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

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STRATEGIES OF ANTIBIOTIC CHOICE FOR IN-PATIENT TREATMENT
Nha Trang, Việt Nam, 12 March 2015

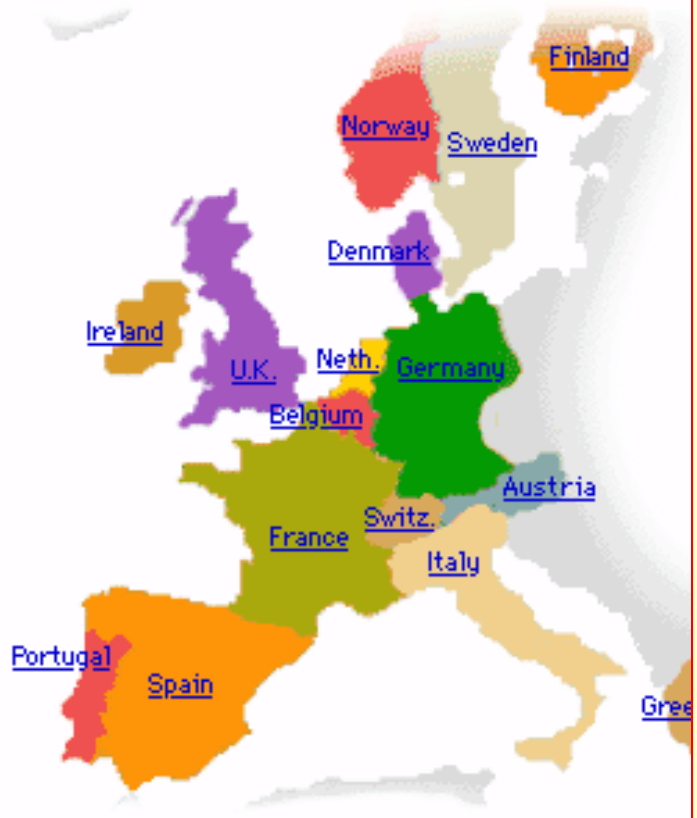
With approval of the Belgian Common Ethical Health Platform – visa no. 15/V1/7383/066684

Disclosures and slides availability

- 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

Belgium



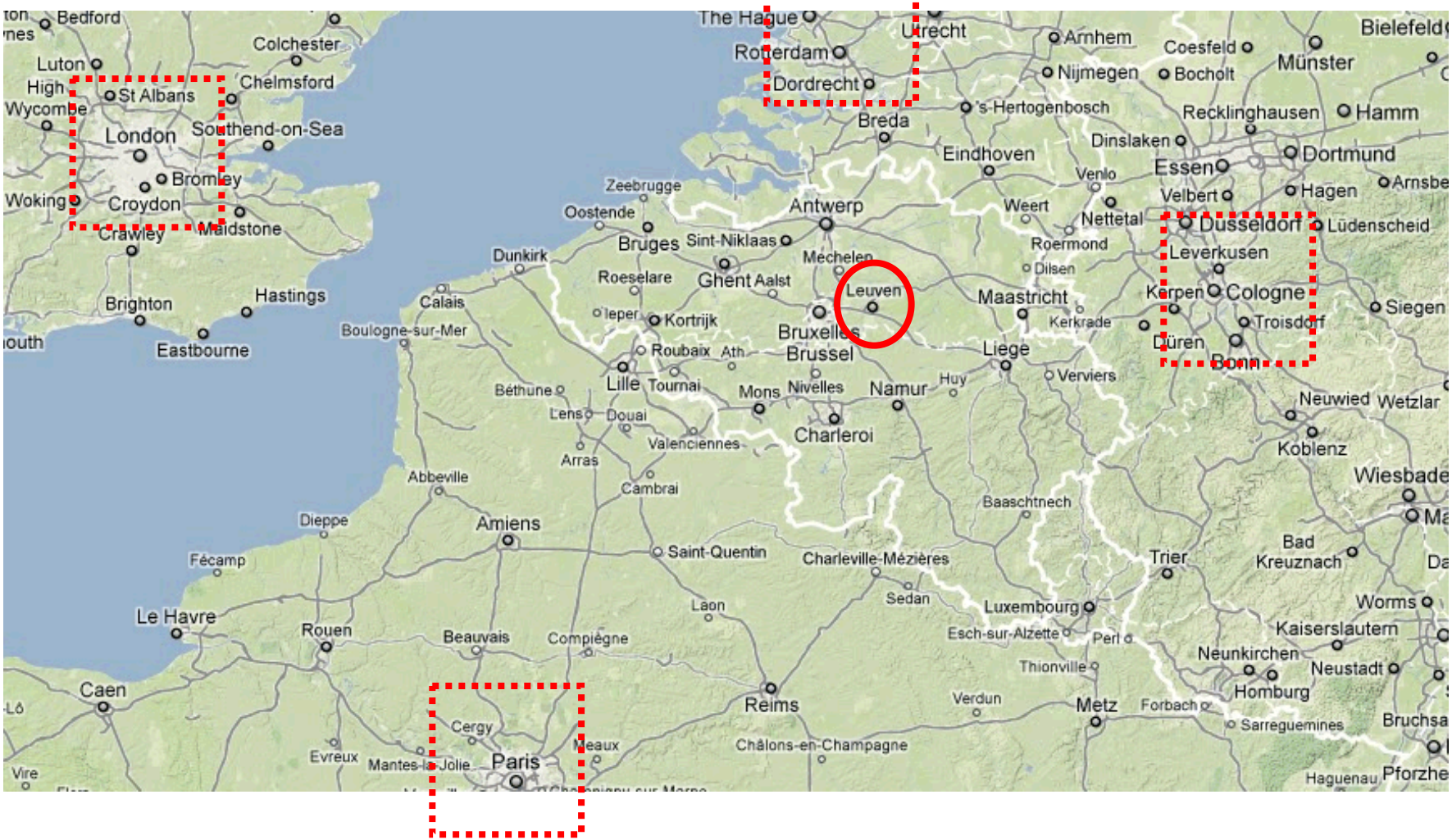
10 millions inhabitants …

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 Prigogyne, 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)

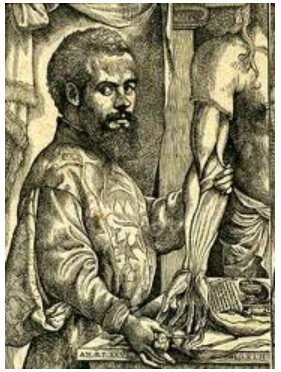


The *Catholic University of Louvain* in brief (2 of 4)

- It was one of the major University 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

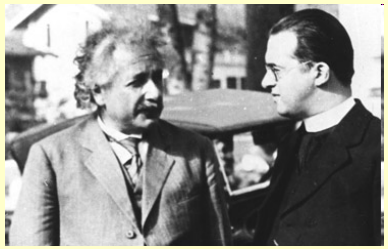
Erasmus



Vesalius

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

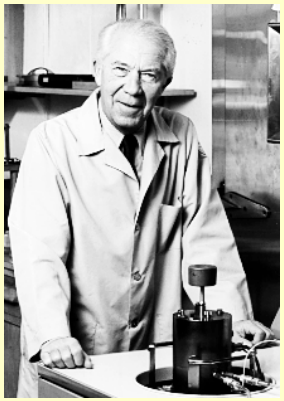
- In the 19th century, teaching was in French but in the early 1900's, a Flemish-speaking section was opened. Courses were given in both languages, attracting many students and celebrities…



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 Universiteit 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 (Woluwé)

Université catholique de Louvain
http://www.uclouvain.be

Katholieke Universiteit Leuven
http://www.kuleuven.be

- Together, the two Universities have about **55,000 students**

What do we do in Brussels ?

- 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)

- Toxicity, medicinal chemistry, and improved schedules of aminoglycosides
- novel antibiotics (and last studied)
  - beta-lactams (ceftaroline…)
  - fluoroquinolones (finafloxacine…)
  - kétolides (solithromycin…)
  - oxazolidinones (tedizolid …)

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

Why Việt Nam ?

We had two young and active Vietnamese post-doctoral fellows

- Dr Pharm. Anh Hoang Nguyen (graduated in France and came to Brussels in 2007-2009; → now at the **University of Pharmacy in Hà Nội**
- Dr PhD Thi Thu Hoai Nguyen (graduated in Germany and came to Brussels in 2009-2011) → now the **International University in Ho Chi Minh**

Why do I come often to Việt Nam ?

Cooperation Programs of the Cellular and Molecular Pharmacology Group of the Louvain Drug Research Institute (Catholic University of Louvain, Brussels, Belgium) - M...

File Edit View History Bookmarks Tools Help

Cooperation Programs of the Cellu...

Cooperation Programs of the Cellular and Molecular Pharmacology Group of the Louvain Drug Research Institute (Catholic University of Louvain, Brussels, Belgium)

Search

Cooperation

The Laboratory is cooperating with foreign countries fpr the implementation of the appropriate use of antibiotics (and related topics) and of clinical phamacy (and related topics) .
This page shows the currently active cooperation programmes.

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2010-2014

Cooperation between the *Université catholique de Louvain* and the the Hanoi University of Pharmacy for the Rational Use of Drugs (with emphasis on antibiotics)

WBI Wallonie-Bruxelles International

TRƯỜNG ĐẠI HỌC DƯỢC HÀ NỘI HANOI UNIVERSITY OF PHARMACY

Project: Vers un usage rationnel des médicaments au milieu hospitalier au travers du renforcement de la capacité des professionnels de la santé en soins pharmaceutiques (Pharmacie clinique) et en évaluation fondée sur les preuves *(Towards a rational use of drugs in the hospital setting through the reinforcement of the professional capabilities of Health Care Providers in Pharmaceutical Care [Clinical Pharmacy] and in Evidence-Based Medicine).*

Places: Hanoi University of Pharmacy -- Bach Mai Hospital -- Viet Duc Hospital (Hanoi, Vietnam)

Supported by Wallonie-Bruxelles-International

1st session (April 2011) | 2d session (October 2011) | 4th session (October-November 2013)

http://www.facm.ucl.ac.be/cooperation.htm

Why do I do when I come to Việt Nam ?

Infectious Diseases in Uong Bi

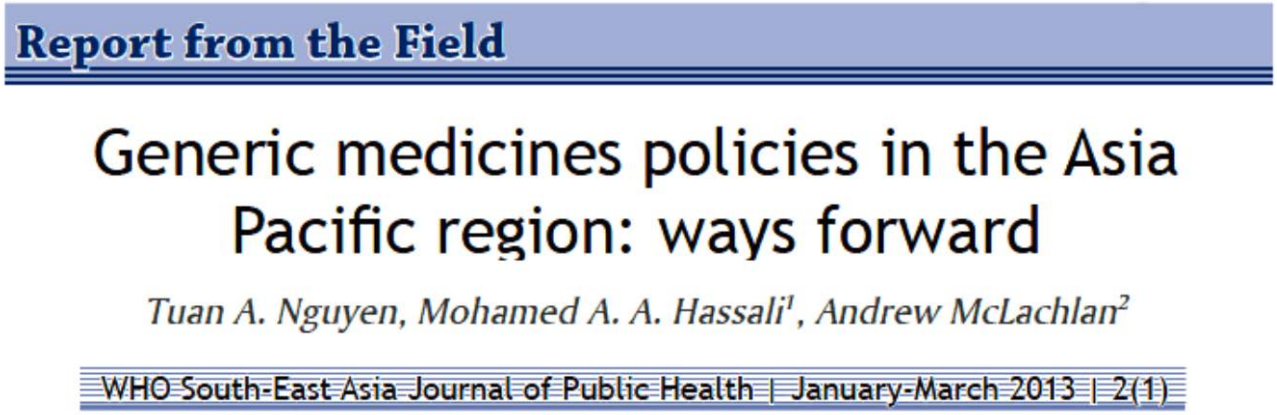
Clinical Pharmacy at HUP

Antibiotic policy in Bach Mai

Since 2010, we come twice a year in Hà Nội to

- develop clinical pharmacy at HUP
- launch antibiotic policy and fighting resistance at Bach Mai and Uhong Bi.

Do we need generics in Việt Nam ?



