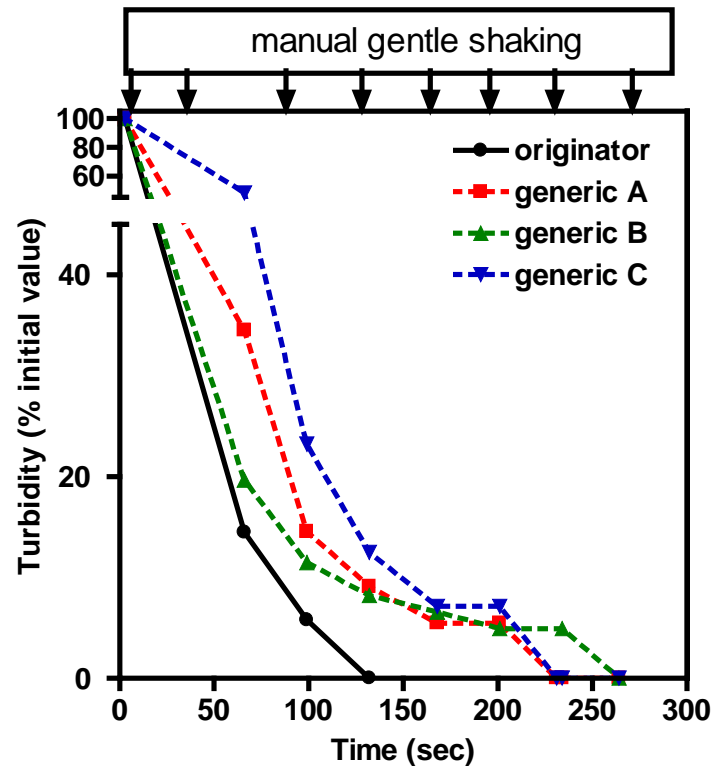
Van Bambeke *et al.*, in preparation
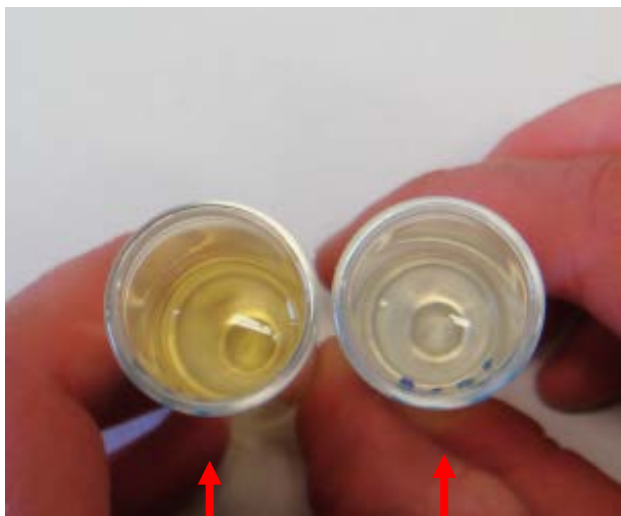
Dissolution of meropenem in Belgium

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

manual gentle shaki...

- or...
- ge...
- ge...
- ge...

Turbidity (% initial value)

100
80
60

40

20

0

0   50   100   150   200   250   300

Time (sec)

originator   generic A   generic B   generic C

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

OD$_{490nm}$ - 24°C

Legend:
- originator (black)
- generic A (red)
- generic B (green)
- generic C (blue)

OD (410 nm) vs incubation time (hours): 0, 1, 2, 4

OD$_{490nm}$ - 37°C

Legend:
- originator (black)
- generic A (red)
- generic B (green)
- generic C (blue)

