Branded vs. generic of antibiotics:

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

Middle East Anti-Infectives Forum
Yas Island, Abu Dhabi, U.A.E
10-11 November 2017

With approval of the Belgian Common Ethical Health Platform – visa no. 17/V1/10411/093945

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)

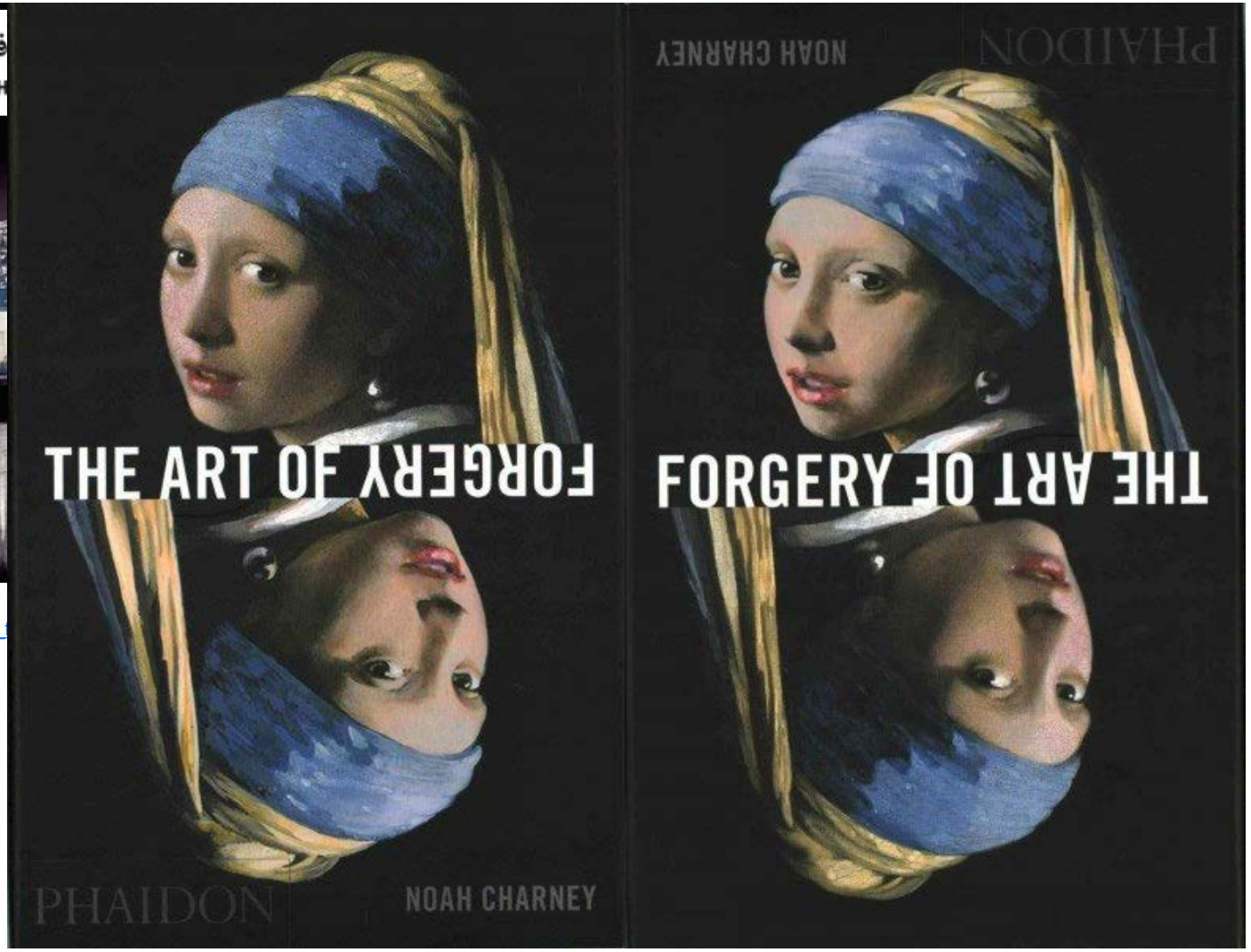
Slides: http://www.facm.ucl.ac.be → Lectures

Abu Dhabi opens an new Museum…

http://static.gulfnews.com/polopoly_fs/1.2085814!/image/3964771986.jpg_gen/derivatives/box_620347/3964771986.jpg
Last visited: 8 Nov 2017

Would you prefer to see there originals or copies ?

http://static.gulfnews.com/polopoly_
Last visited: 8 Nov 2017



https://www.npr.org/2015/06/23/412244490/could-the-masterpiece-be-a-fake-profit-revenge-and-the-art-of-forgery
Last visited: 8 Nov 2017

Why choosing a "generic" antibiotic ?

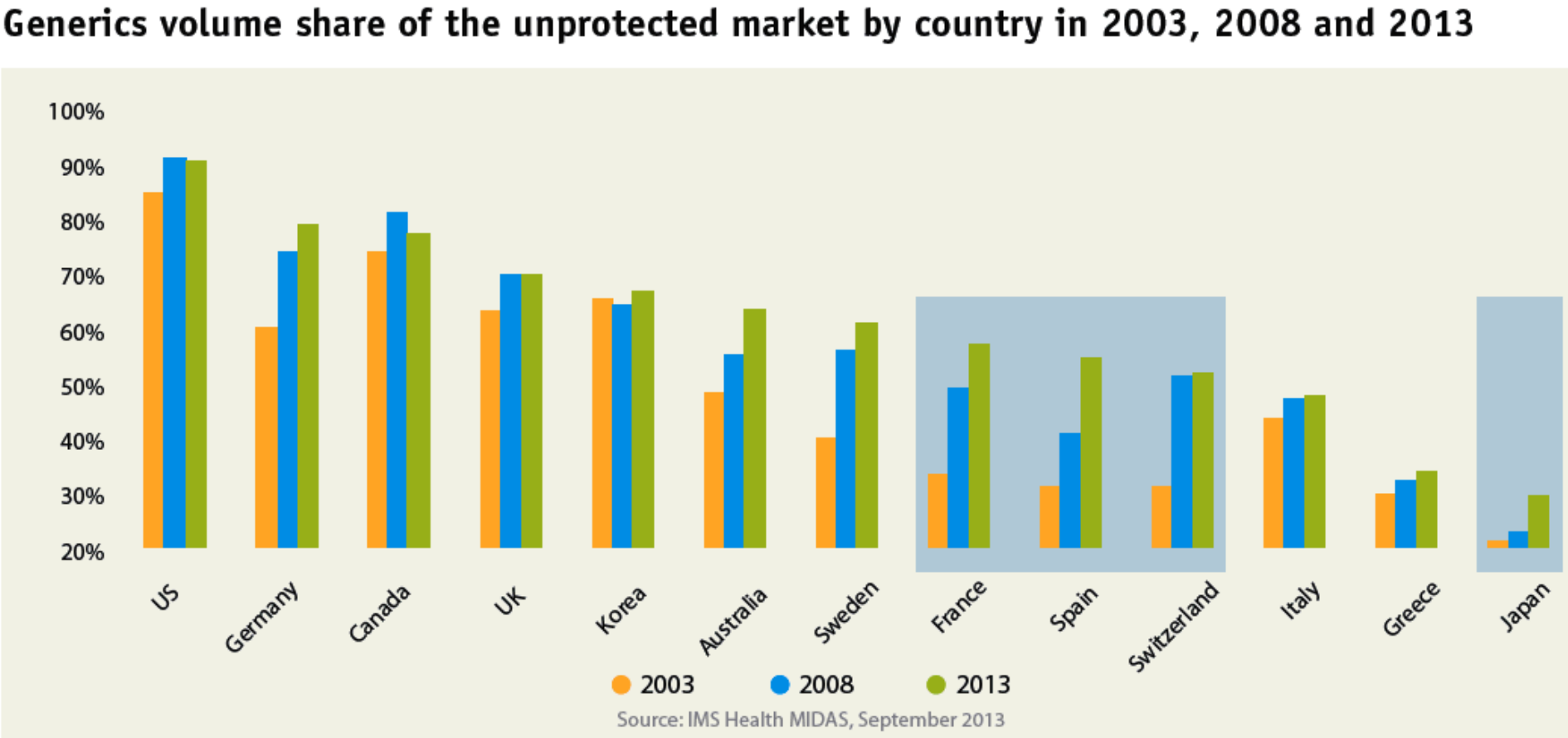
1. Because it is like airlines: low cost is better…
2. Because they have the same quality as the original ones…
3. Because they can be produced locally (in my country)
   (as opposed to countries of "Big Pharma")…
4. Because my patients / my hospital / my country has/have limited resources…
5. Because "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...

Much cheaper !