Report from the Field

Generic medicines policies in the Asia Pacific region: ways forward

Tuan A. Nguyen, Mohamed A. A. Hassali[1], Andrew McLachlan[2]

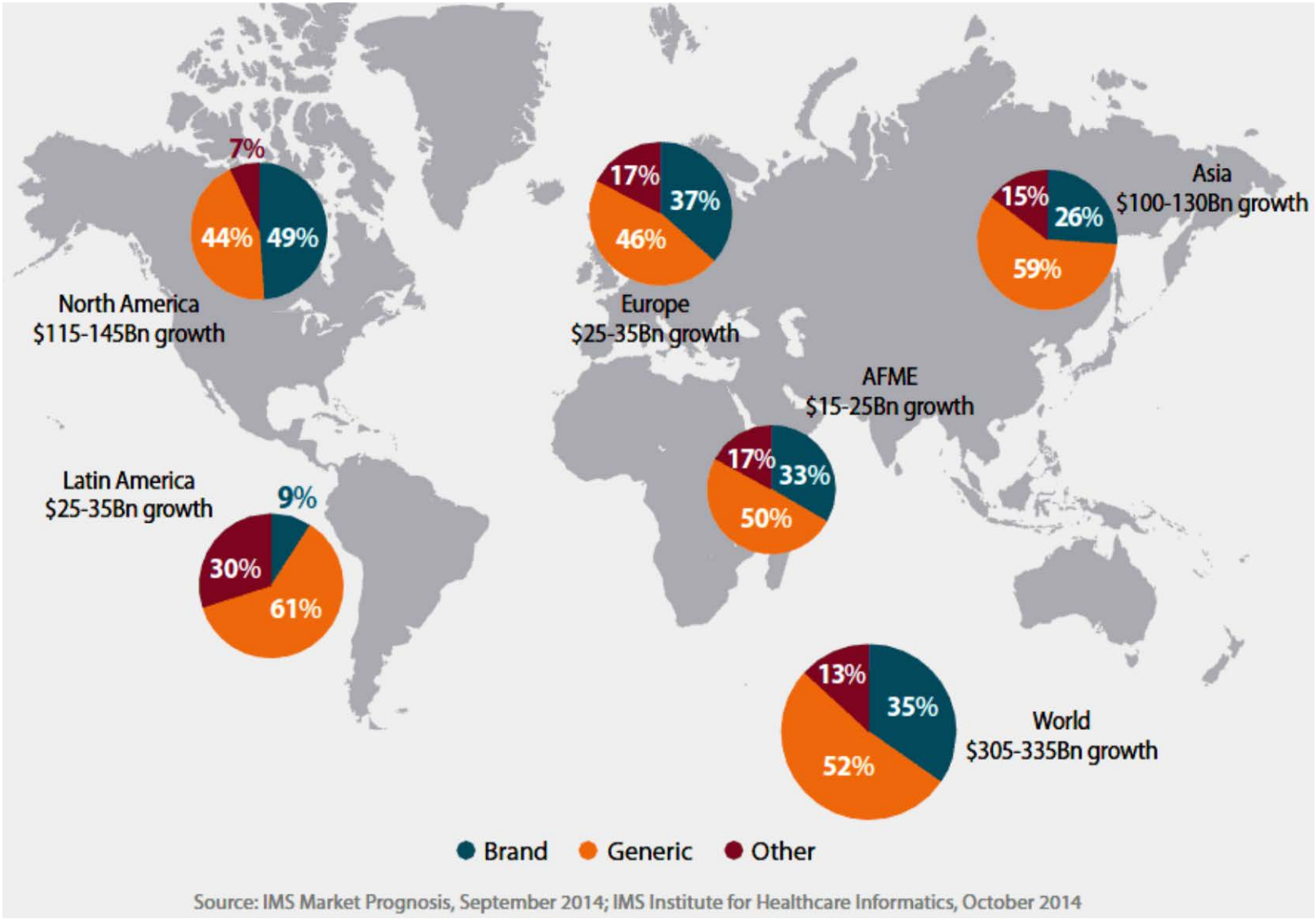
WHO South-East Asia Journal of Public Health | January-March 2013 | 2(1)

- Lack of access to new (patented) medicines (Intellectual Property Rights)
- Insufficient commercial incentives for the Innovating Pharmaceutical Industry to develop new medicines
- Lack of access to existing medicines because of patients' inability to pay for them.

So now, we see in Việt Nam fluoroquinolones… coming from all over the world

Daiichi (Japan) is actually the originator !

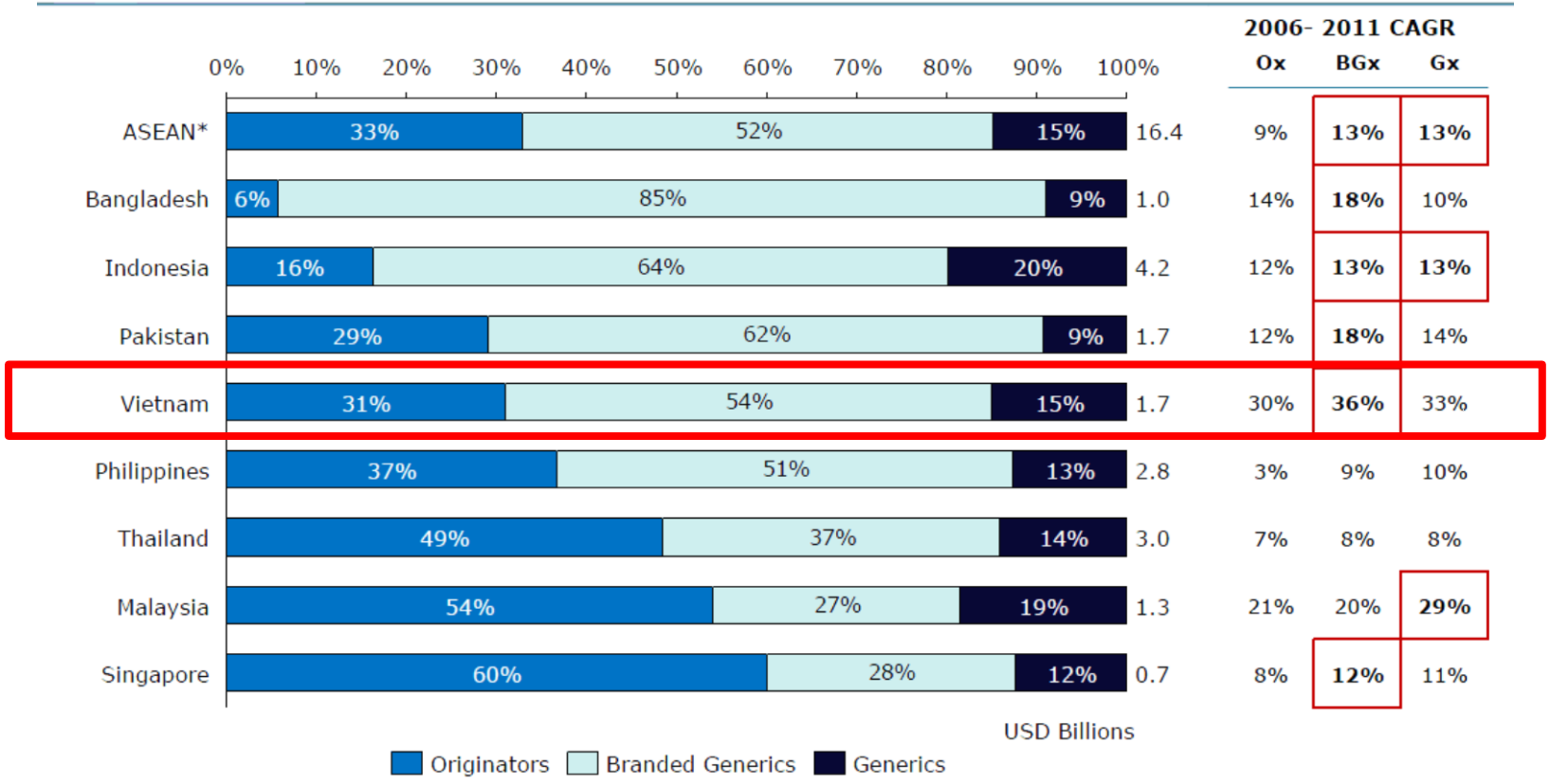
But Việt Nam is no exception…



And here are the figures for Việt Nam *vs* other Asian countries

Generic penetration varies across SEA and has increased overall across countries

Expanded SEA *Overall* Market – Originator vs Generic Penetration (2011)



Source: IMS Analysis, IMS MIDAS Data

ims consulting group

http://www.imshealth.be/deployedfiles/imshealth/Global/Content/Healthcare/Life%20Sciences%20Solutions/Generics/pharmerging_landscape.pdf
Last accessed: 13/02/2015

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...

Much cheaper !

However, the increase in generic medicines uptake does not automatically translate to savings or improvement in affordable access if pricing policies fail to ensure low prices of generic medicines. This was witnessed from several regional countries, where generic prices were only slightly lower than the originator brand prices (e.g., in Australia) or in some cases even higher (e.g., in Malaysia).

Nguyen et al. WHO South-East Asia Journal of Public Health; January-March 2013 | 2(1)
http://www.who-seajph.org/article.asp?issn=2224-3151;year=2013;volume=2;issue=1;spage=72;epage=74;aulast=Nguyen
(last visited: 13/02/2015)

What shall we discuss?

1. A **political choice** (US and EU … and Việt Nam)
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

But what about Việt Nam ?

BỘ Y TẾ	CỘNG HÒA XÃ HỘI CHỦ NGHĨA VIỆT NAM Độc lập - Tự do - Hạnh phúc
Số: 44/2014//TT-BYT	*Hà Nội, ngày 25 tháng 11 năm 2014*

THÔNG TƯ

Quy định việc đăng ký thuốc

Căn cứ Luật dược số 34/2005/QH11 ngày 14 tháng 6 năm 2005;

Căn cứ Nghị định số 63/2012/NĐ-CP ngày 31 tháng 8 năm 2012 của Chính phủ quy định chức năng, nhiệm vụ, quyền hạn và cơ cấu tổ chức của Bộ Y tế;

Theo đề nghị của Cục trưởng Cục Quản lý dược và Vụ trưởng Vụ Trang thiết bị và Công trình y tế,

Bộ trưởng Bộ Y tế ban hành Thông tư quy định việc đăng ký thuốc.

3. *Thuốc generic* là một thuốc thành phẩm được sản xuất không có giấy phép nhượng quyền của công ty có thuốc phát minh và được đưa ra thị trường nhằm thay thế một thuốc phát minh sau khi bằng sáng chế hoặc các độc quyền đã hết hạn.

But what about Việt Nam ?

BỘ Y TẾ	CỘNG HÒA XÃ HỘI CHỦ NGHĨA VIỆT NAM Độc lập - Tự do - Hạnh phúc
Số: 44/2014//TT-BYT	*Hà Nội, ngày 25 tháng 11 năm 2014*

Căn c

Căn c

Chính phủ qu

Theo đ

thiết bị và Cô

Bộ trư

2. Hồ sơ đăng ký lần đầu đối với thuốc generic (chỉ áp dụng đối với thuốc hóa dược), bao gồm:

a) Phần I. Hồ sơ hành chính và thông tin sản phẩm;

b) Phần II. Hồ sơ chất lượng;

3. Hồ sơ đăng ký lại, bao gồm:

a) Phần I. Hồ sơ hành chính và thông tin sản phẩm;

b) Phần II. Hồ sơ chất lượng: Trường hợp hồ sơ đăng ký lần đầu đã chuẩn bị theo hồ sơ kỹ thuật chung ASEAN (ACTD) hoặc theo mẫu của khu vực thỏa thuận quốc tế về hòa hợp (ICH- CTD) và đáp ứng các yêu cầu kỹ thuật chung của ASEAN, khi đăng ký lại chỉ yêu cầu nộp tiêu chuẩn và phương pháp kiểm nghiệm thành phẩm;

ASEAN bioequivalence regulations in Asia are “in work”

ASEAN Develops Mutual Recognition Arrangement for Bioequivalence Study Reports

on Wednesday, 22 October 2014. Posted in 2014, ASEAN Secretariat News

Workshop on the Development of A Mutual Recognition Arrangement of Bioequivalence Reports

JAKARTA, 22 October 2014 - A two-day workshop for representatives of Pharmaceutical Product Working Group (PPWG) or the National Drug Regulatory Authorities from ASEAN Member States was held on 20-21 October in Jakarta, Indonesia. An expert from EU presented background issues and international requirements for registration of generic drugs and for bioequivalence studies.

- The PPWG has actively worked to advance harmonisation and recognition arrangements for acceptance of Bioequivalence (BE) Study Reports produced by Bioequivalence Centres in ASEAN.
- The workshop resulted in recommendations on the content of the mutual recognition arrangement (MRA) for further consideration by PPWG.
- The MRA is targeted for completion by 2015.

http://www.asean.org/news/asean-secretariat-news/item/asean-develops-mutual-recognition-arrangement-for-bioequivalence-study-reports?category_id=513
Last accessed: 13/02/2015

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

Are you happy about the law(s) ?