OD (410 nm) vs incubation time (hours): 0, 1, 2, 4
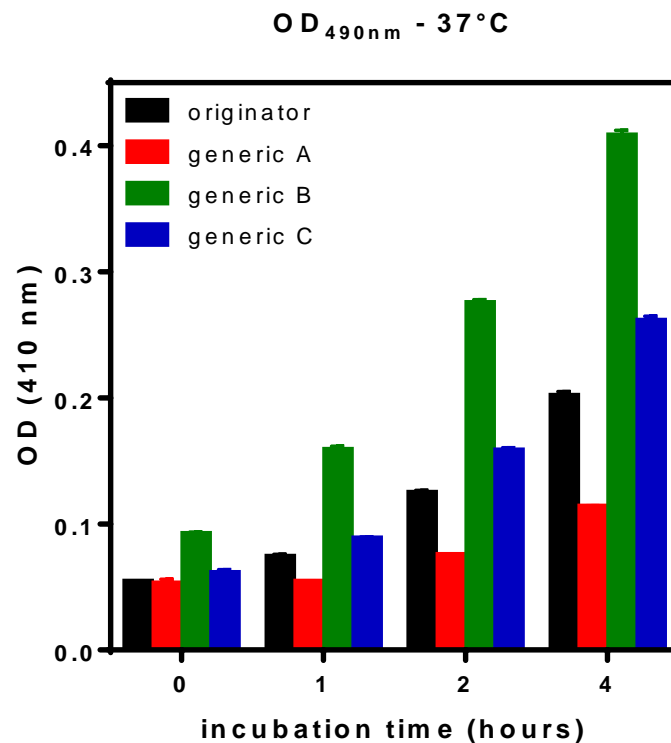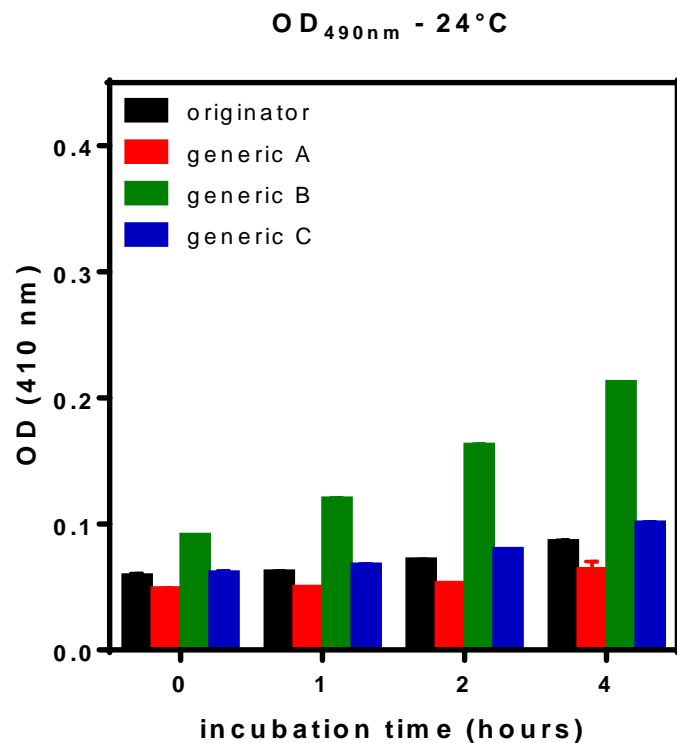
Van Bambeke *et al.*, in preparation

Impurities in ciprofloxacin…

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

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.
© 2007 Elsevier B.V. All rights reserved.