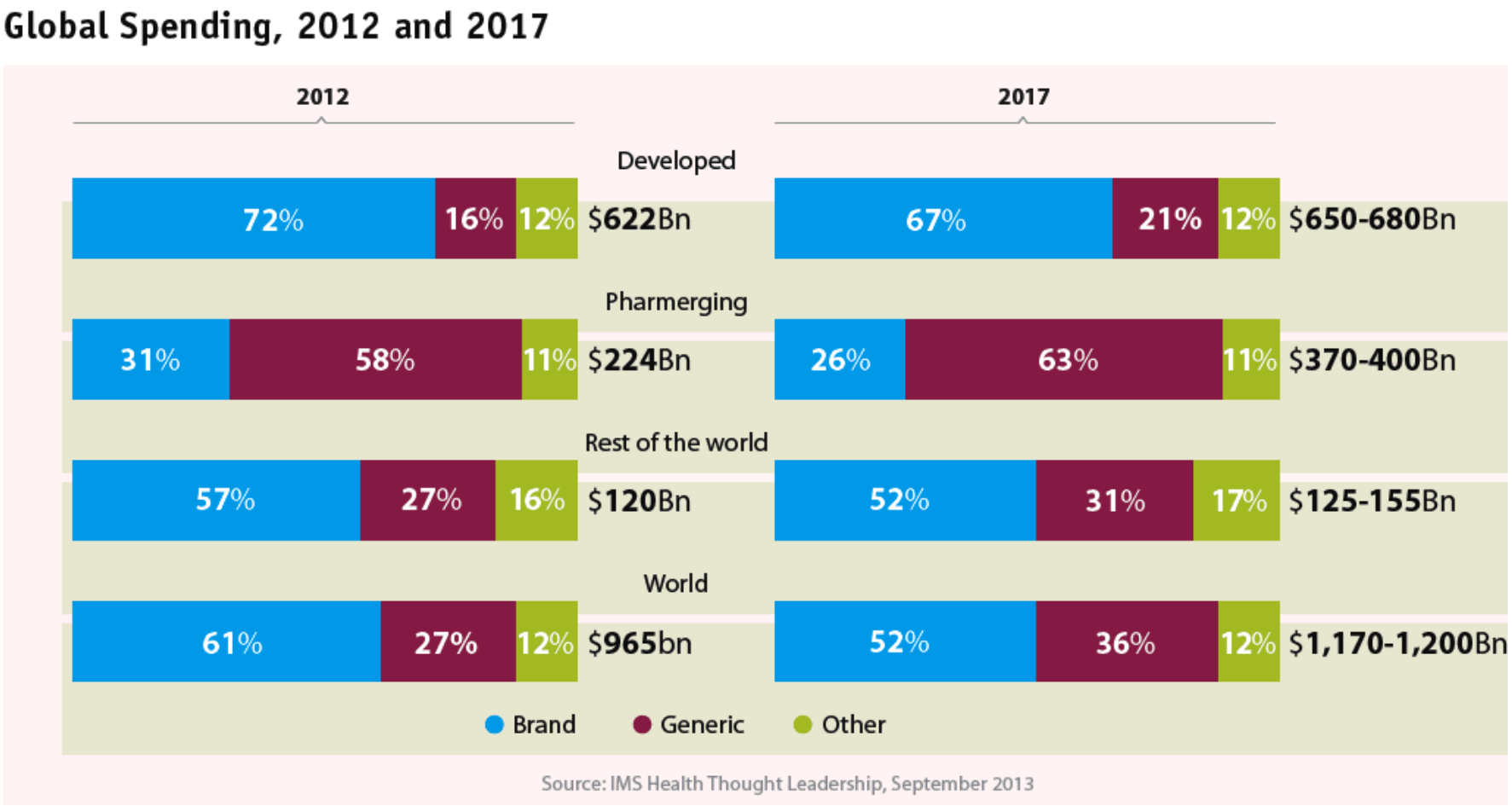
Generics across countries in volumes …



Volume measured in Standard Units. Unprotected Market: Never and No longer Protected Products

Source: The Global Use of Medicines: Outlook through 2017. Report by the IMS Institute for Healthcare Informatics
Available from http://www.imshealth.com/en/thought-leadership/quintilesims-institute/reports/global-use-of-medicines-outlook-through-2017#ims-form
Last visited: 15 Oct 2017

Branded *vs* Generics in spending…



Spending in US$ with variable exchange rates.
Pharmerging: China, Brazil, Russia, India, Mexico, Turkey, Venezuela, Poland, Argentina, Saudi Arabia, Indonesia, Colombia, Thailand, Ukraine, South Africa, Egypt, Romania, Algeria, Vietnam, Pakistan and Nigeria.

Source: The Global Use of Medicines: Outlook through 2017. Report by the IMS Institute for Healthcare Informatics
Available from http://www.imshealth.com/en/thought-leadership/quintilesims-institute/reports/global-use-of-medicines-outlook-through-2017#ims-form
Last visited: 15 Oct 2017

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
Last accessed: 17 Oct 2017

- 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
  Last accessed: 17 Oct 2017
- **Product-Specific Guidances for Generic Drug Development**:
  https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm
  Last accessed: 20 Oct 2017

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://eur-lex.europa.eu/legal-content/EN/TXT/?uri=LEGISSUM:l21230 (and navigate from there [frequent updates])
Last accessed: 17 Oct 2017

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…

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: 17 Oct 2017

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)

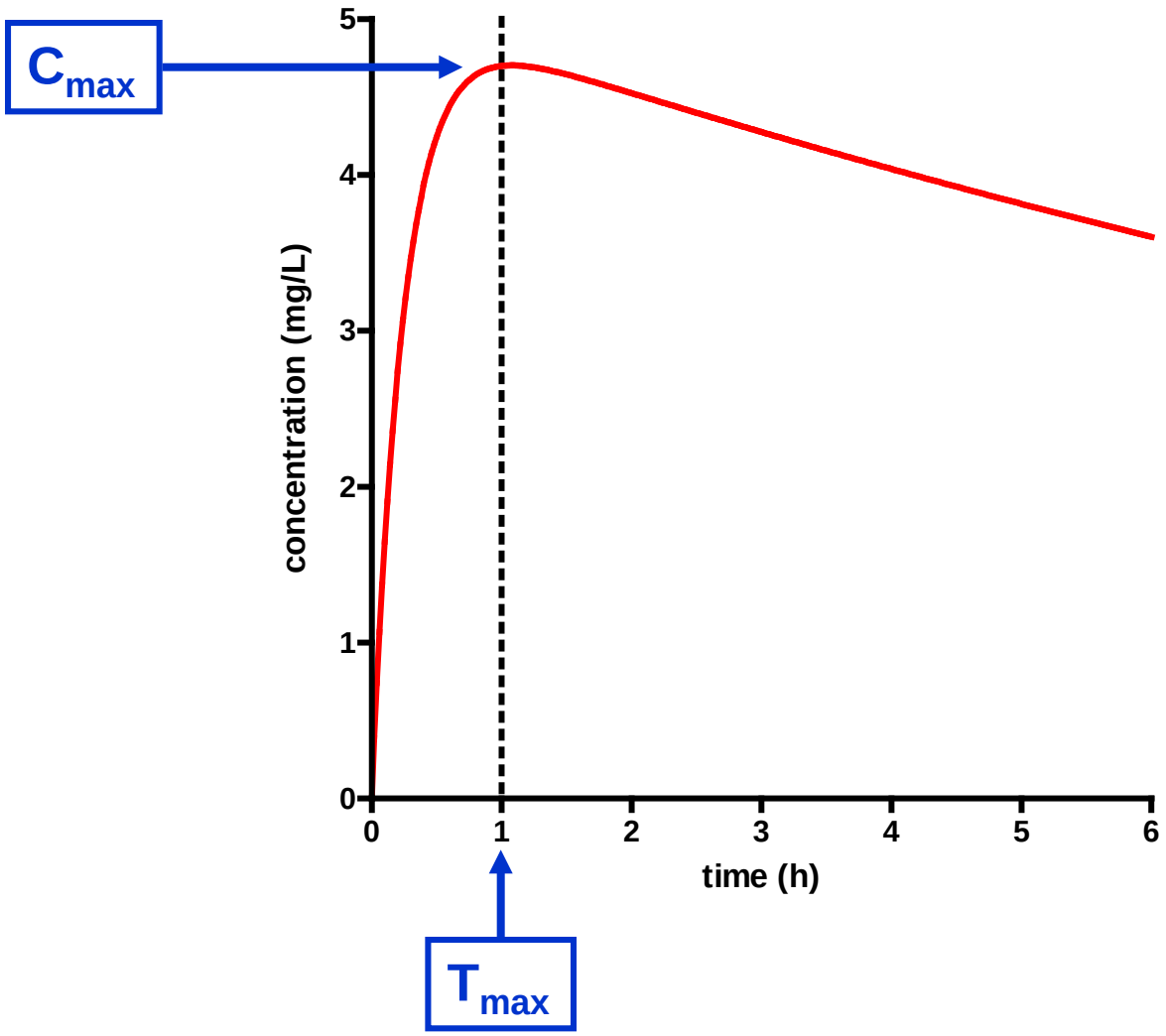
    → **extent of absorption**
  - **C_{max}** (the maximum plasma concentration of the active substance)