1. **The US and EU laws are enough and we only need to follow them…**
2. **An ASEAN regulation is essential and should be further developed…**
3. **We need a law specific to Việt Nam …**
4. **We do not need any law (Industry will autoregulate it-self)…**
5. **I have no opinion because I'm not an expert (I'm a doctor)…**

Please, vote now (1 choice)

What shall we discuss?

1. The US and the EU laws (and Asia)
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)

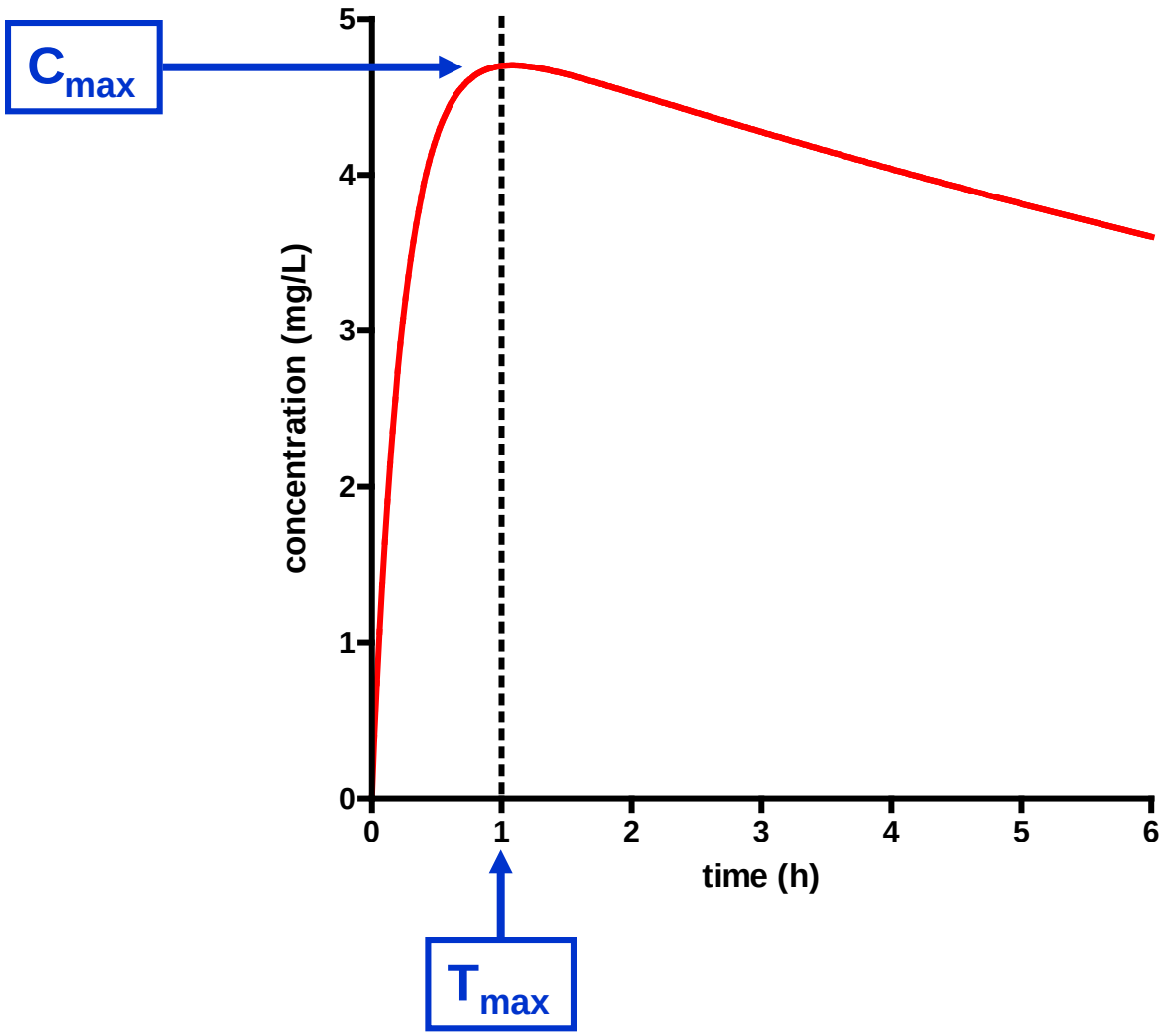
    → **extent of absorption**
  - **C_{max}** (the maximum plasma concentration of the active substance)

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

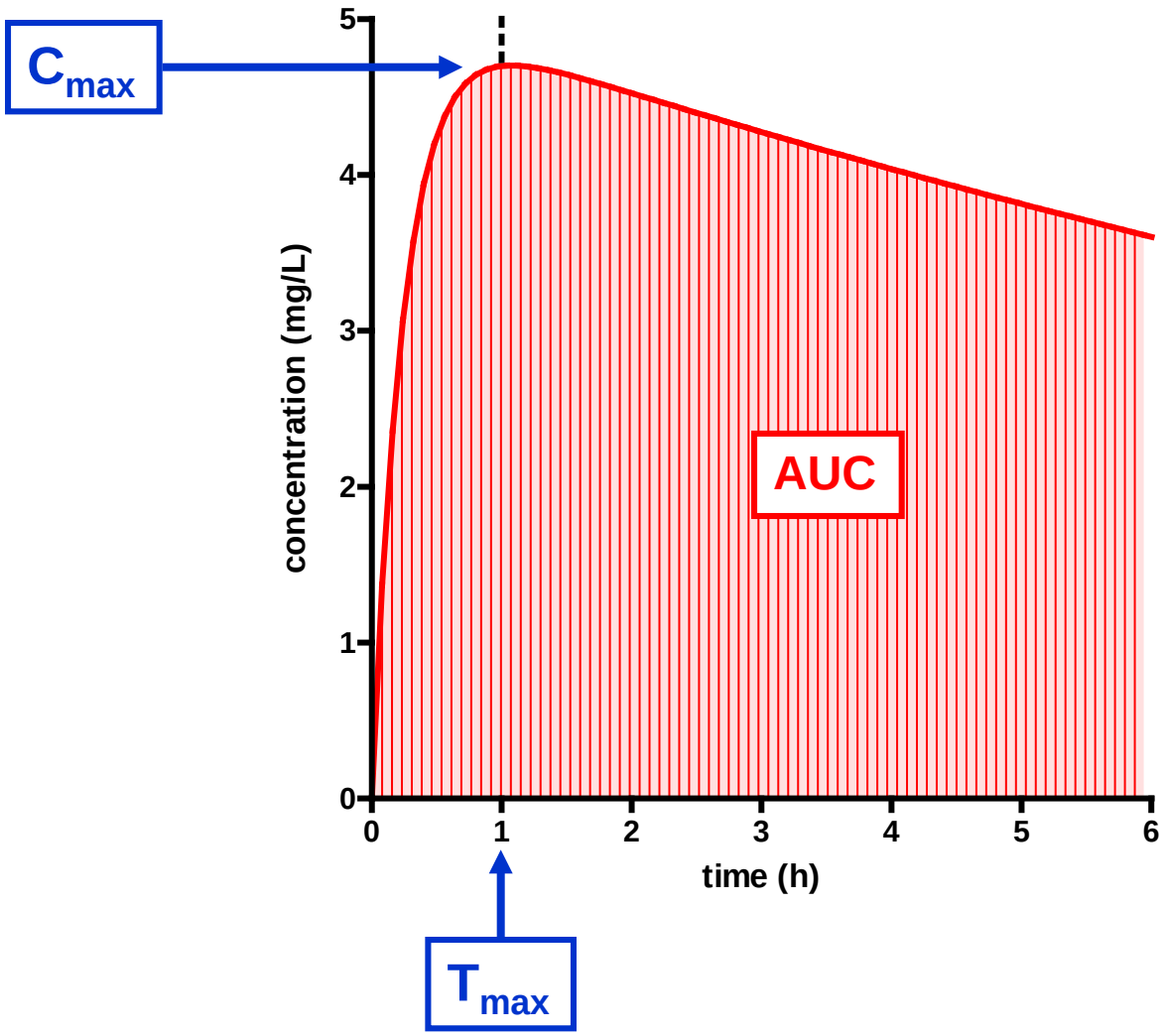
    → **rate of absorption**

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.