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

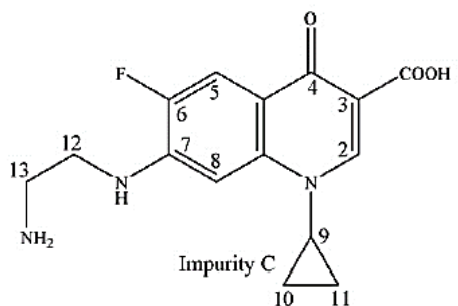# Impurities in ciprofloxacin

This is a synthesis precursor !
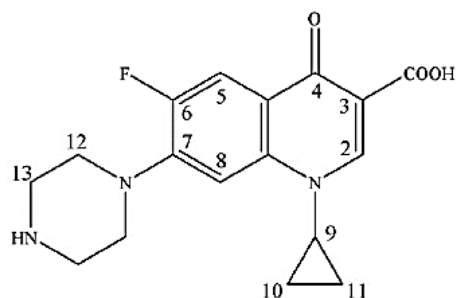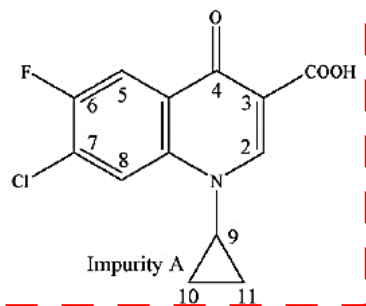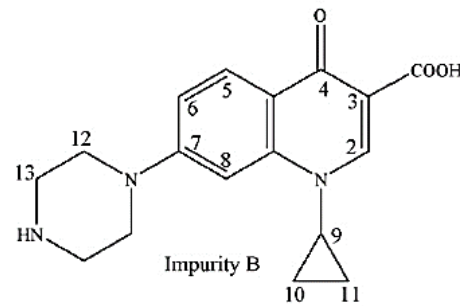
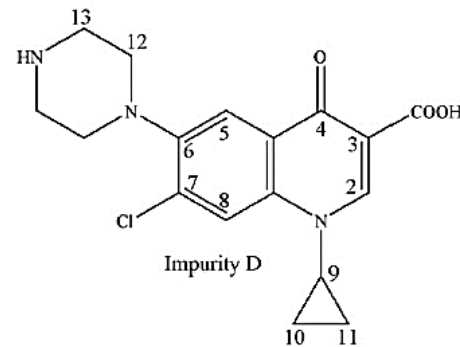Fig. 1. Structure of ciprofloxacin and its main impurities.

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

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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

MEDIPLANET
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 !