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

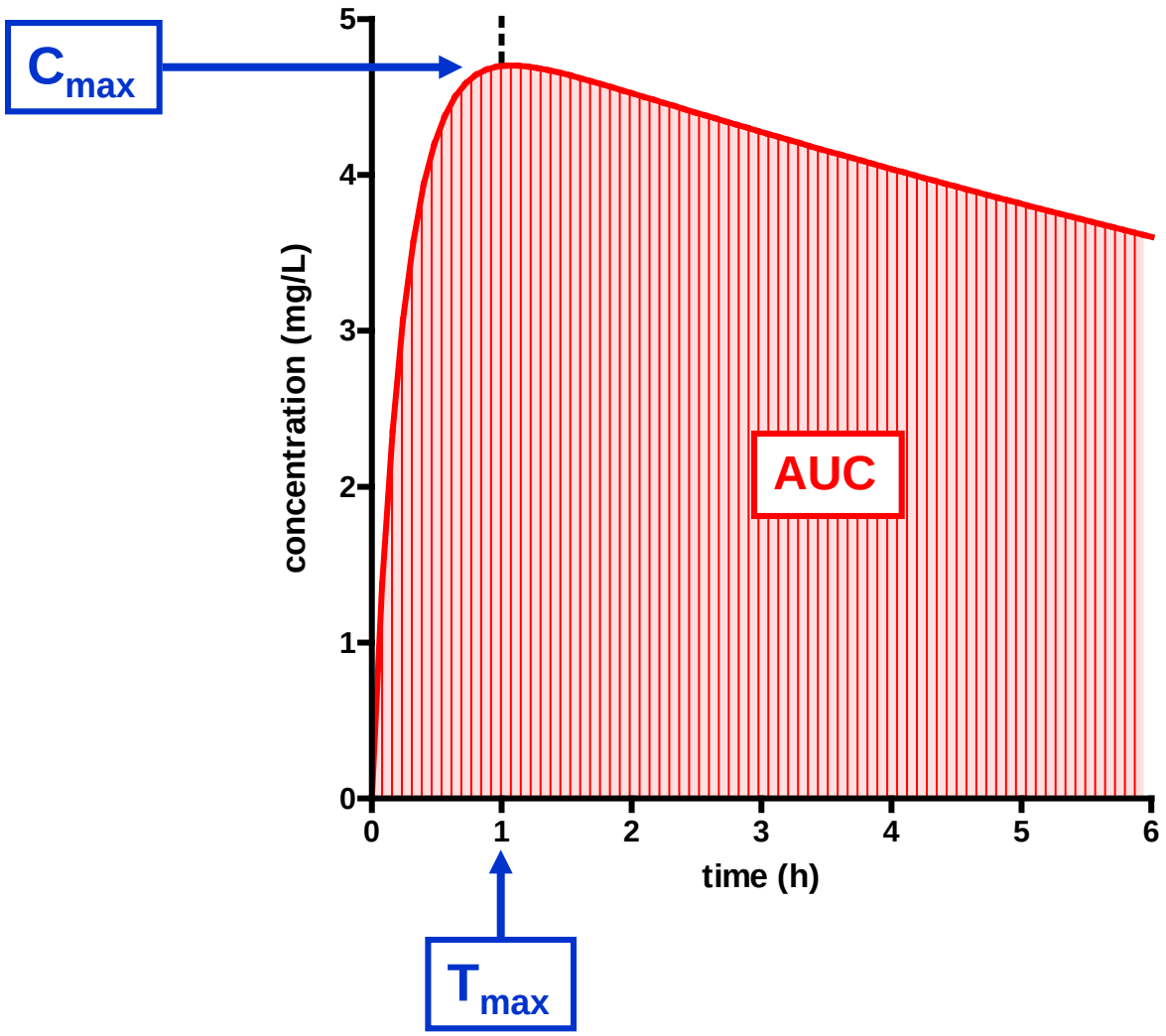
    → **rate of absorption**

1. Hauschke et al. Bioequivalence Studies in Drug Development – Methods and Applications, John Wiley & Sons Ltd. (UK), 2007. Available from the Publisher (17 Oct 2017)
2. Benet LZ: Understanding bioequivalence testing. Transplant.Proc. 31 (Suppl 3A): 7S-9S, 1999 – PMID 10330950
3. Niazi SK: Handbook of Bioequivalence Testing, "Drugs and the Pharmaceutical Sciences", vol. 171, Informa Healthcare (New York), 2007. Free download (17 Oct 2017)