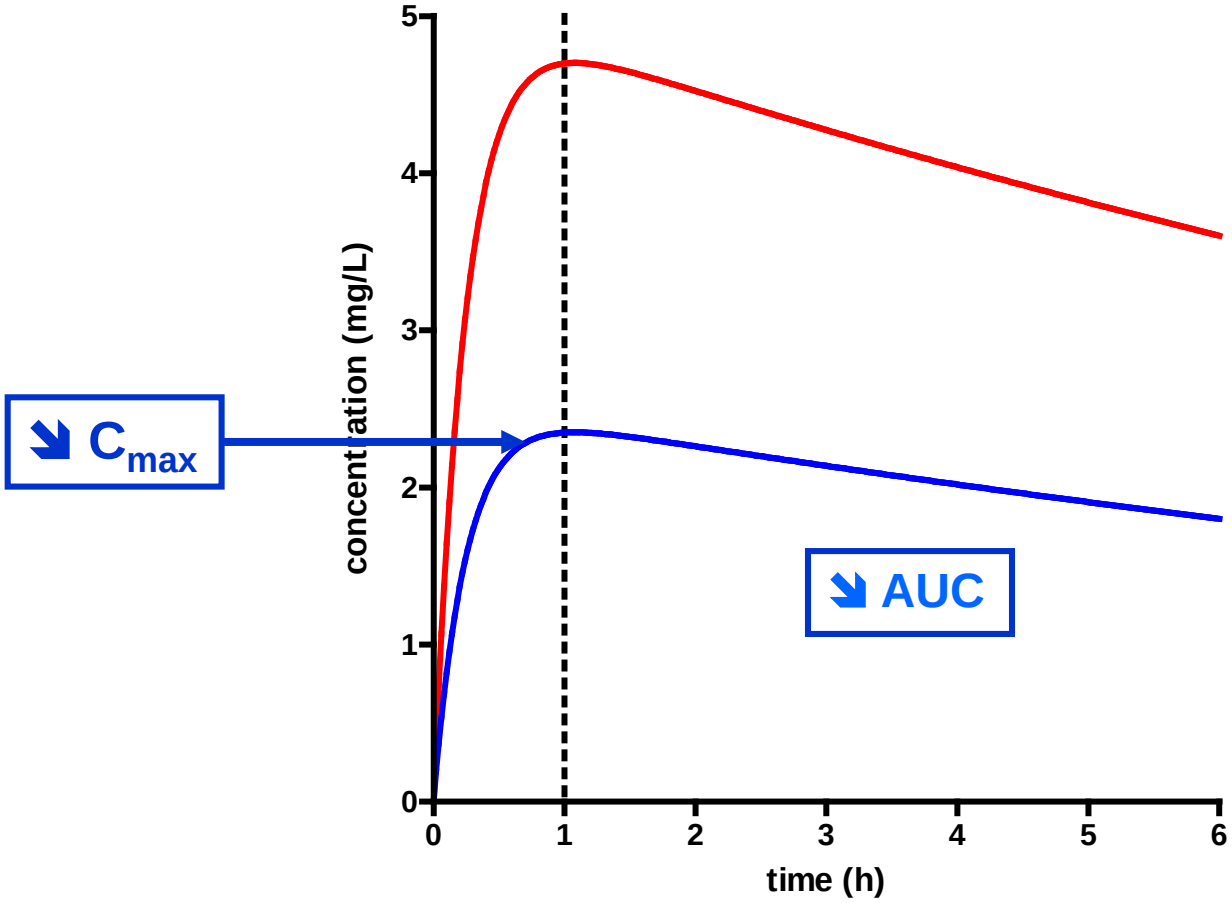
AUC – C_{max} – T_{max}



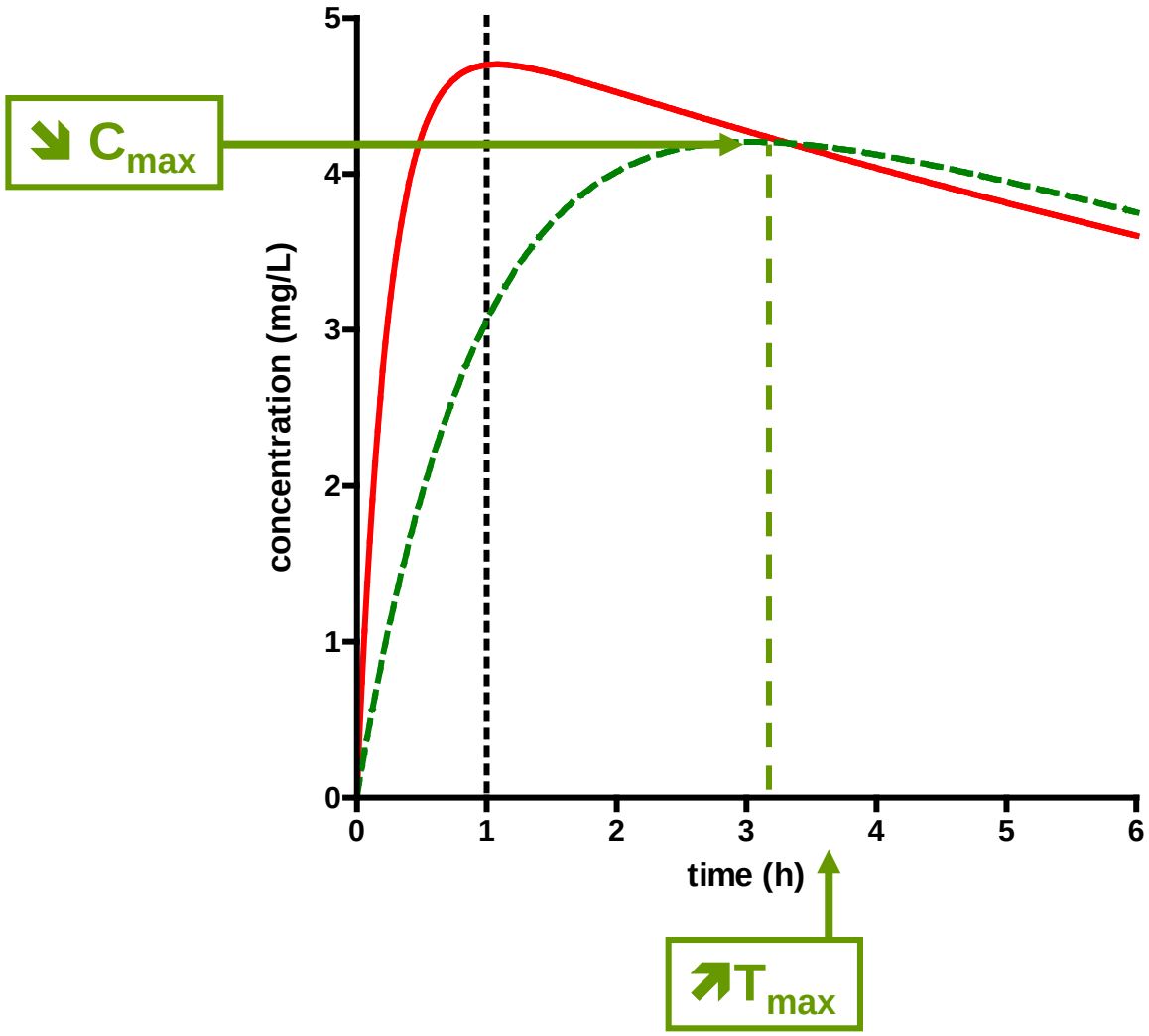
AUC – C_{max} – T_{max}



What if the absorption is decreased ?

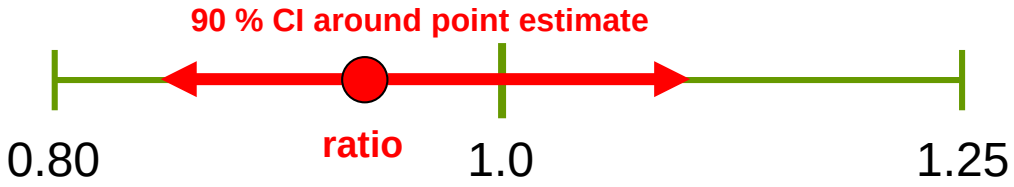


What if absorption is delayed ?



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**.



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**

* 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

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.

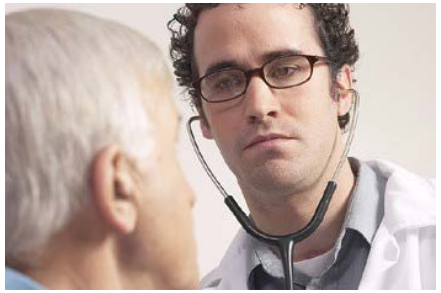
Please, vote now (1 choice)

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).

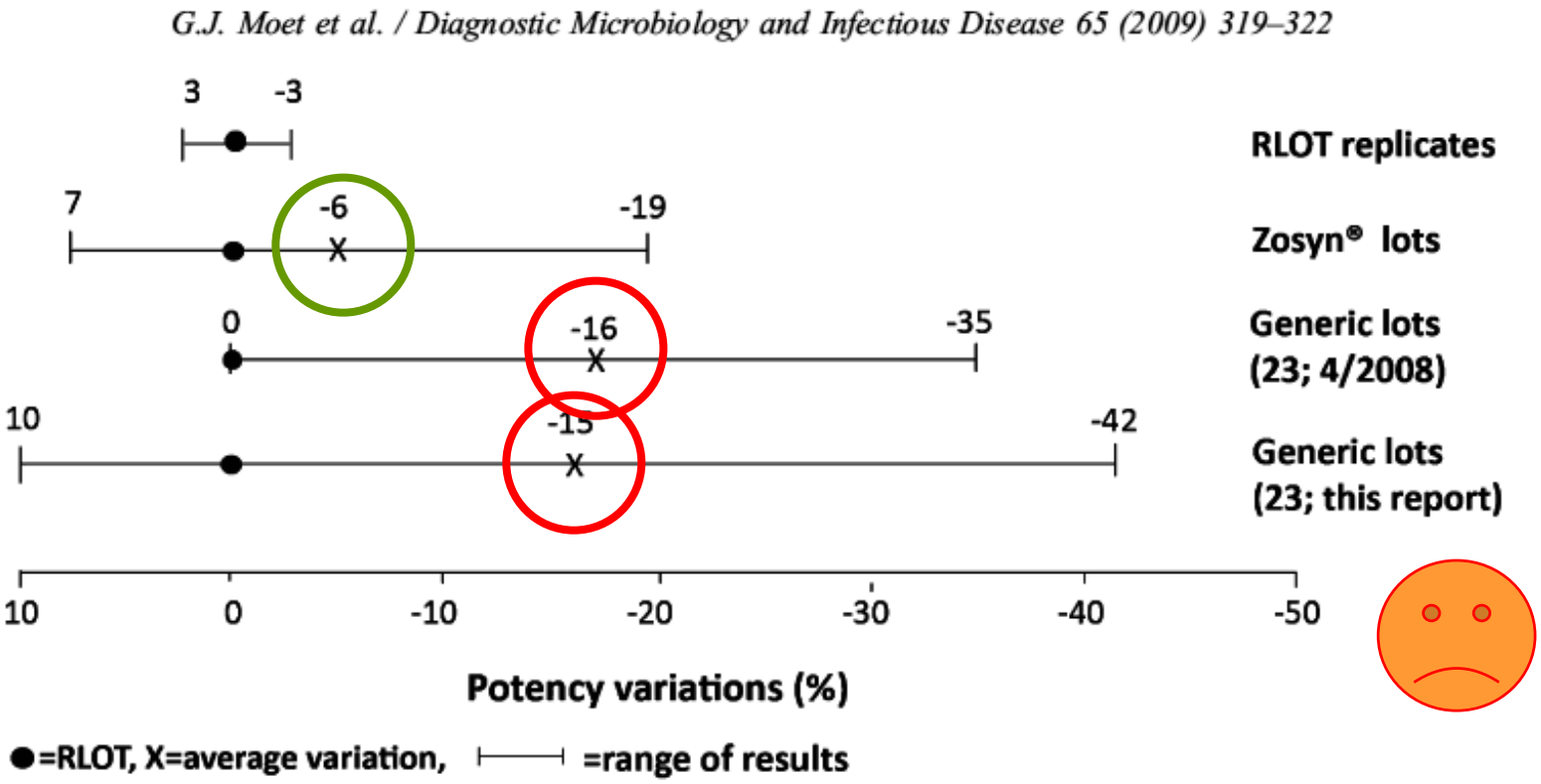


Fig. 1. Extent of potency variations among 4 groups of experiments with piperacillin/tazobactam intravenous injection lots.

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

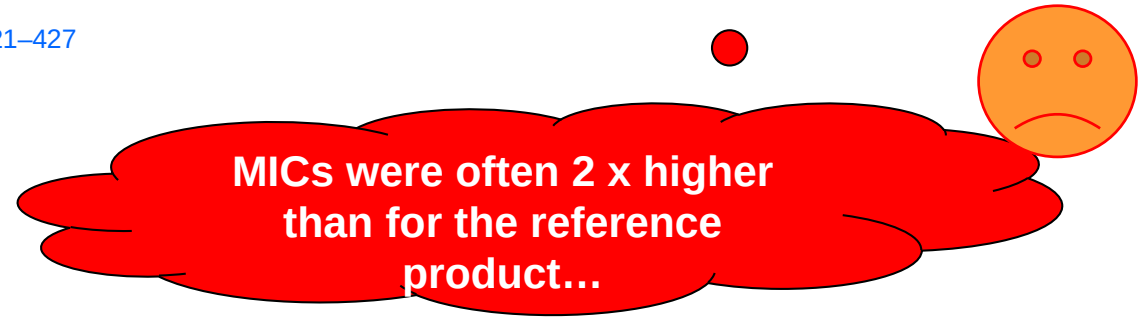
MIC values (vancomycin)

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	–

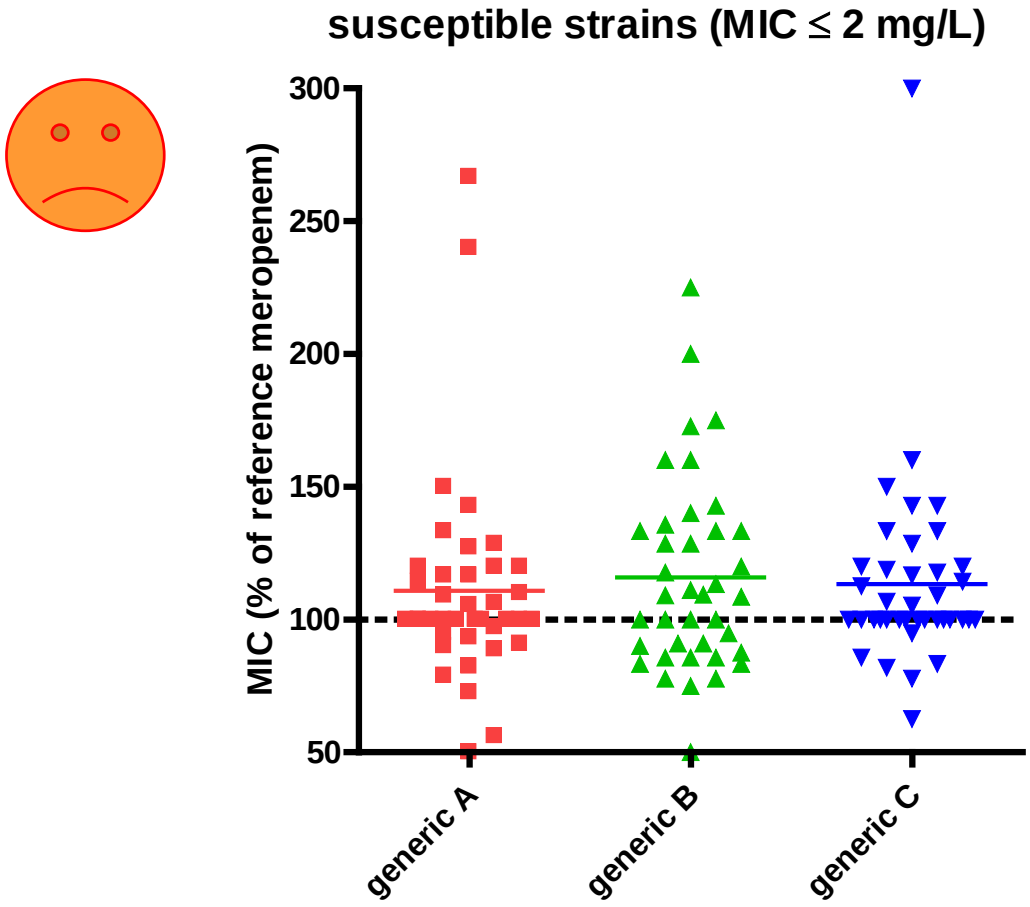
MRSA methicillin-resistant *Staphylococcus aureus*[a]Note that the distribution of one minimal inhibitory concentration (1 MIC) shows the identical rate with the brand drug: MIC was determined by broth micro-dilution method using powder in each drug vial