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

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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 also have the problem of the counterfeited drugs
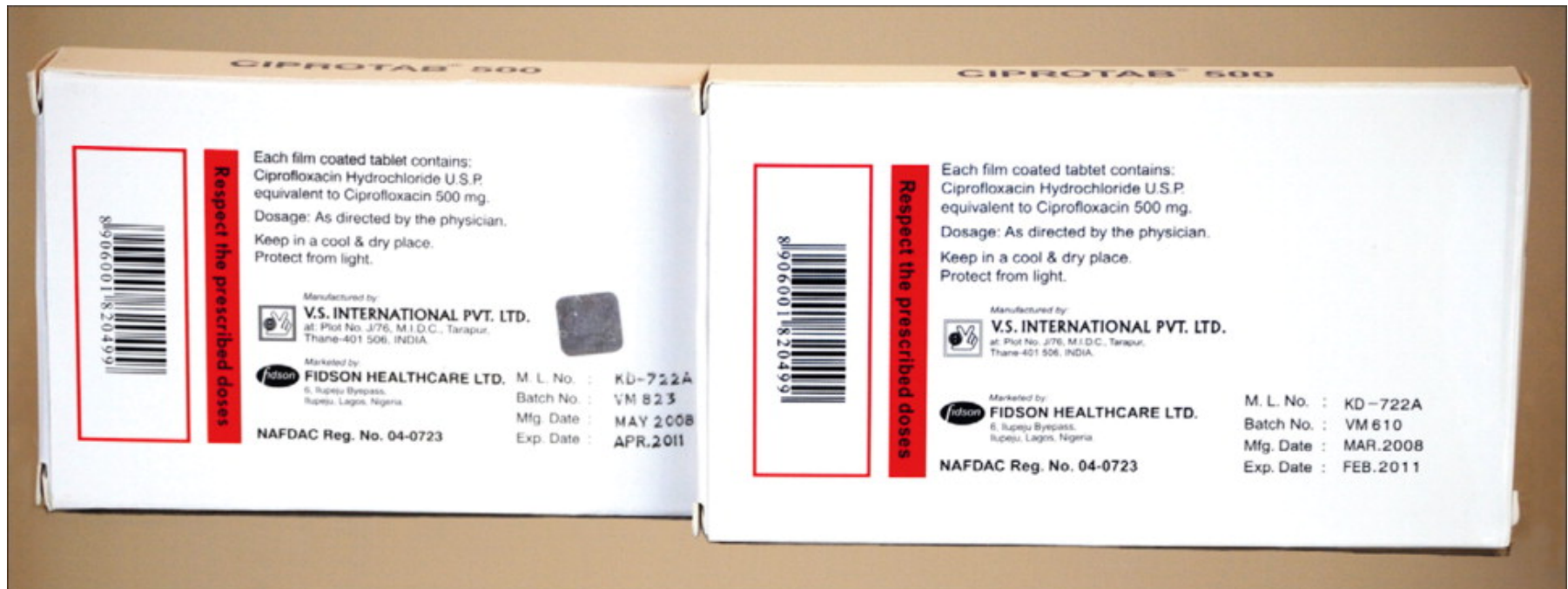
Packs bought at pharmacies in Lagos, Nigeria
The only noticeable difference is that the real package has a hologram on the back (left). The fake was two-thirds talcum powder and contained no ciprofloxacin. Even holograms can be faked.
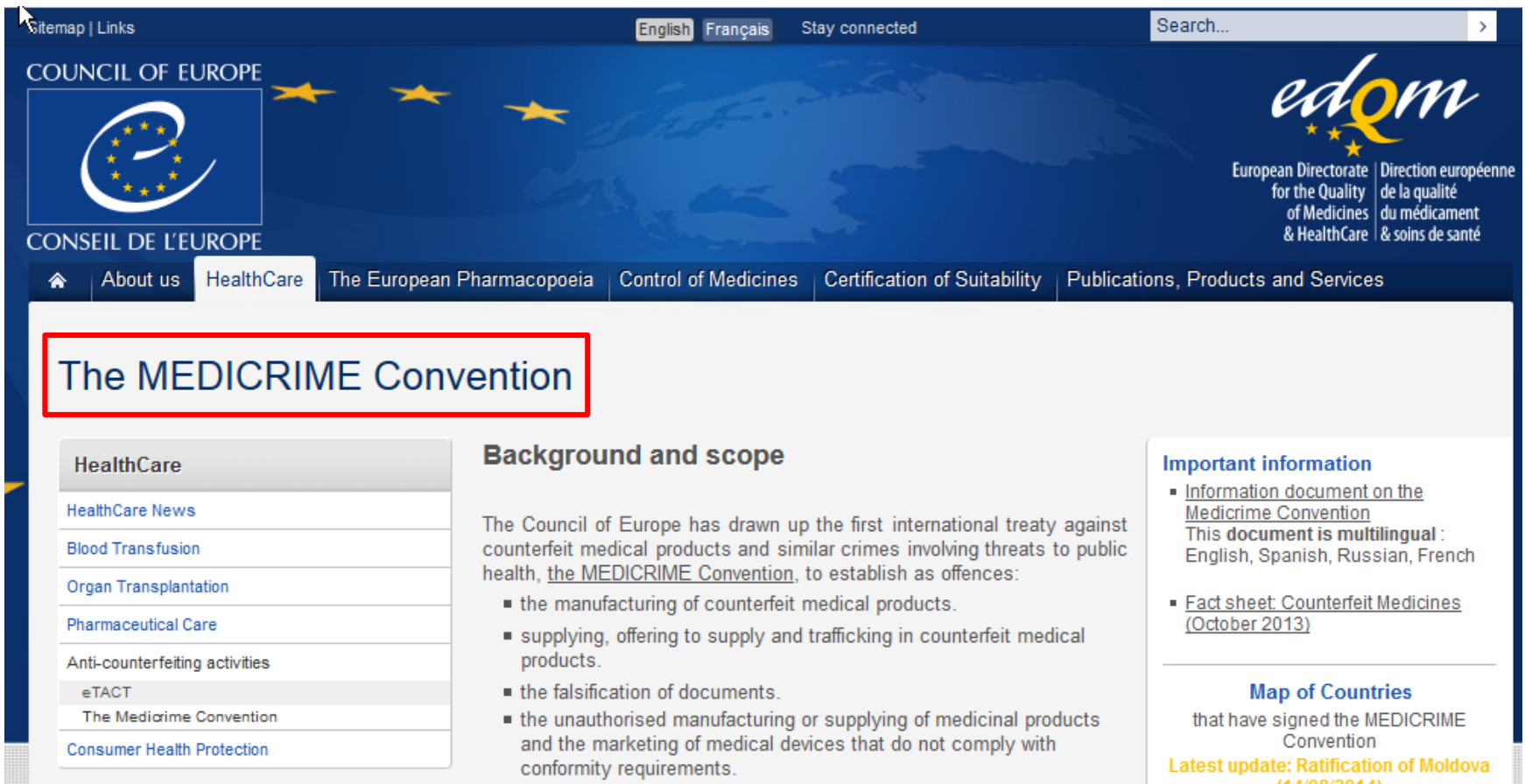
➢ **25% of drugs sold worldwide are substandard and 50% in some Countries…**
➢ **It hurts low and middle income countries the most…**

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

An European action is ongoing … but is costly

An European action is ongoing … but is costly

MEDICRIME: which countries ?