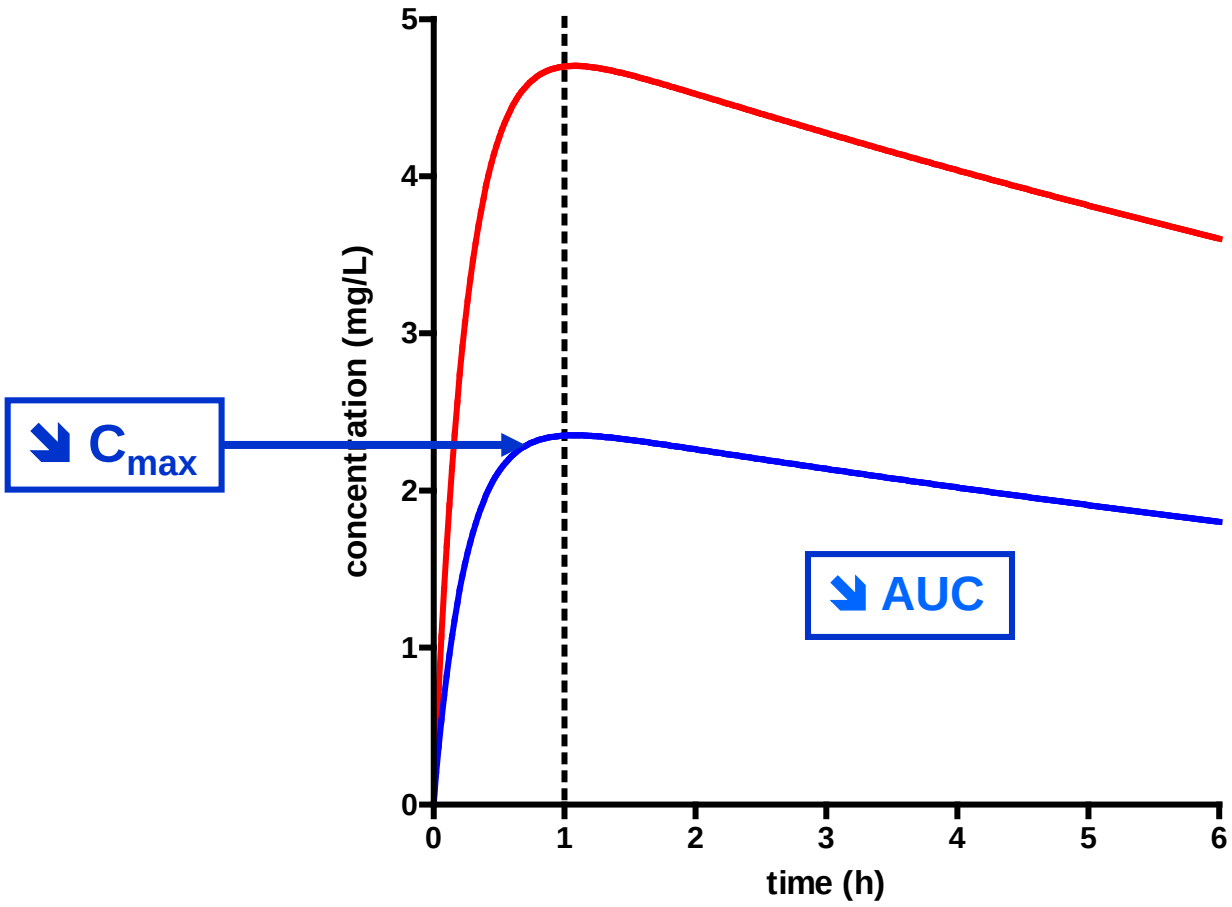
AUC – C_{max} – T_{max}



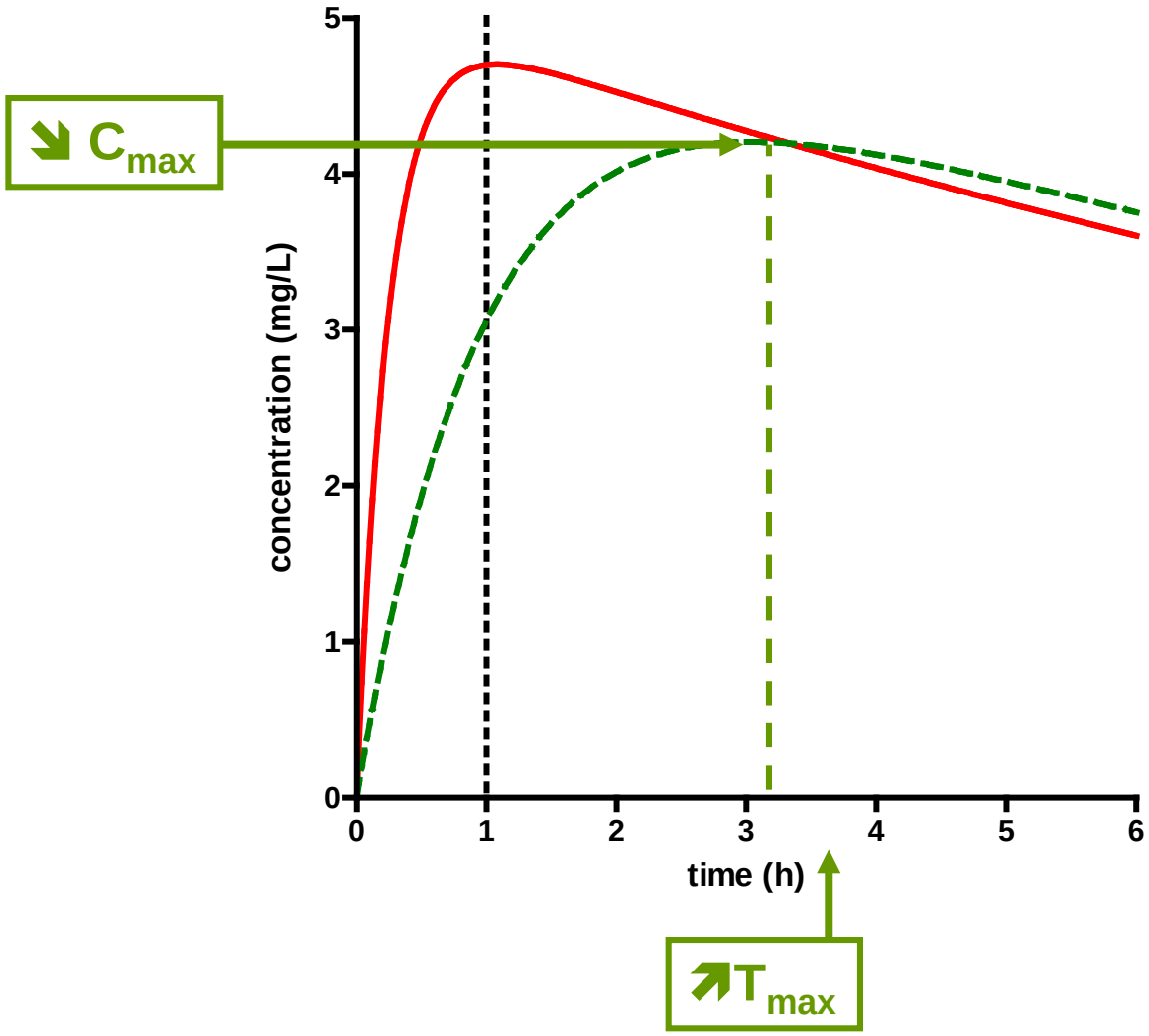
AUC – C_{max} – T_{max}



What if the absorption is decreased ?

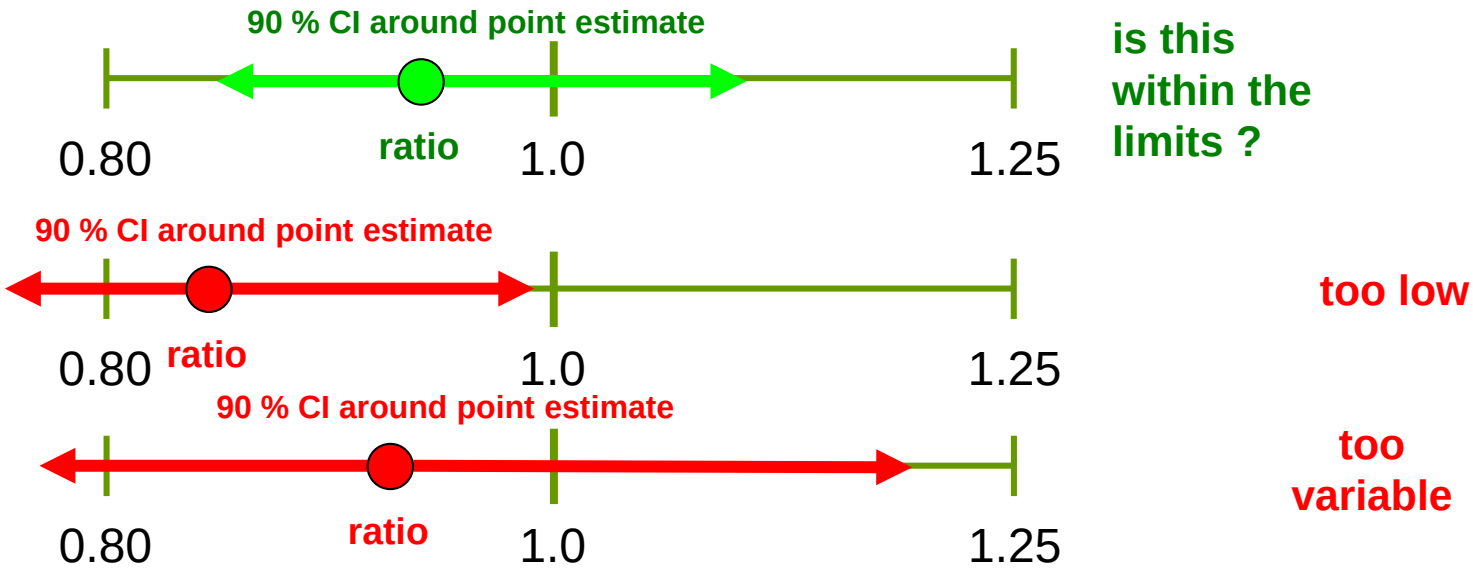


What if absorption is delayed ?



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**.

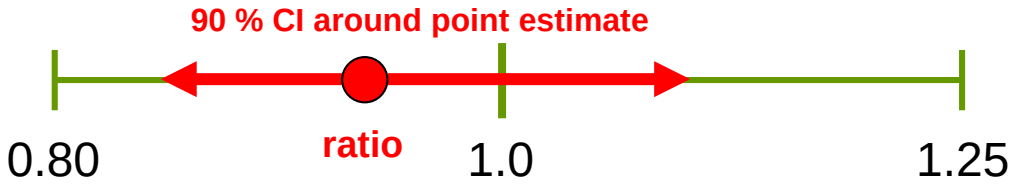


* Guideline to the Investigation of Bioequivalence, London, 20 January 2010 - Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf (Last accessed: 17 Oct 2017)

** Guidance for Industry (BIOEQUIVALENCE GUIDANCE) - Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM377465.pdf (Draft Guidance 2013 - Last accessed: 17 Oct 2017)
http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm052363.pdf (Last accessed: 17 Oct 2017)

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 $\mathbf{C_{max}}$ are within range, the generic should have the same bioavailability as the reference
2. statistical evaluation of $\mathbf{T_{max}}$ 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]

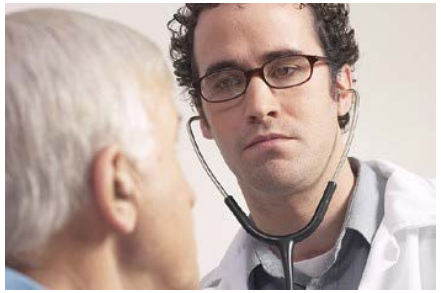
[1] Tothfalusi *et al.* Eur J Health Econ (2014) 15 (Suppl 1):S5–S11 – PMID 24832831
[2] Ahn & Lee, Ungyong Tonggye Yongu (2011) 24(3): 495–503 – PMID 23805045
[3] Lee *et al*. Nature Biotechnology (2013) 31:220-226 – PMID 23471071

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).

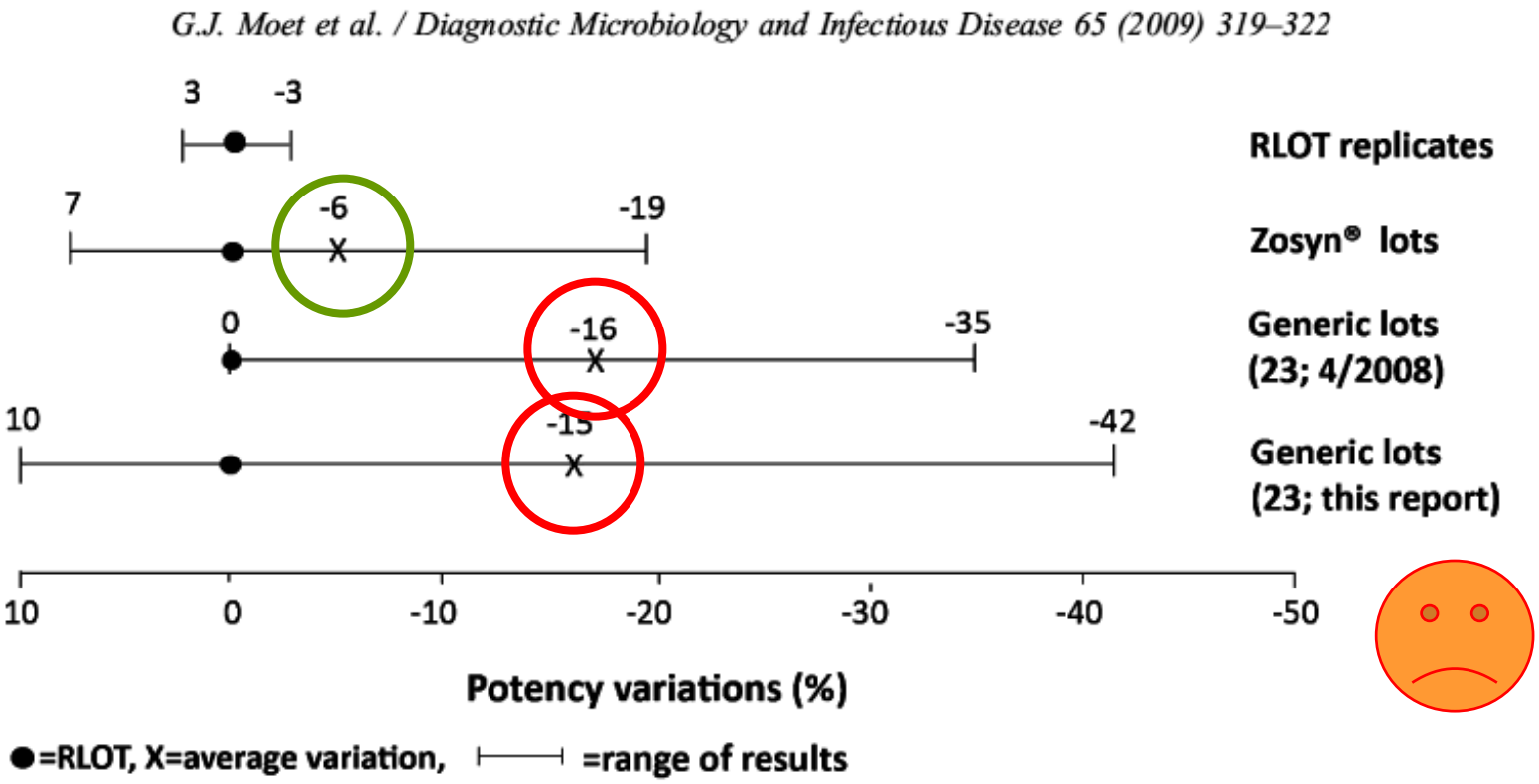


Fig. 1. Extent of potency variations among 4 groups of experiments with piperacillin/tazobactam intravenous injection lots.