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

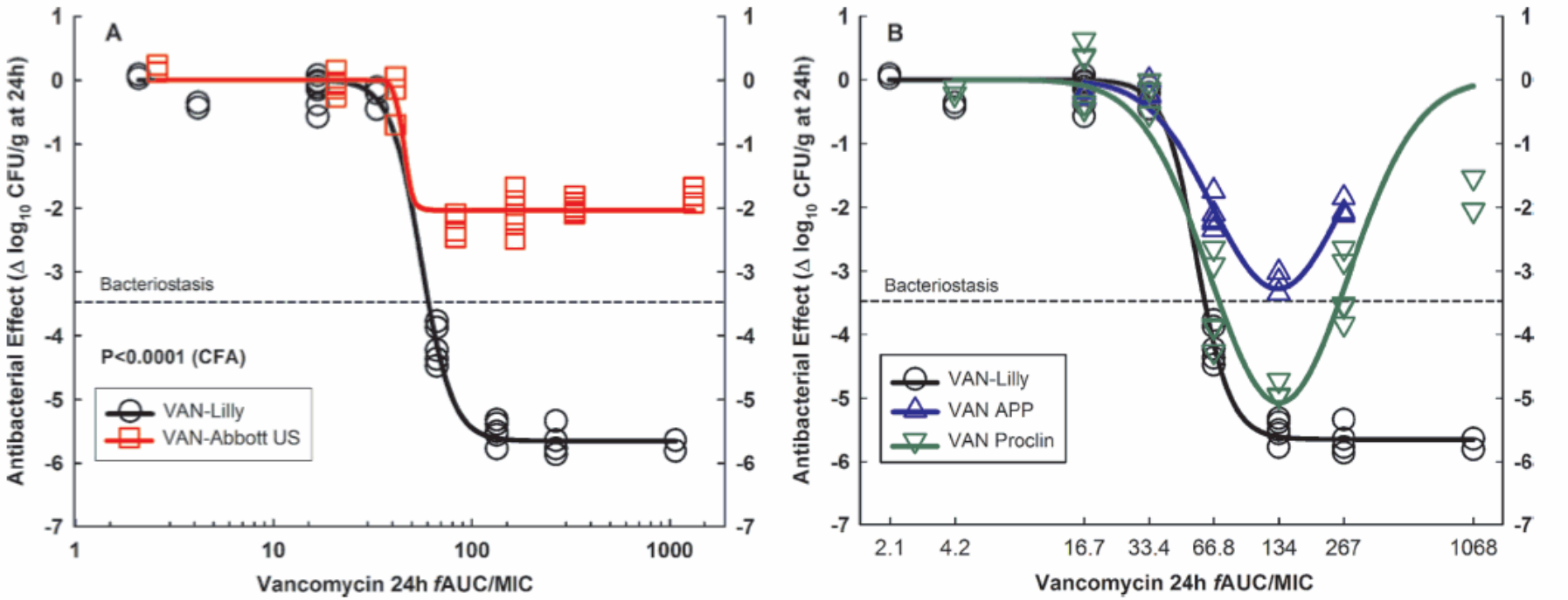


FIG. 1. *In vivo* efficacy against *S. aureus* GRP-0057 (years 2002 and 2003) at a low inoculum (4.30 ± 0.05 $\log_{10}$ CFU per thigh when subcutaneous treatment q1h started). Vancomycin generic products are compared with the innovator (VAN-Lilly) in dose-effect experiments (2.34 to 1,200 mg/kg per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

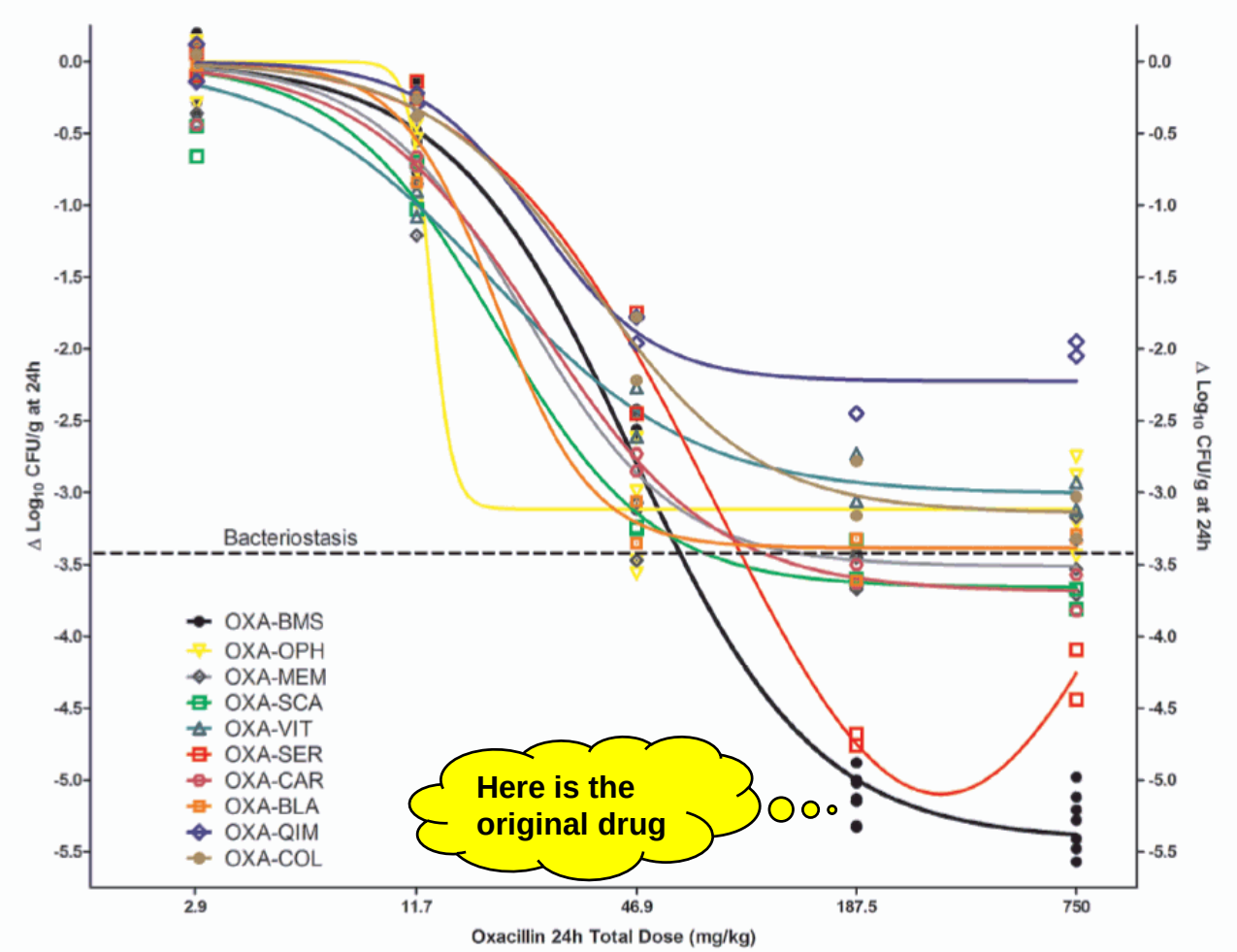


Figure 3 Dose-response relationship of the innovator and 9 generic products of oxacillin in the neutropenic mouse thigh infection model. OXA-BMS (innovator, black curve) and 8 generics fitted to Hill's sigmoid model, while generic product OXA-SER fitted to the Gaussian U-shaped model (red curve). Regardless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

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.

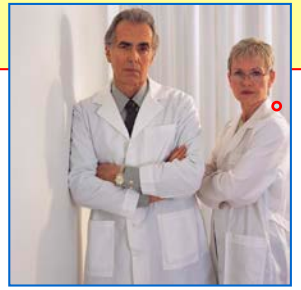
In agreement with Manning and Smith,[41] it is necessary to underline the importance that clinician's change their attitude toward pharmacovigilance and post-marketing surveillance systems, which can help to identify the lack of efficacy during the treatment with generic formulations.

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, vote now (1 choice)

Dissolution of meropenem in Japan

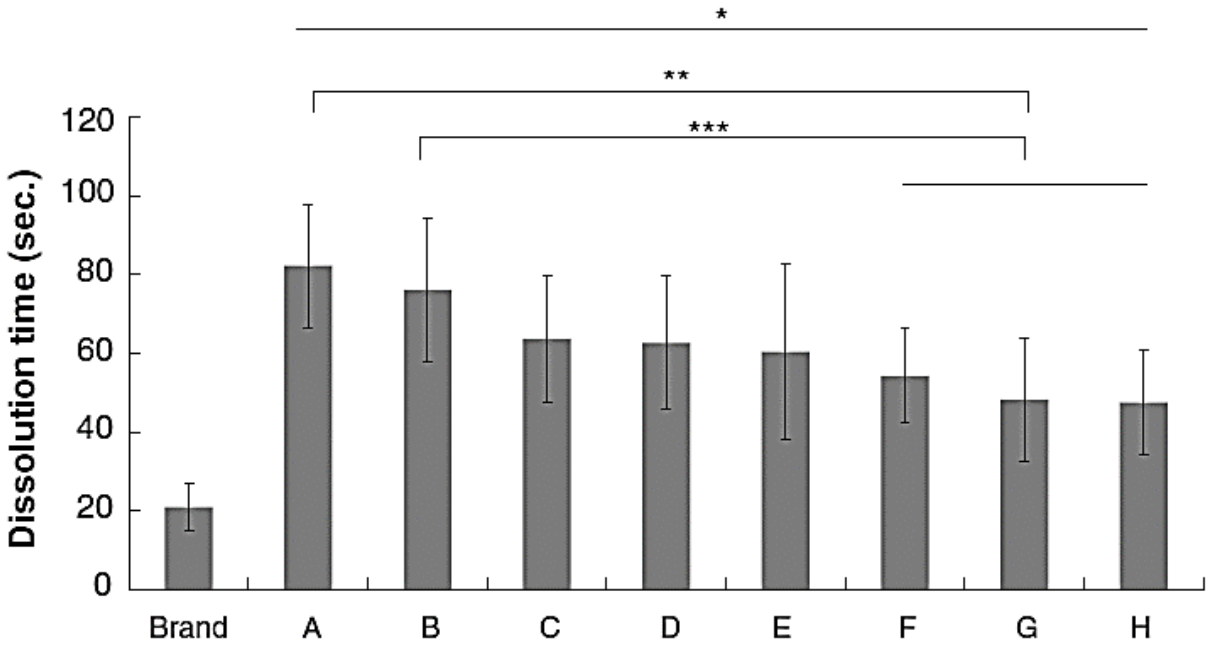


Fig. 3 Comparison of dissolution time between brand name meropenem and eight generics. *A–H* Generic products of meropenem. $*P < 0.001$ versus brand name drug; $**P < 0.001$ versus generic A drug; $***P < 0.001$ versus generic B drug