Medication No Falsification
Council of Europe Medicrime Convention
www.coe.int/medicrime

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
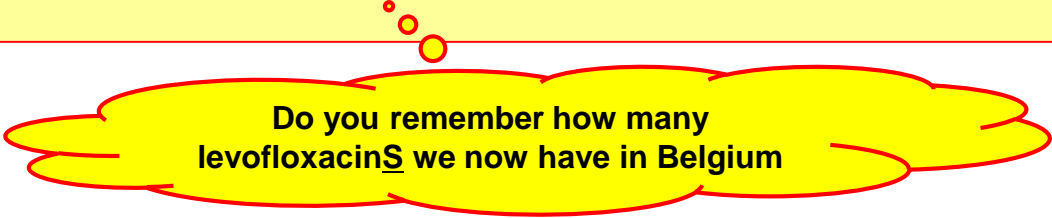- Ukraine 20/08/2012

Legend:
- Signatures of Member States of the Council of Europe
- Signatures of Non-member States of the Council of Europe
- Ratifications of the Medicrime Convention

https://www.edqm.eu/medias/images/medicrime_world_map_with_list_english.jpg
Last accessed: 20/02/2015
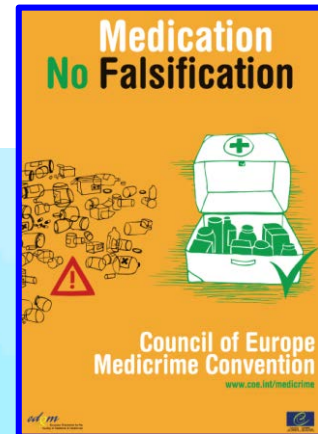
3rd round of conclusions and discussion

- 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)

Do you remember how many levofloxacinS we now have 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 !**