Moet *et al.* Diagnostic Microbiology and Infectious Disease 2009;65:319–322 – PMID 19822271

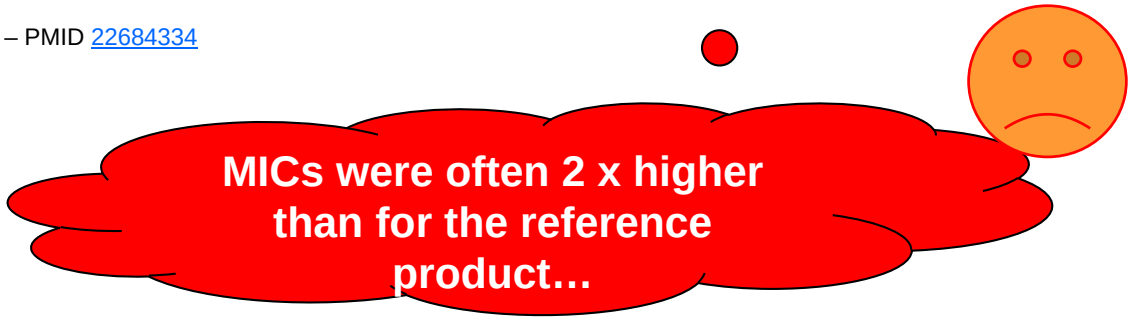
MIC values (vancomycin)

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	–

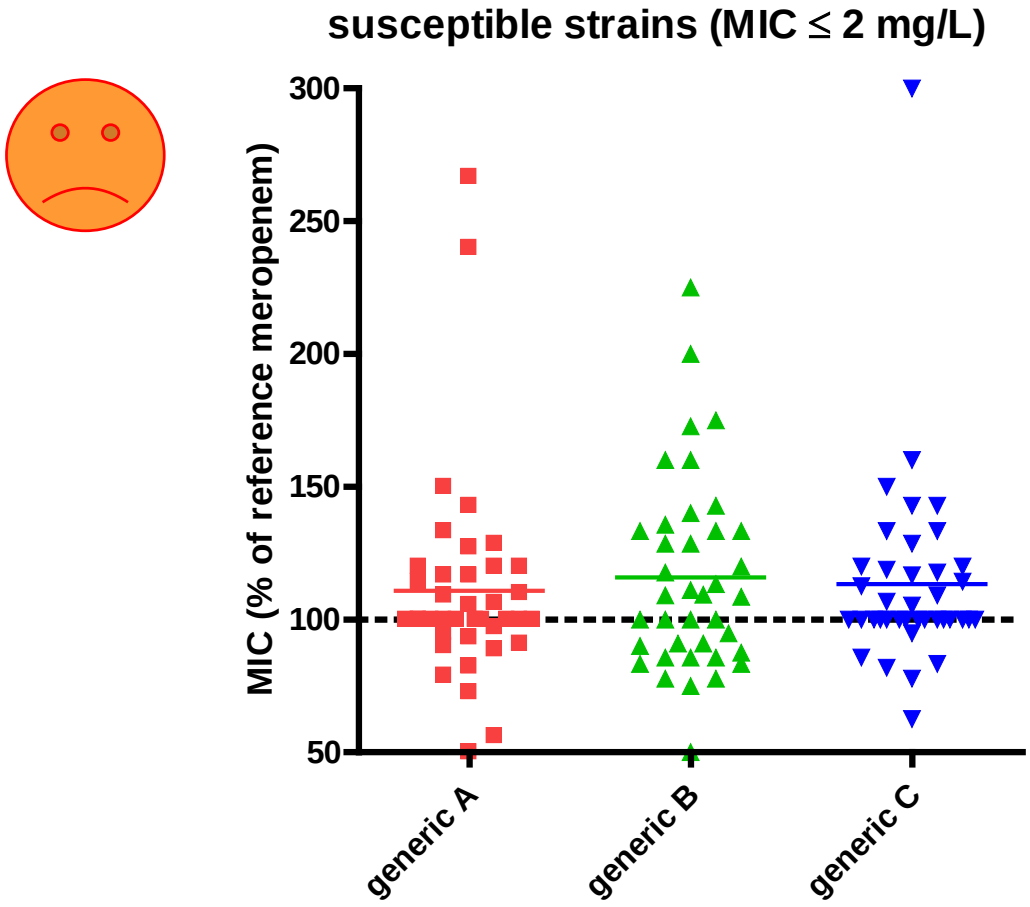
MRSA methicillin-resistant *Staphylococcus aureus*[a]Note that the distribution of one minimal inhibitory concentration (1 MIC) shows the identical rate with the brand drug: MIC was determined by broth micro-dilution method using powder in each drug vial

Fujimura & Watanabe J Infect Chemother (2012) 18:421–427 – PMID 22684334



MIC values (meropenem) in Belgium

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



Van Bambeke *et al*., unpublished

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

Neutropenic mouse thigh infection model

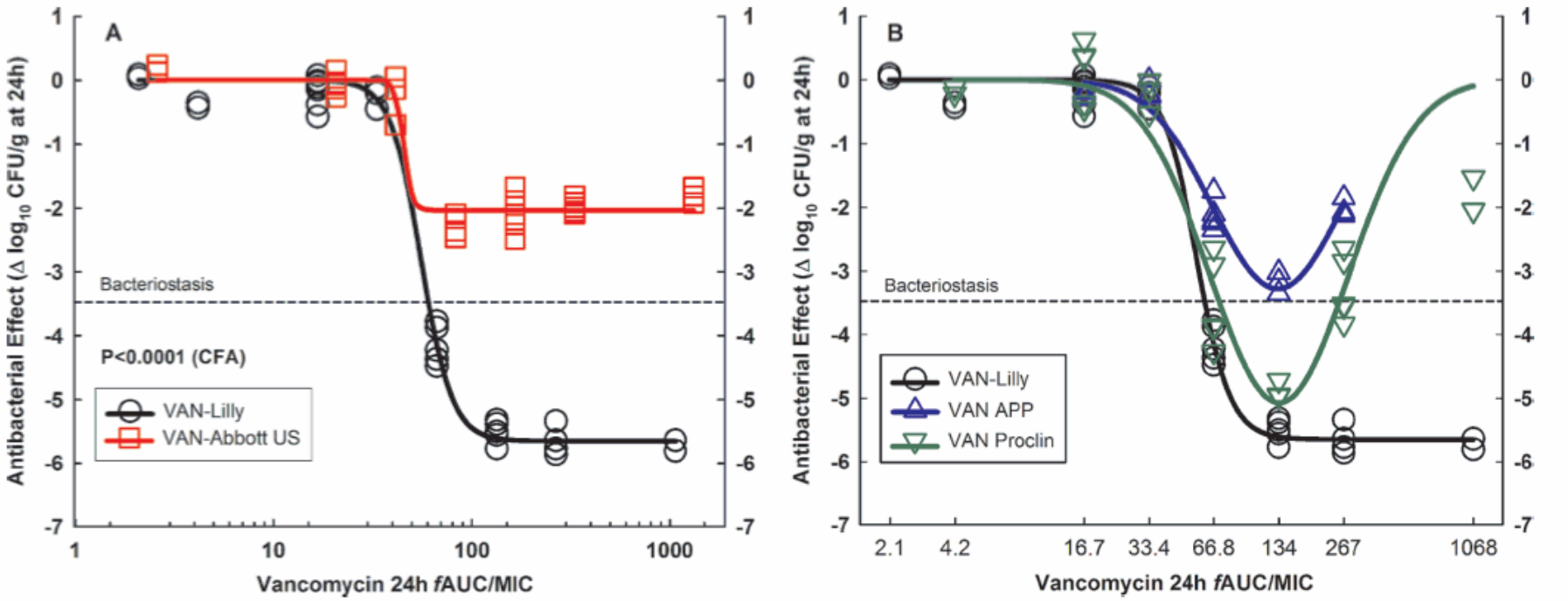


FIG. 1. *In vivo* efficacy against *S. aureus* GRP-0057 (years 2002 and 2003) at a low inoculum (4.30 ± 0.05 $\log_{10}$ CFU per thigh when subcutaneous treatment q1h started). Vancomycin generic products are compared with the innovator (VAN-Lilly) in dose-effect experiments (2.34 to 1,200 mg/kg per 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 – PMID 20547818