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

Crystals size in meropenem in Japan

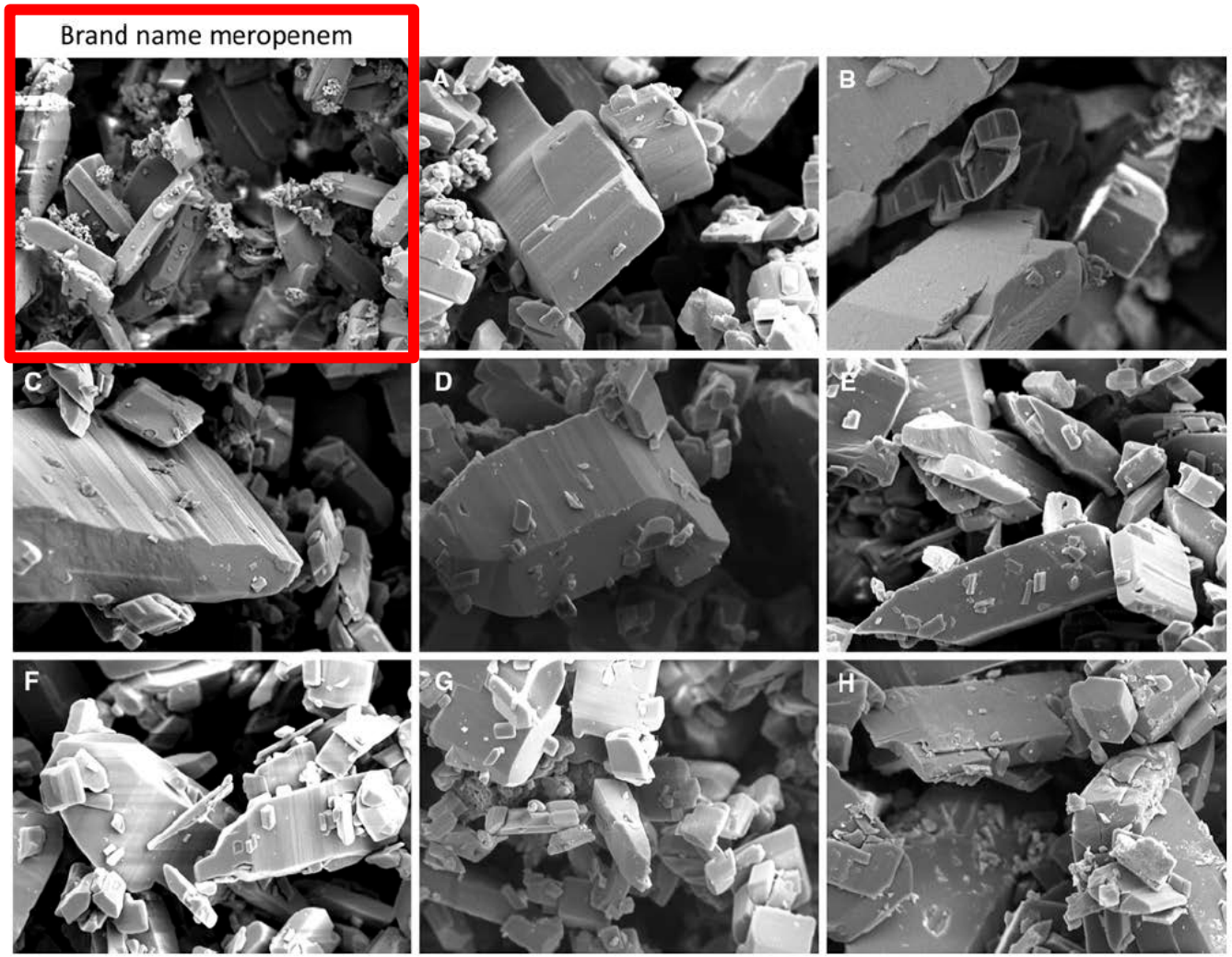
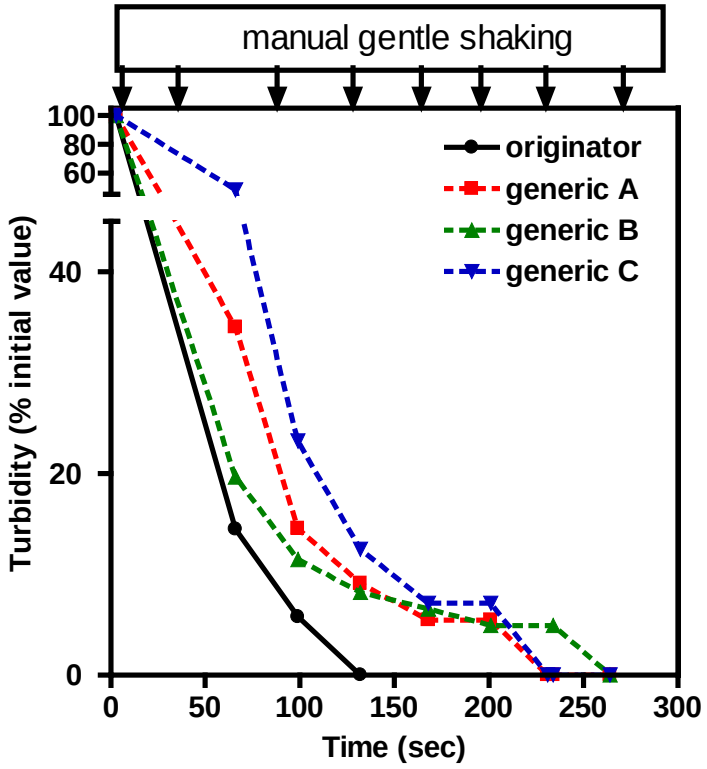


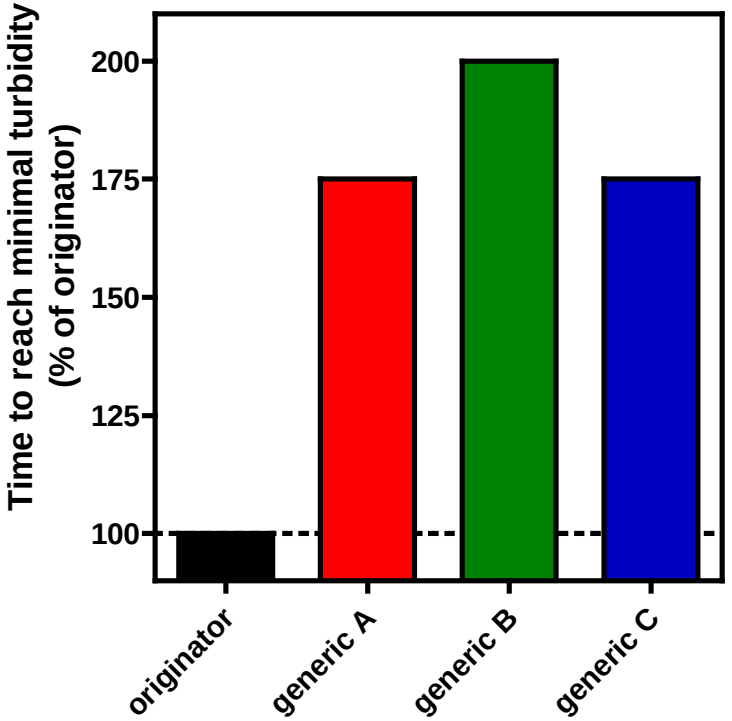
Fig. 4 Electron micrographs of drug particles of brand name meropenem and eight generics. **a–h** Generic products of meropenem. ×1,000

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)
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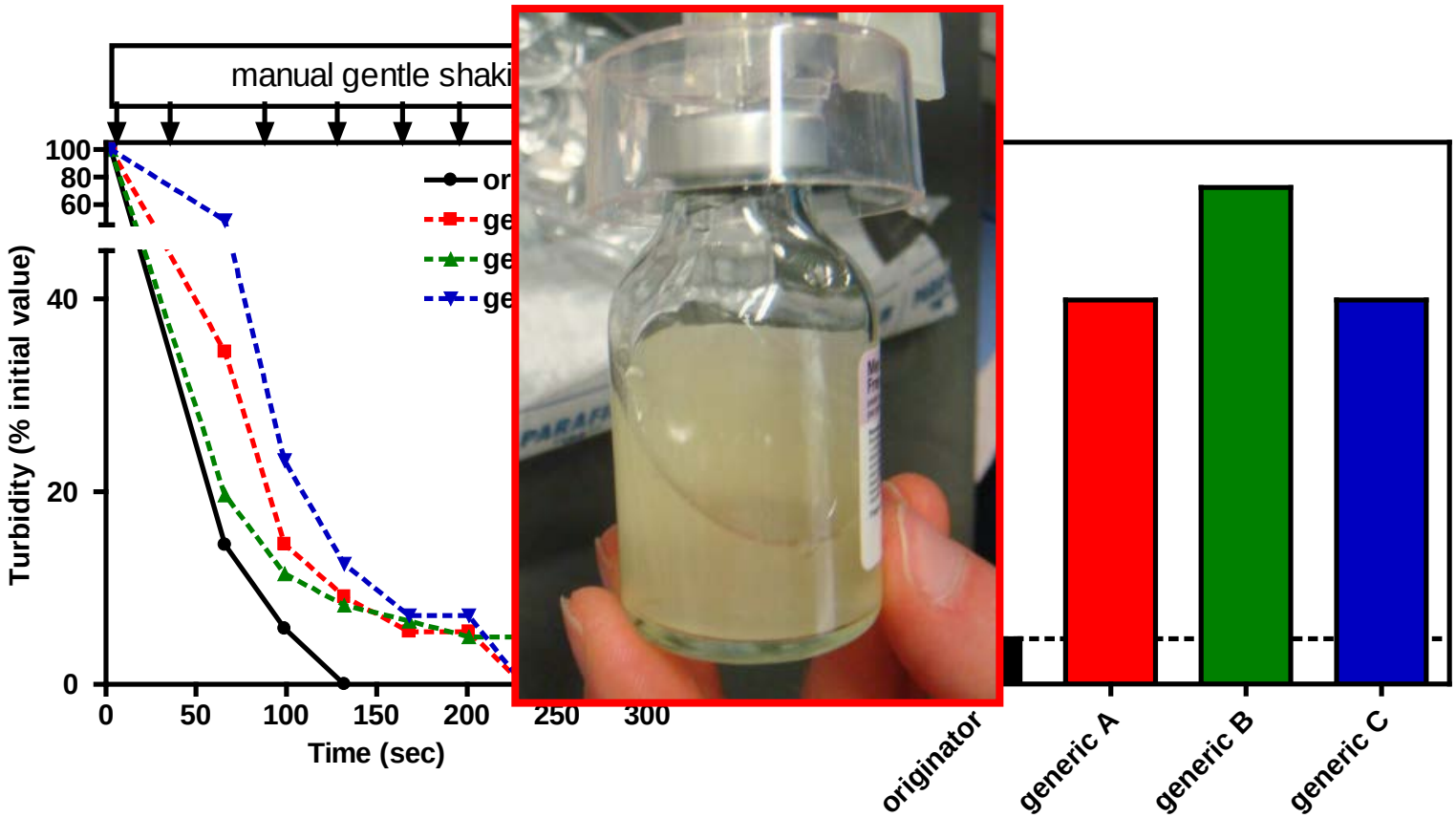
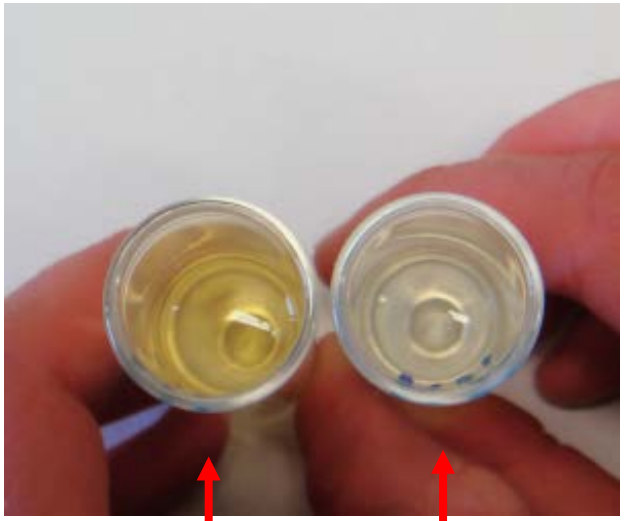
room temperature