We are facing contradictory situations

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"…
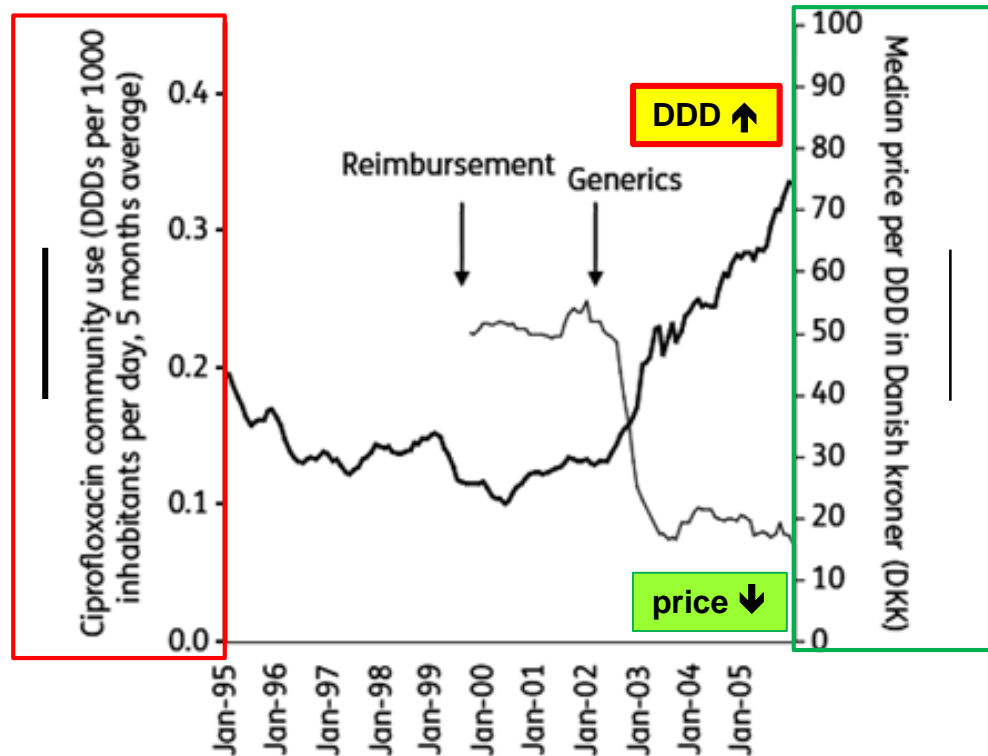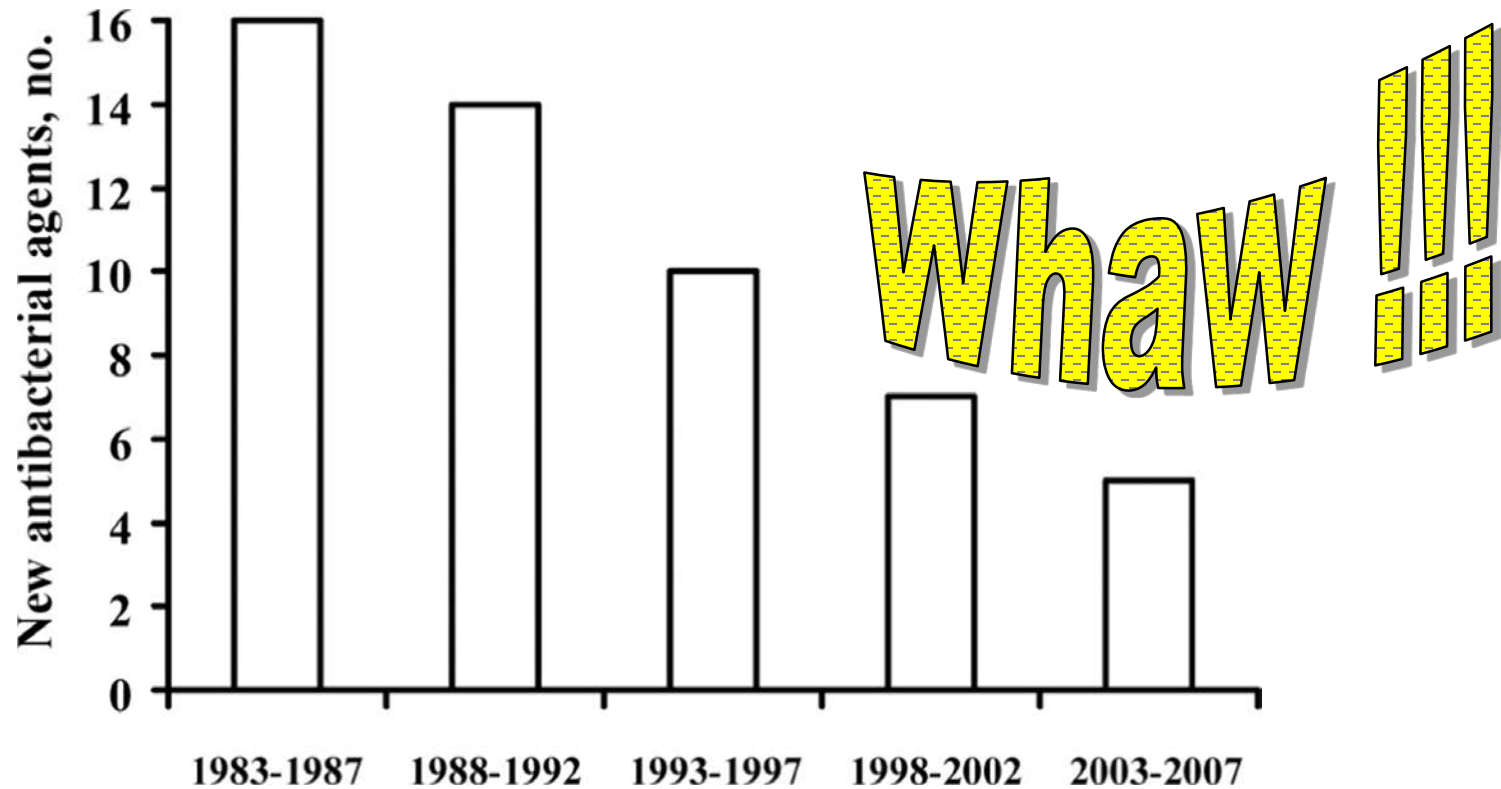## *The sour Danish Experience*