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

Neutropenic mouse thigh infection model

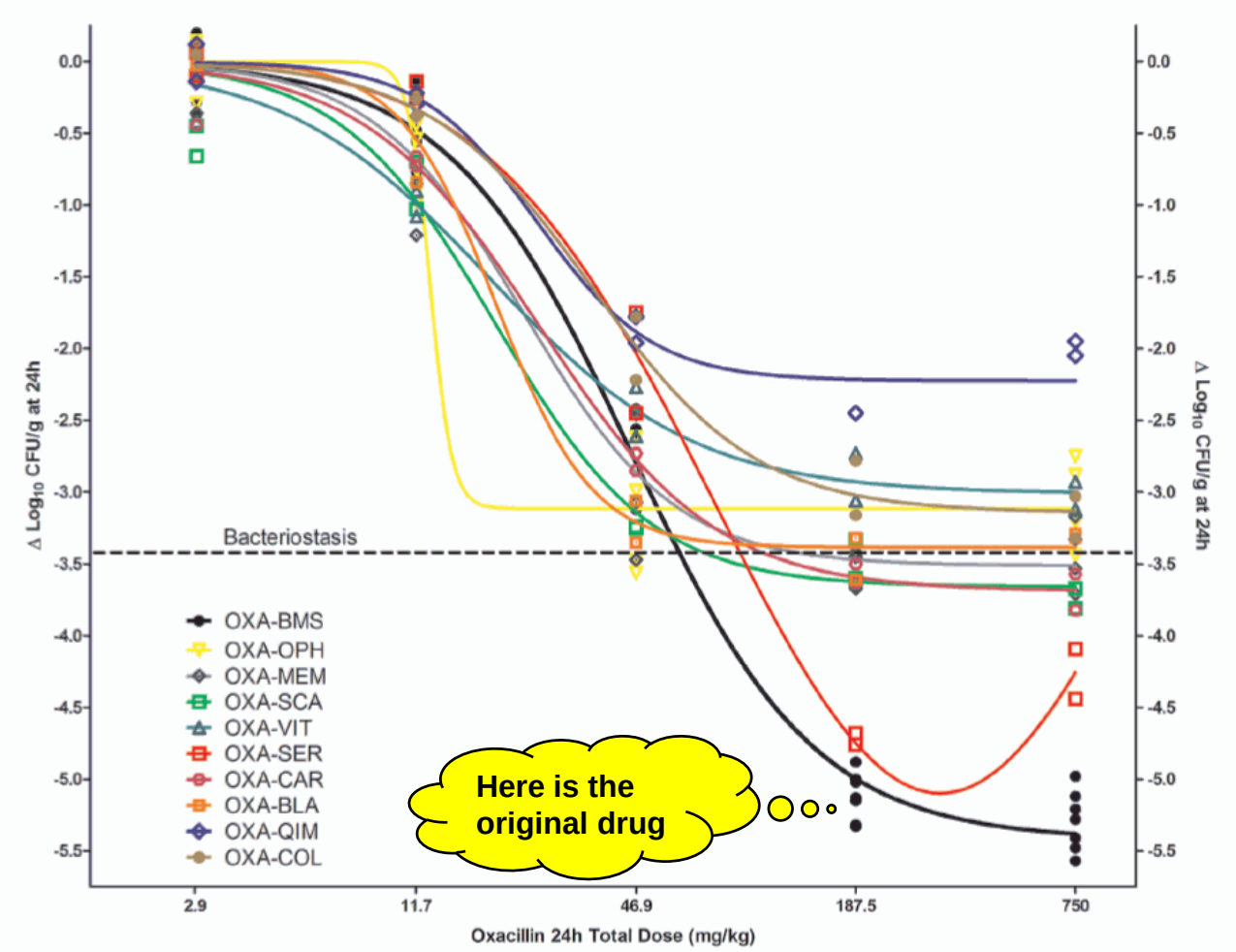


Figure 3 Dose-response relationship of the innovator and 9 generic products of oxacillin in the neutropenic mouse thigh infection model. OXA-BMS (innovator, black curve) and 8 generics fitted to Hill's sigmoid model, while generic product OXA-SER fitted to the Gaussian U-shaped model (red curve). Regardless 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 Infect Dis. 2010 Jun 4;10:153 – PMID 20525378

A series of other papers raising questions…

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

International Journal of Antimicrobial Agents 48 (2016) 753–756

journal homepage: www.elsevier.com/locate/ijantimicag

Short Communication

Post-marketing surveillance of generic amoxicillin using a microbiological assay and pharmacokinetic approach in rats

Livia I.S. de Mattos [a], Fausto K. Ferraris [a], Tiago S.C. Machado [a], Thais M. de Brito [a], Amanda S. Chaves [a], Heliana M. Pereira [b], Douglas P. Pinto [b], Diego M.D. da Silva [b], Fabio C. Amendoeira [a,*,1]

[a] Instituto Nacional de Controle de Qualidade em Saúde, Fundação Oswaldo Cruz, (INCQS/Fiocruz), Av. Brasil, 4365—Manguinhos, Rio de Janeiro, RJ 21040-900, Brazil
[b] Laboratório de Farmacocinética, Fundação Oswaldo Cruz (Fiocruz), Manguinhos, Rio de Janeiro, RJ, Brazil

Contents lists available at ScienceDirect

Diagnostic Microbiology and Infectious Disease

Diagnostic Microbiology and Infectious Disease 85 (2016) 347–351

journal homepage: www.elsevier.com/locate/diagmicrobio

Antimicrobial Susceptibility Studies

Bioequivalence and in vitro antimicrobial activity between generic and brand-name levofloxacin

Hsin-Yun Sun [a], Hsiao-Wei Liao [b], Meng-Huei Sheng [c], Hui-Min Tai [a], Ching-Hua Kuo [b,d], Wang-Huei Sheng [a,*]

[a] Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan
[b] School of Pharmacy, College of Medicine, National Taiwan University, Taipei, Taiwan
[c] Jia-Nan University of Pharmacy and Science, Tainan, Taiwan
[d] Department of Pharmacy, National Taiwan University Hospital, Taipei, Taiwan

pharmaceutics

MDPI

Pharmaceutics 2017, 9, 18; doi:10.3390/pharmaceutics9020018

Article

Quality Attributes and In Vitro Bioequivalence of Different Brands of Amoxicillin Trihydrate Tablets

Moawia M. Al-Tabakha [1,*], Khairi M. S. Fahelelbom [2], Dana Emad Eddin Obaid [2] and Sadik Sayed [2]

1 Pharmaceutics Unit, College of Pharmacy and Health Sciences, Ajman University, P.O. Box 346, Ajman, UAE
2 Department of Pharmaceutical Sciences, College of Pharmacy, Al-Ain University of Science and Technology, P.O. Box 64141, Al Ain, UAE; khairi.mustafa@aau.ac.ae (K.M.S.F.); dana.obaid@aau.ac.ae (D.E.E.O.); sadik.sayed@aau.ac.ae (S.S.)
* Correspondence: sphmaa@hotmail.com; Tel.: +971-6-705-6208

G Model
JIPH-687; No. of Pages 2

ARTICLE IN PRESS

Contents lists available at ScienceDirect

Journal of Infection and Public Health

journal homepage: http://www.elsevier.com/locate/jiph

Letter to the Editor

Relative potency of different generic brands of Piperacillin–Tazobactam: Implications for public health

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

International Journal of Antimicrobial Agents 49 (2017) 189–197

journal homepage: www.elsevier.com/locate/ijantimicag

In vivo pharmacodynamics of piperacillin/tazobactam: implications for antimicrobial efficacy and resistance suppression with innovator and generic products

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

[a] GRIPE (Grupo Investigador de Problemas en Enfermedades Infecciosas), Facultad de Medicina, Universidad de Antioquia, Medellín, Antioquia, Colombia
[b] Infectious Diseases Unit, Hospital Universitario San Vicente Fundación, Medellín, Colombia

Piperacillin/tazobactam generics and resistance

PLOS ONE

RESEARCH ARTICLE

Impact on Bacterial Resistance of Therapeutically Nonequivalent Generics: The Case of Piperacillin-Tazobactam

Carlos A. Rodriguez[1], Maria Agudelo[1,2], Yudy A. Aguilar[1], Andres F. Zuluaga[1], Omar Vesga[1,2]*

1 GRIPE (*Grupo Investigador de Problemas en Enfermedades Infecciosas*), Facultad de Medicina, Universidad de Antioquia, Medellín, Colombia, 2 Infectious Diseases Unit, Hospital Universitario San Vicente Fundación, Medellín, Colombia

Rodriguez *et al.* PLoS One. 2016;11:e0155806 - PMID 27191163

After only 24 hours of treatment in the neutropenic murine thigh infection model, the generic amplified the resistant subpopulation up to 20-times compared with the innovator.