Van Bambeke *et al*., in preparation

Impurities in meropenem: coloured compounds

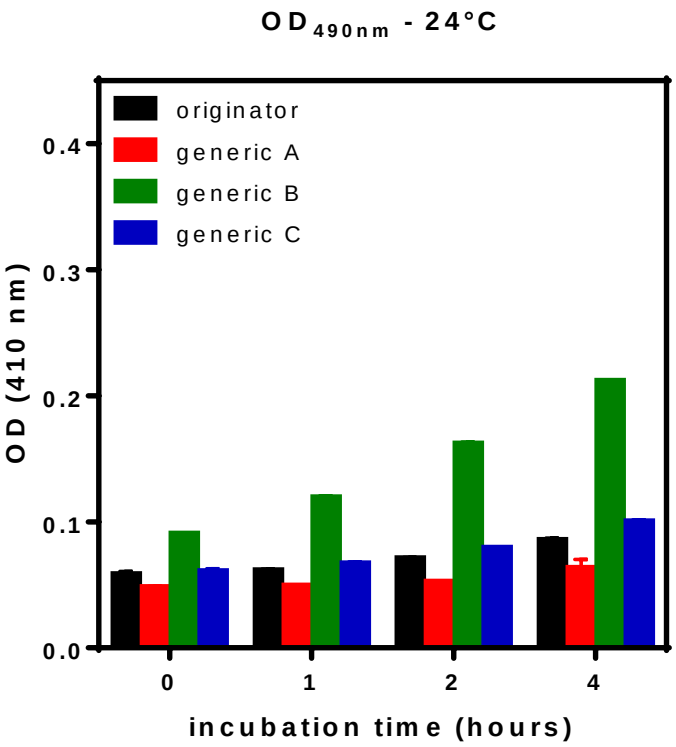


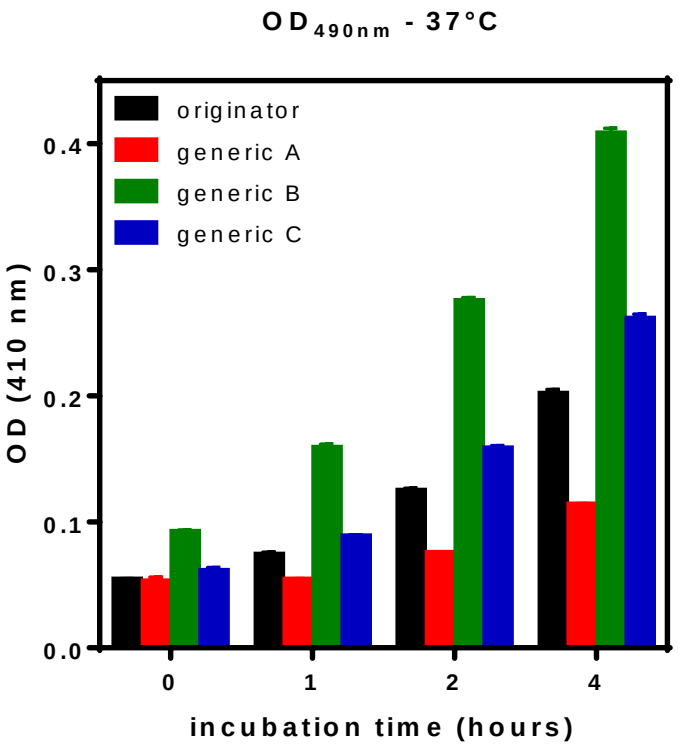
generic B **originator**

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 !

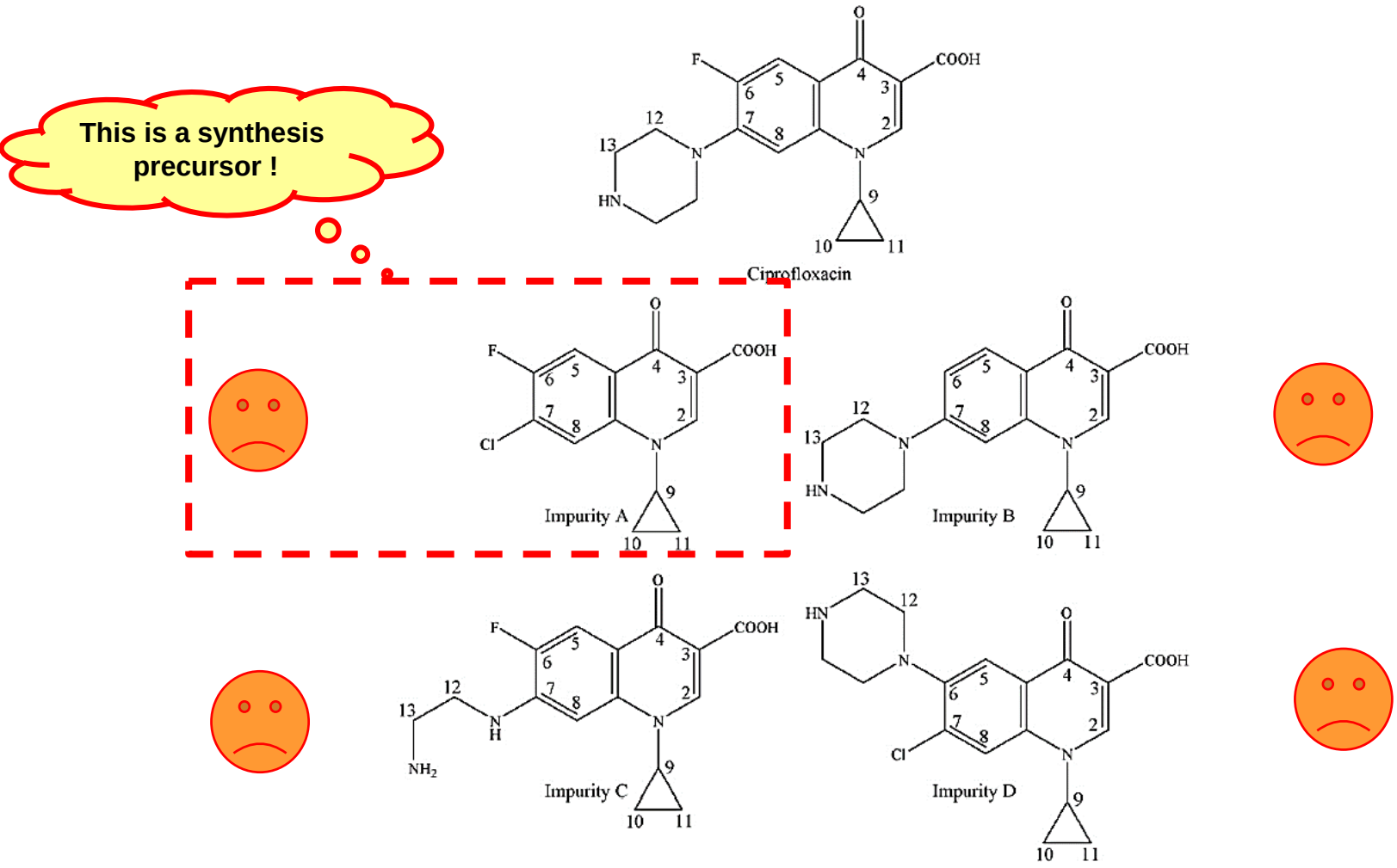


Fig. 1. Structure of ciprofloxacin and its main impurities.

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

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

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

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

Are such fears possible in Việt Nam ?

Key barriers

A number of barriers to the development and implementation of a comprehensive generic medicines policy was documented in the workshop.

The first is the mistrust in the pharmaceutical quality of available generic medicine products in some countries in terms of safety and efficacy.

The lack of clear bioequivalence assessment systems as a regulatory requirement in generic medicines registration or lack of appropriately skilled inspectors and monitoring to ensure the quality of generic medicine products was reportedly attributable to this mistrust.

This may be an Industry's argument

This is exactly what we are seeing in Europe

Nguyen et al. WHO South-East Asia Journal of Public Health; January-March 2013 | 2(1)
http://www.who-seajph.org/article.asp?issn=2224-3151;year=2013;volume=2;issue=1;spage=72;epage=74;aulast=Nguyen
(last visited: 13/02/2015)

We should also address the problem of counterfeited drugs

Packs bought at pharmacies in Lagos, Nigeria

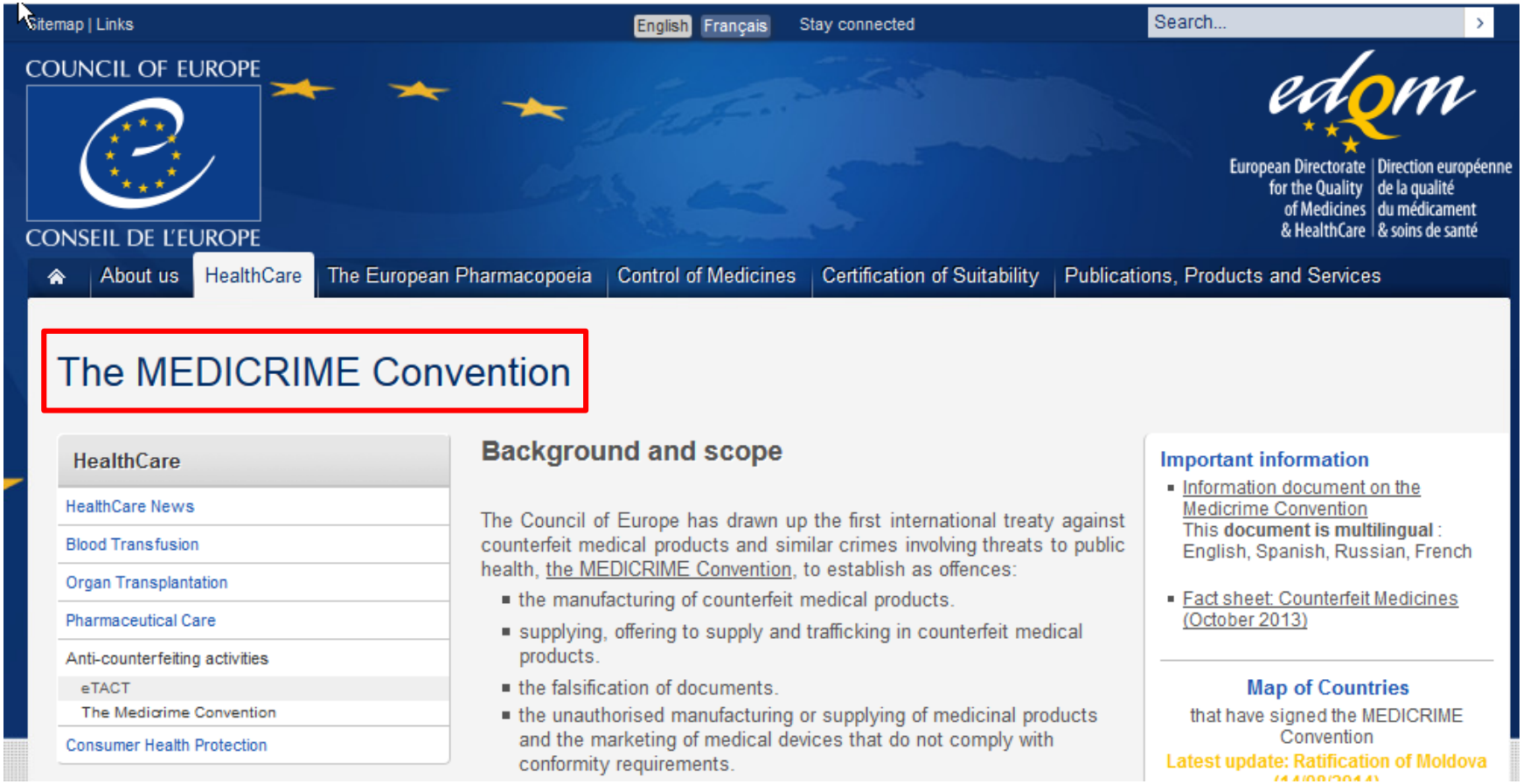
The only noticeable difference is that the real package has a hologram on the back (left). The fake was two-thirds talcum powder and contained no ciprofloxacin. Even holograms can be faked.

- **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.