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
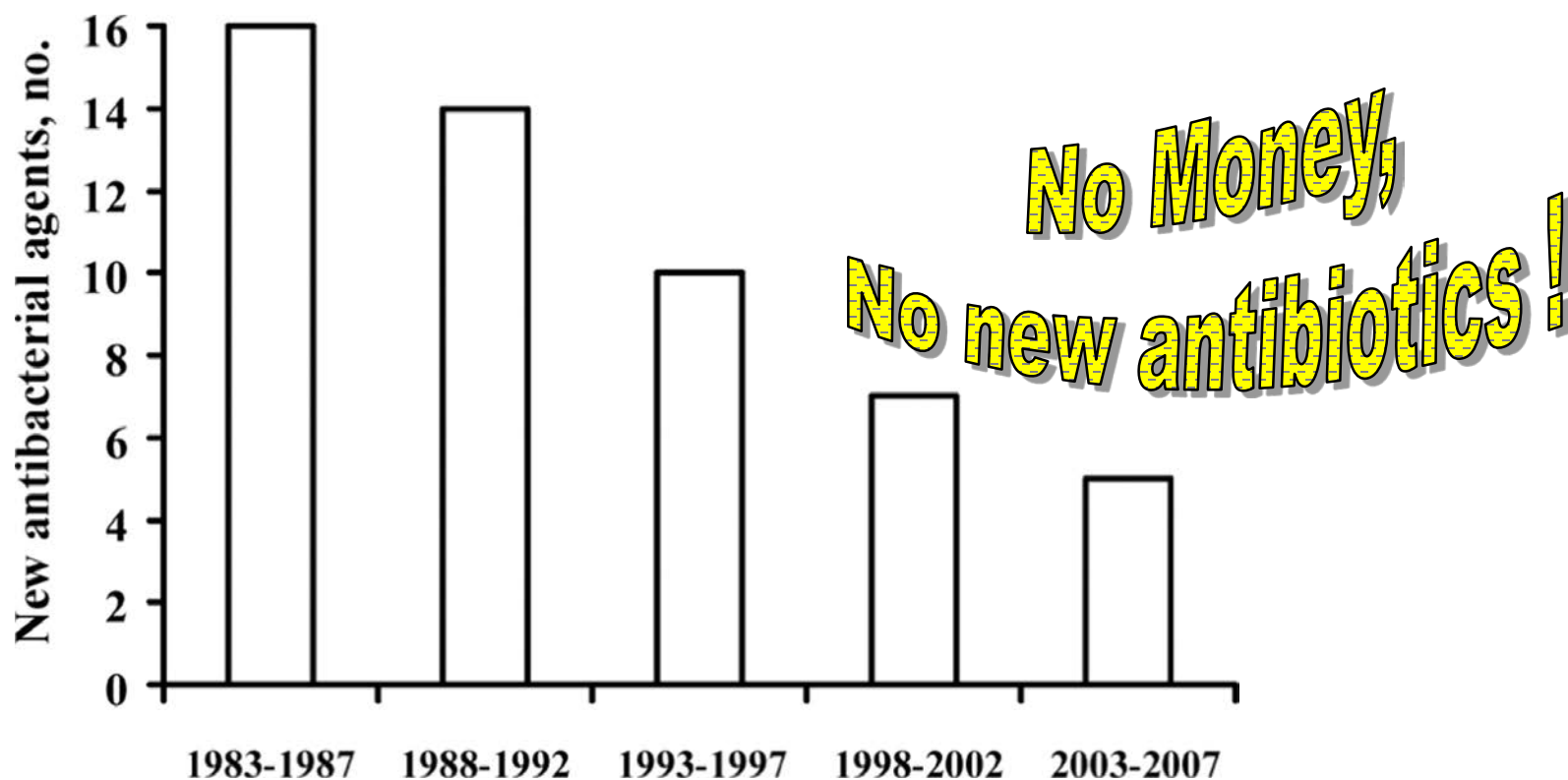per 1000 inhabitants per day.

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

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 …

AMERICAN SOCIETY FOR MICROBIOLOGY

ASMsociety

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

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

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) is critical and should go beyond simple declarations and initial lot analysis…

- **Antibiotics are a precious commodity** that should not be lost. Misuse through low prices may cause **HUGE expenses in the future**…

Thank you for your attention!

And ask questions