Piperacillin/tazobactam generics and resistance

PLOS ONE

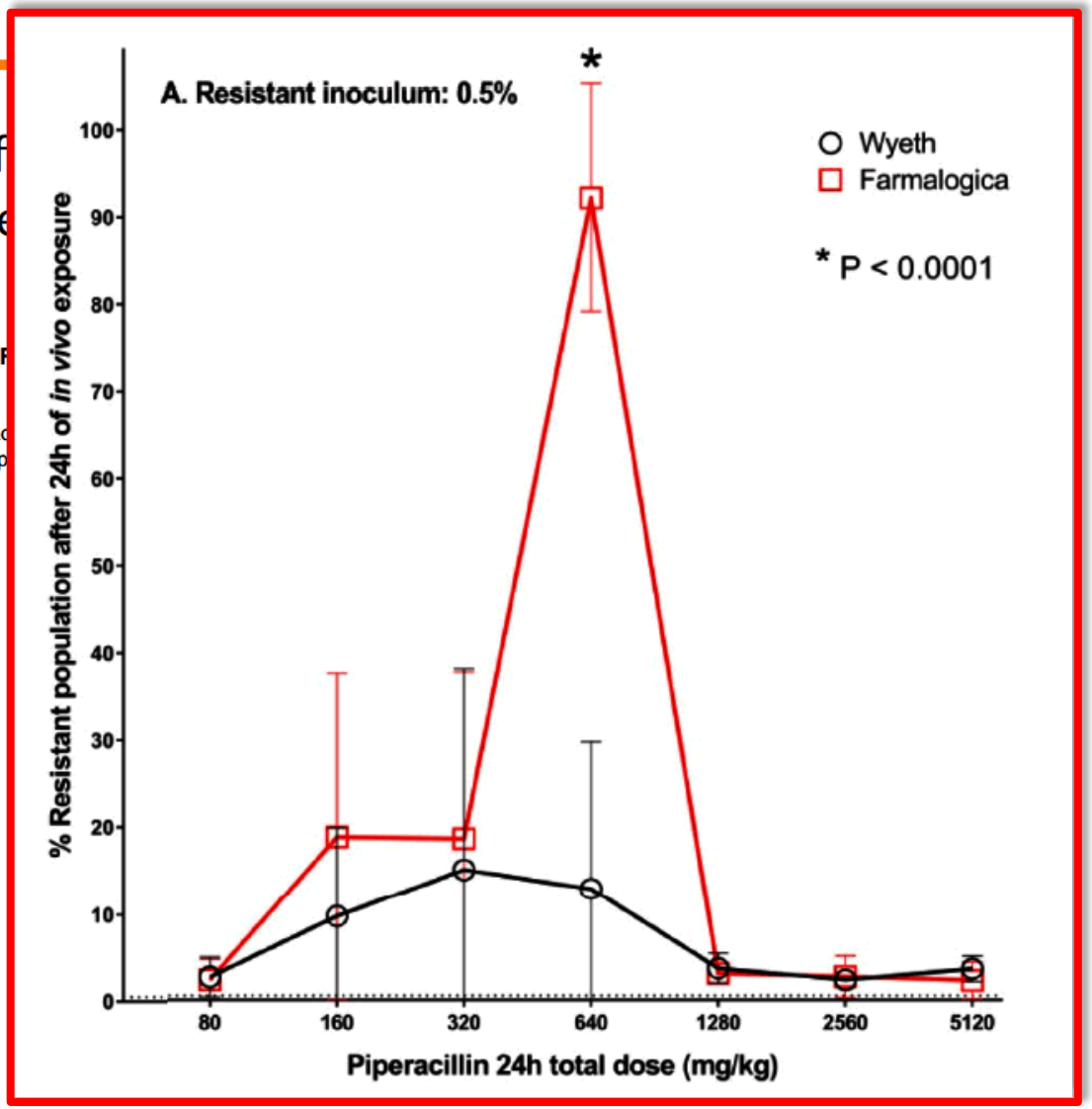
RESEARCH ARTICLE

Impact on Bacterial Resistance of Therapeutically Nonequivalent Ge Case of Piperacillin-Tazobactam

Carlos A. Rodriguez[1], Maria Agudelo[1,2], Yudy A. Aguilar[1], Andres F Omar Vesga[1,2]*

1 GRIPE (*Grupo Investigador de Problemas en Enfermedades Infecciosas*), Fac Universidad de Antioquia, Medellín, Colombia, 2 Infectious Diseases Unit, Hosp Vicente Fundación, Medellín, Colombia

Rodriguez *et al.* PLoS One. 2016;11:e0155806 - PMID 27191163



Resistance proportion after *in vivo* exposure of a mixed *E. coli* population to innovator (Wyeth) and generic (Farmalogica). The generic significantly enriched the resistant subpopulation at 640 mg/kg per day (P<0.0001), without differences at the other doses.

But pharmacodynamics equivalence can also be demonstrated

AAC Journals.ASM.org

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]

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

Rodriguez *et al.* Antimicrob Agents Chemother 2015;59:53-58 - PMID 25313208

But pharmacodynamics equivalence can also be demonstrated

AAC Journals.ASM.org

Antimicrob Agents Ch

Impact on Resistance of the Us Generics: the Case of Ciproflox

Carlos A. Rodriguez,[a,b] Maria Agudelo,[a,b,d] Andres F. Zu

GRIPE: Grupo Investigador de Problemas en Enfermedades Infecciosas,[a] D
University of Antioquia, Medellin, Colombia; Infectious Diseases Unit, Hosp

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

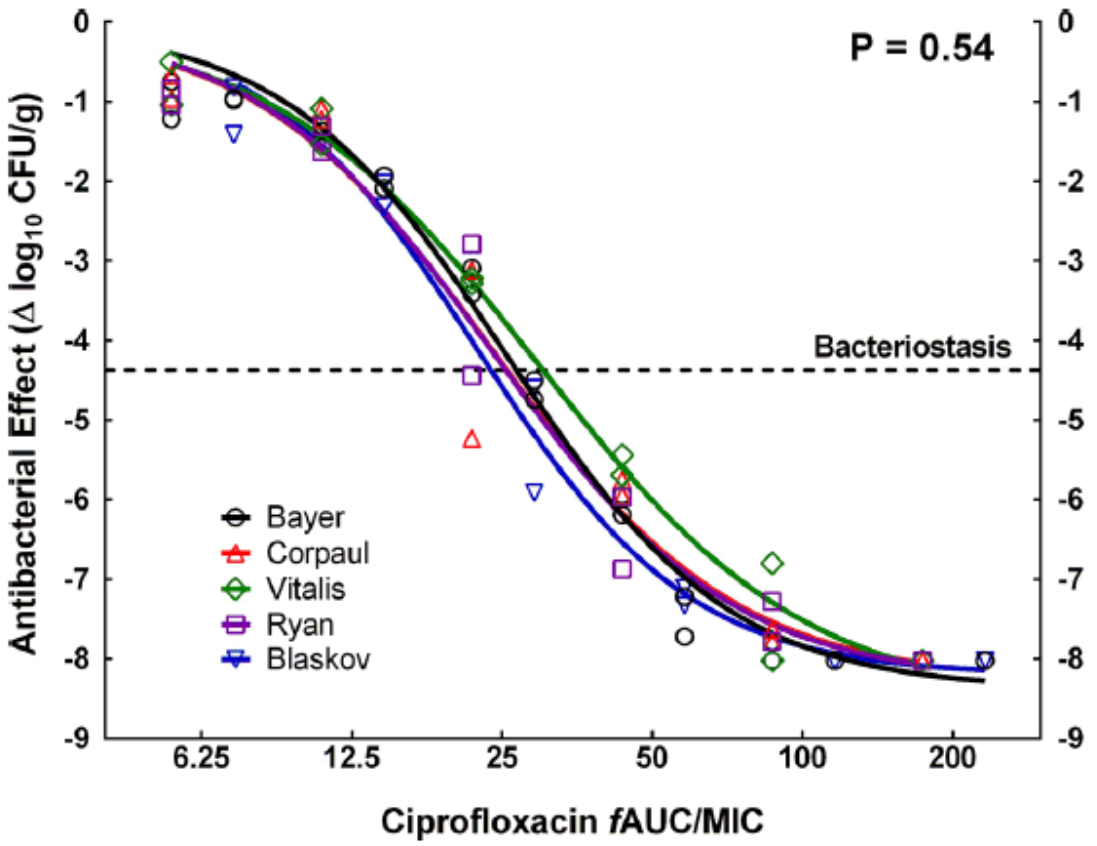


FIG 1 *In vivo* exposure-response relationship of ciprofloxacin against *P. aeruginosa* PAO1, comparing the innovator and four generic products. Global CFA indicated that all data belonged to the same population and could be described by a single curve, confirming the therapeutic equivalence of the generics.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

Rodriguez *et al.* Antimicrob Agents Chemother 2015;59:53-58 - PMID 25313208

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

Gallelli *et al.* J Pharmacol Pharmacother. 2013;4(Suppl 1):S110-114 - PMID 24347975

"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

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.

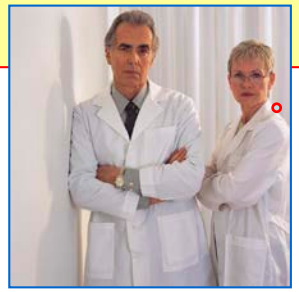
ACKNOWLEDGMENTS

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

Gallelli *et al.* J Pharmacol Pharmacother. 2013;4(Suppl 1):S110-114 - PMID 24347975