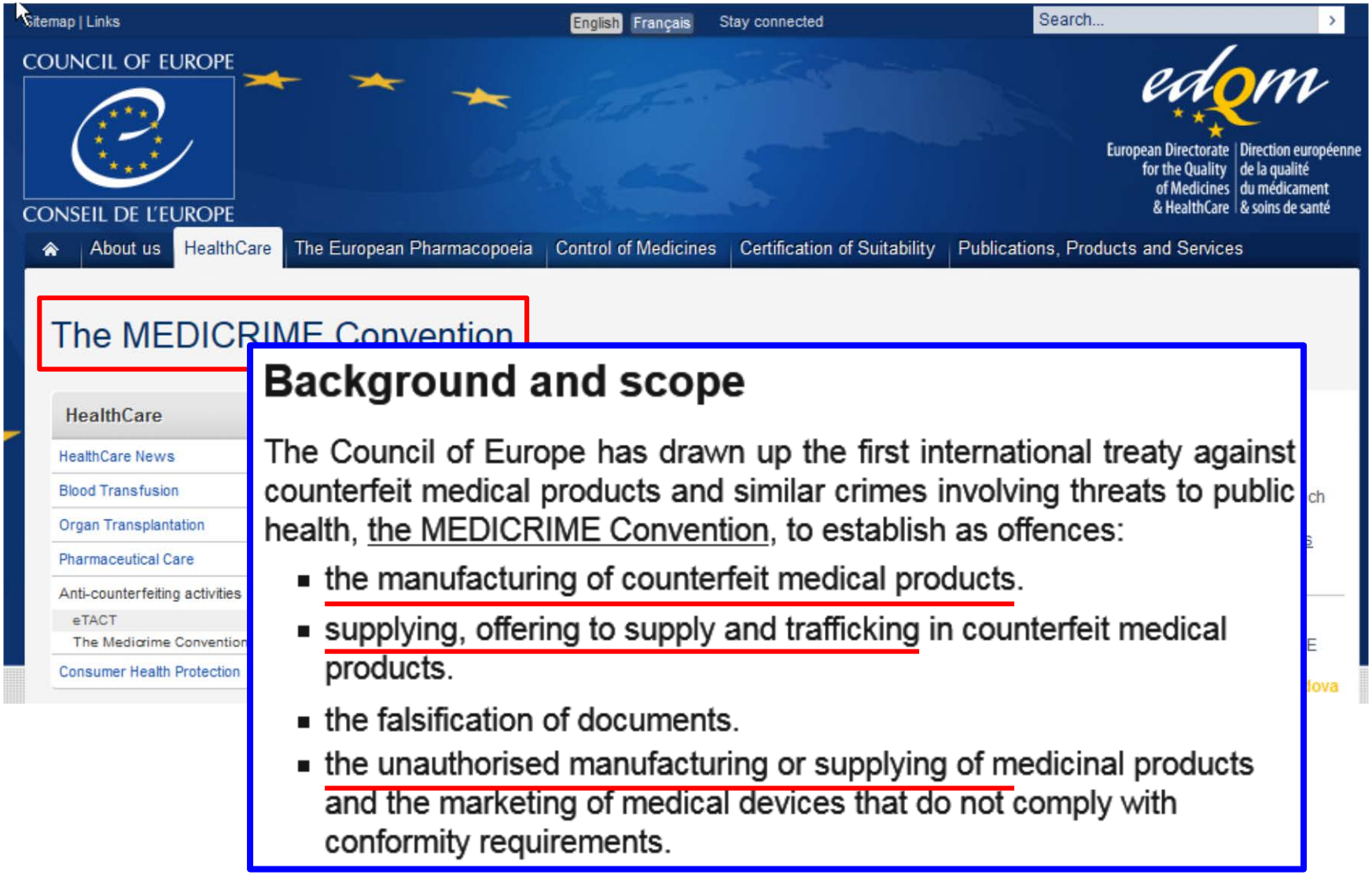
Slide kindly communicated by S. Opal

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



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 levofloxacin<u>S</u> 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 …

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

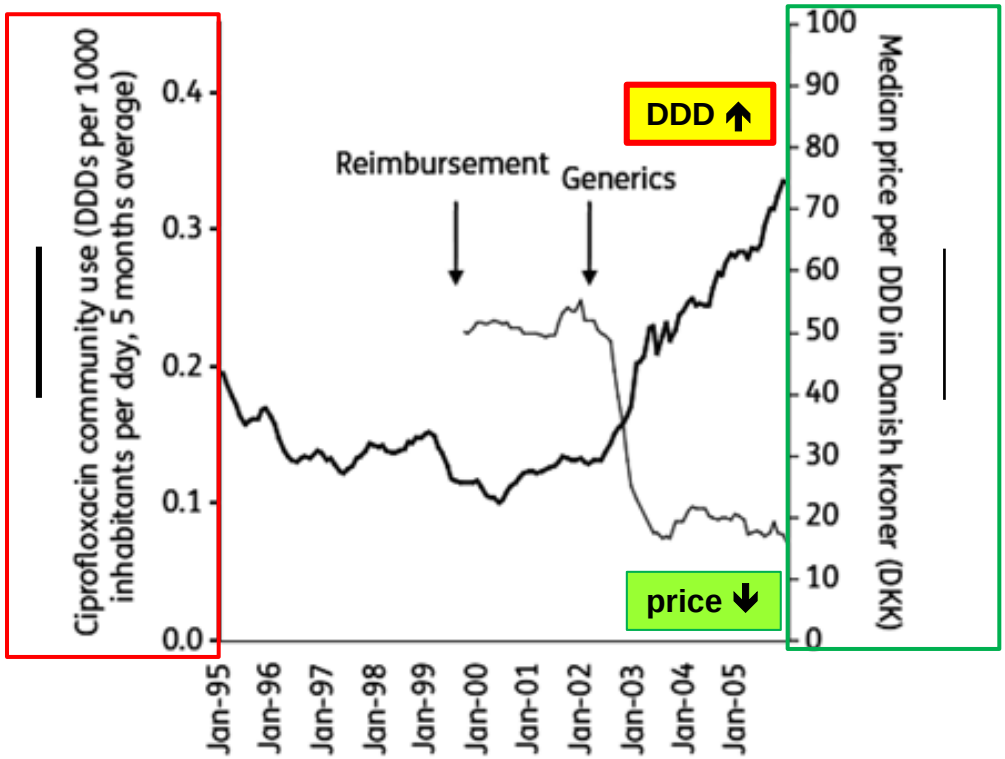
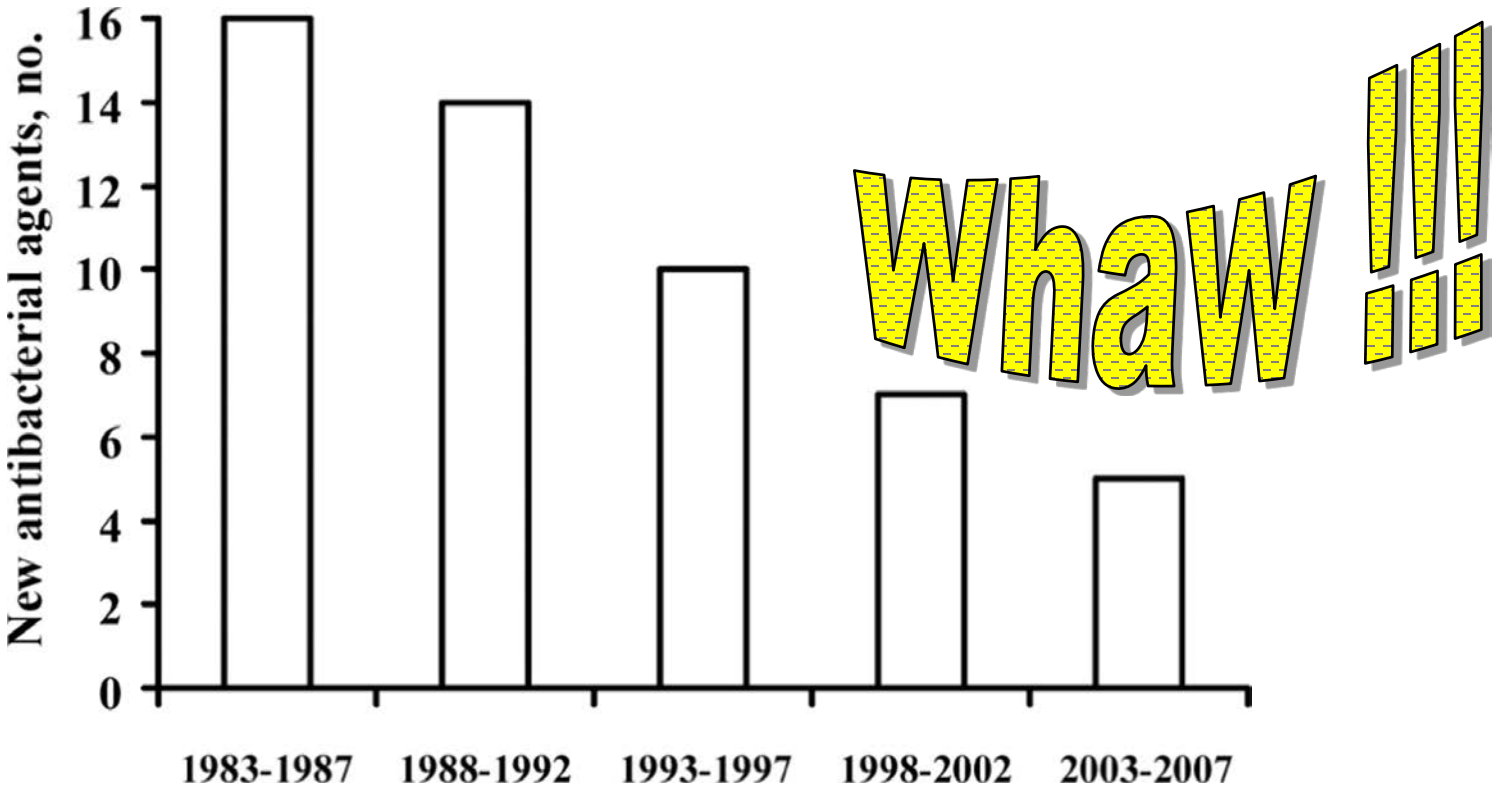


Figure 1.

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.

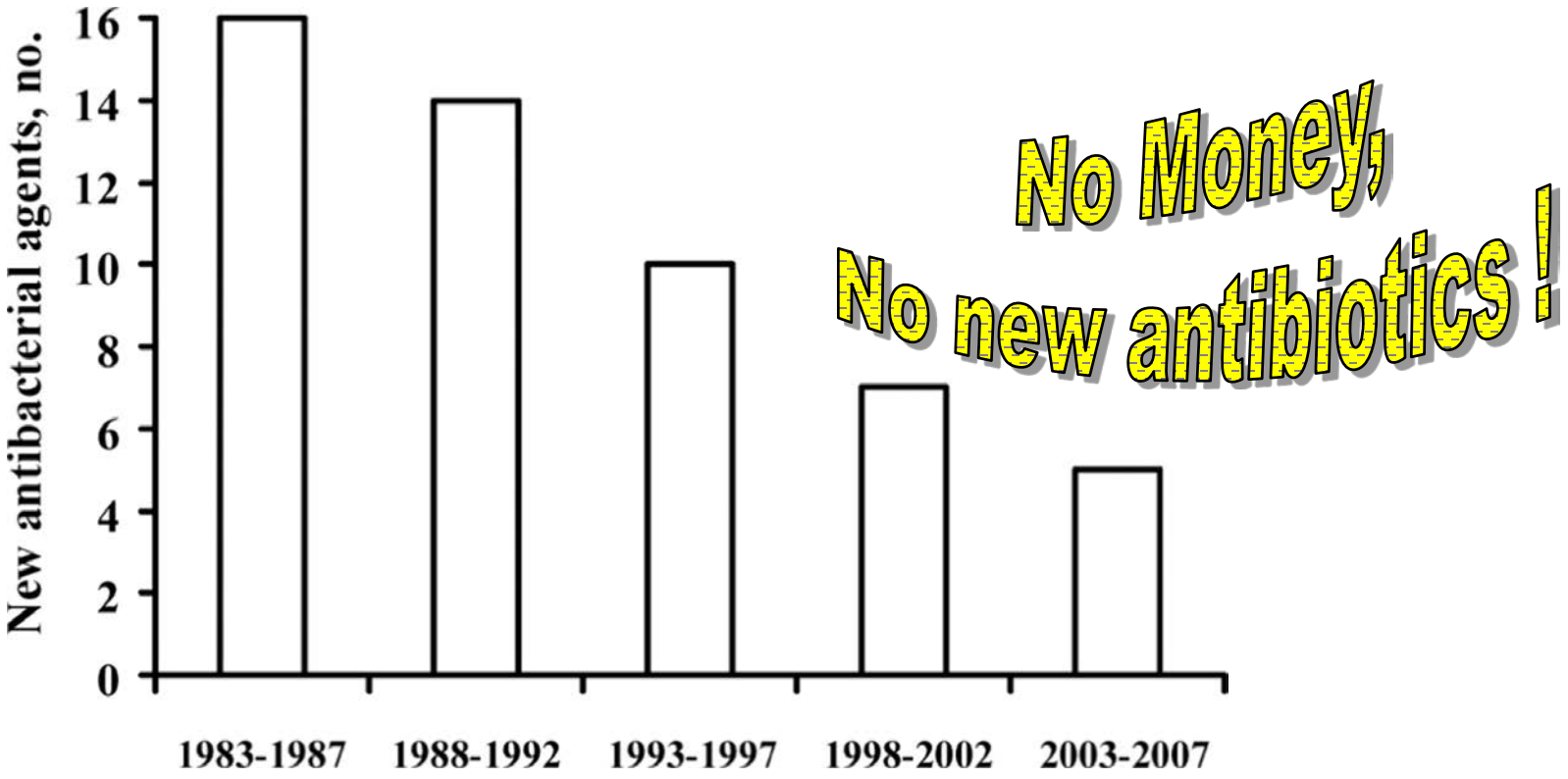
Jensen *et al.* J Antimicrob Chemother 2010; 65:1286–1291

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 …

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 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