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

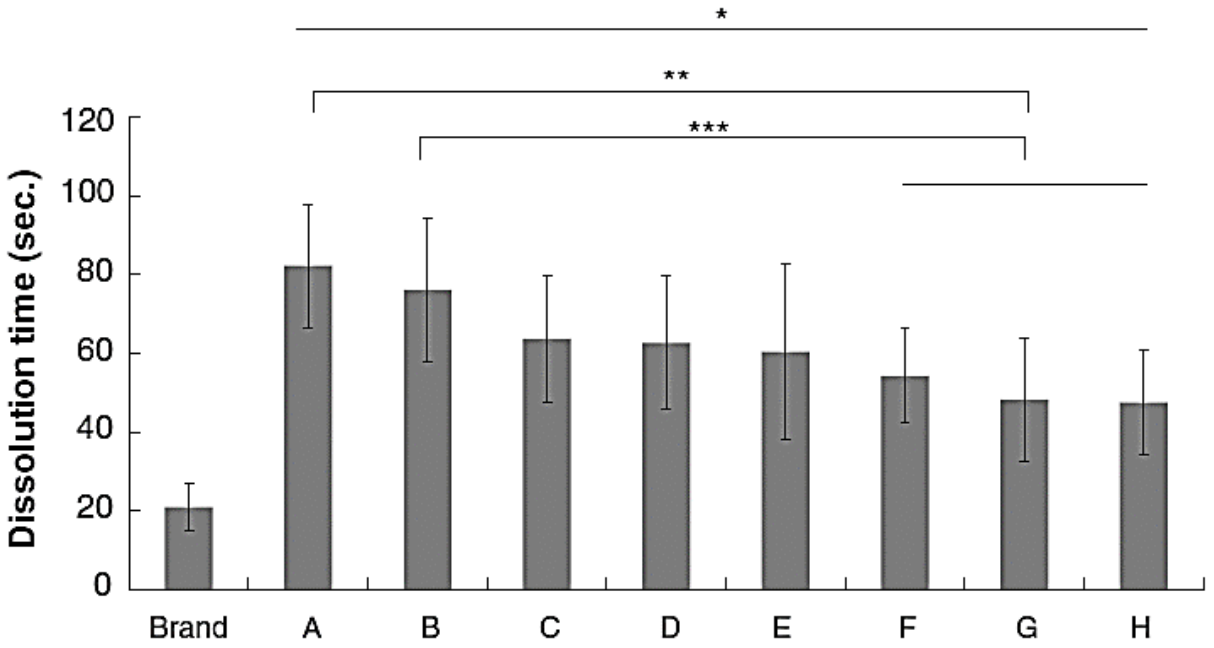


Fig. 3 Comparison of dissolution time between brand name meropenem and eight generics. *A–H* Generic products of meropenem. $*P < 0.001$ versus brand name drug; $**P < 0.001$ versus generic A drug; $***P < 0.001$ versus generic B drug

Fujimura & Watanabe J Infect Chemother (2012) 18:421–427 – PMID 22684334

Crystals size in meropenem in Japan

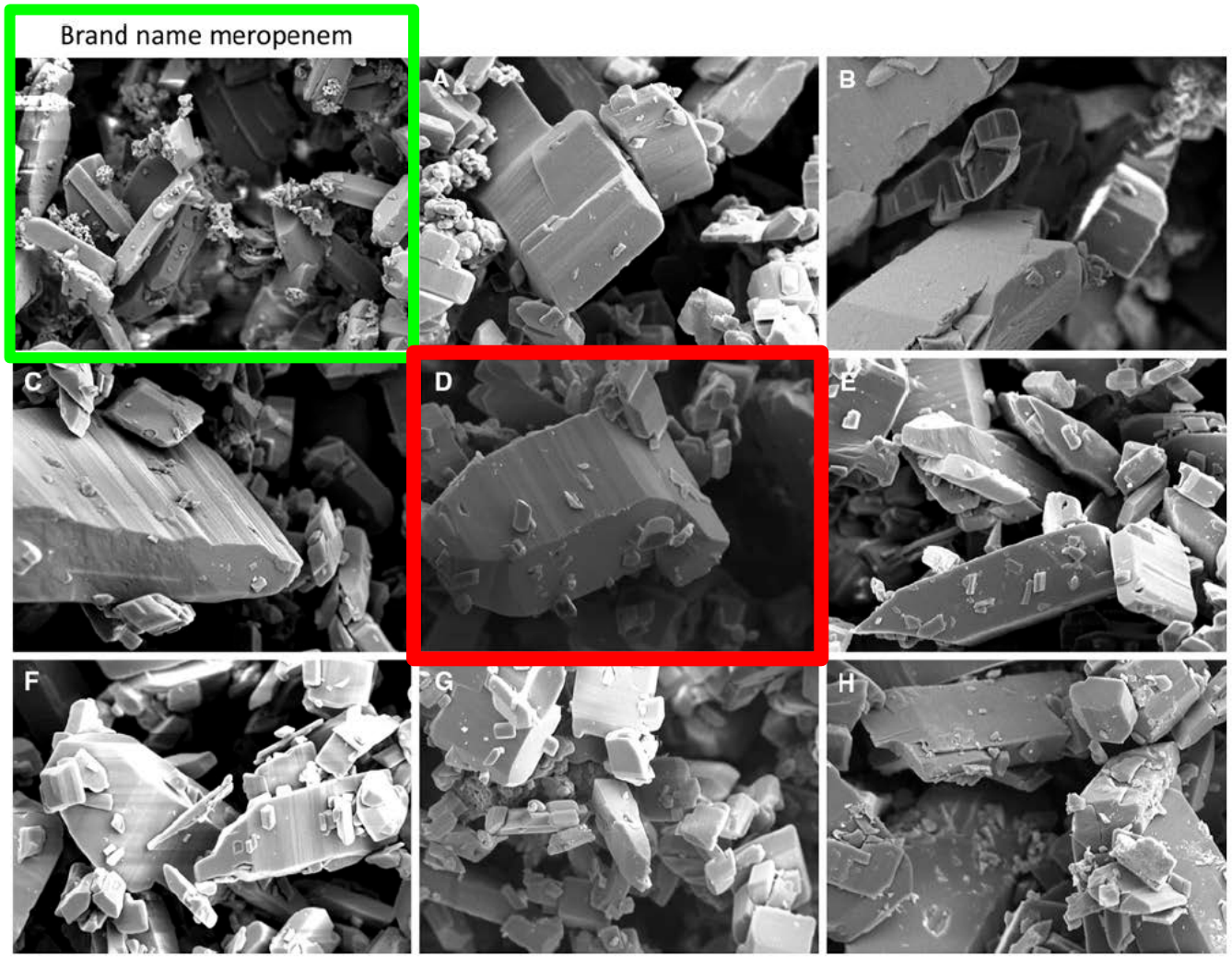
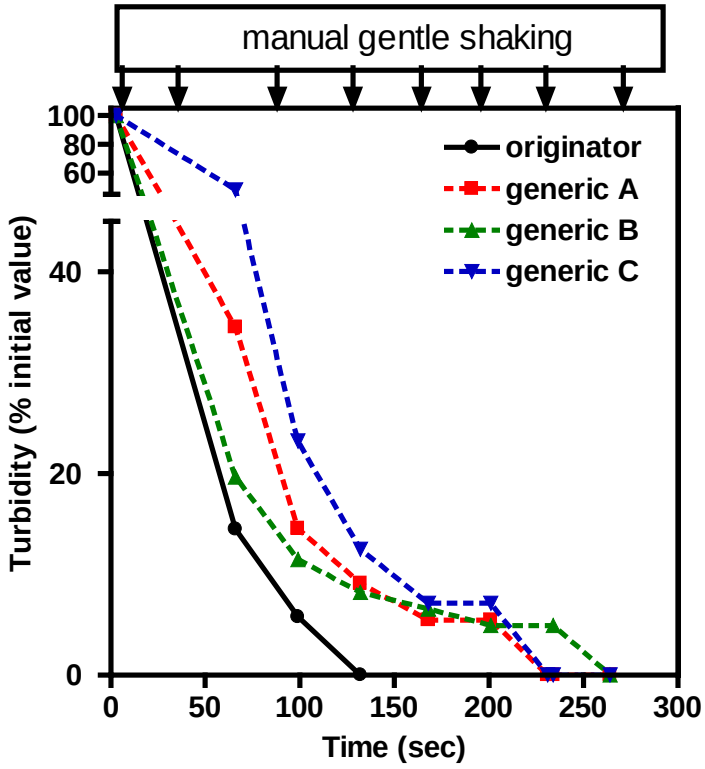


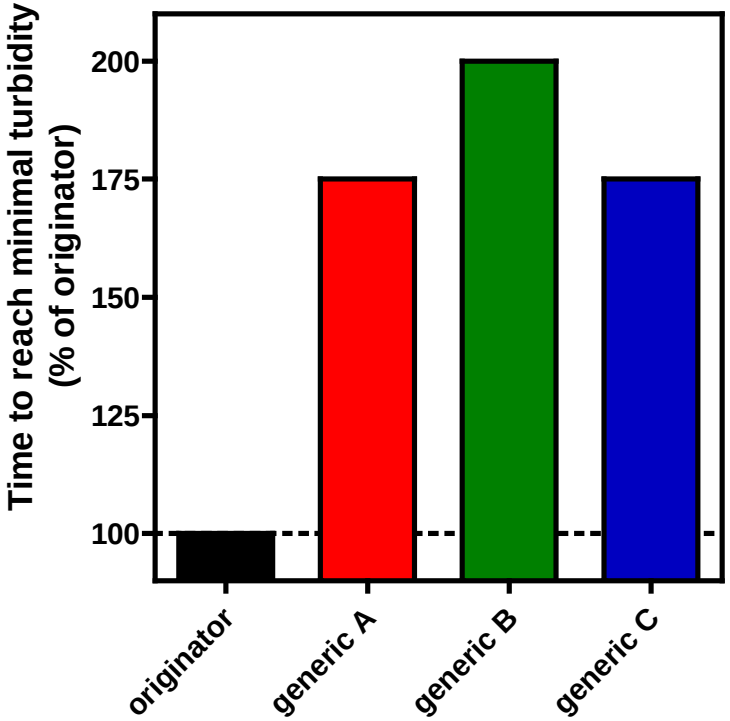
Fig. 4 Electron micrographs of drug particles of brand name meropenem and eight generics. **a–h** Generic products of meropenem. ×1,000

Fujimura & Watanabe J Infect Chemother (2012) 18:421–427 – PMID 22684334

Dissolution of meropenem in Belgium

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

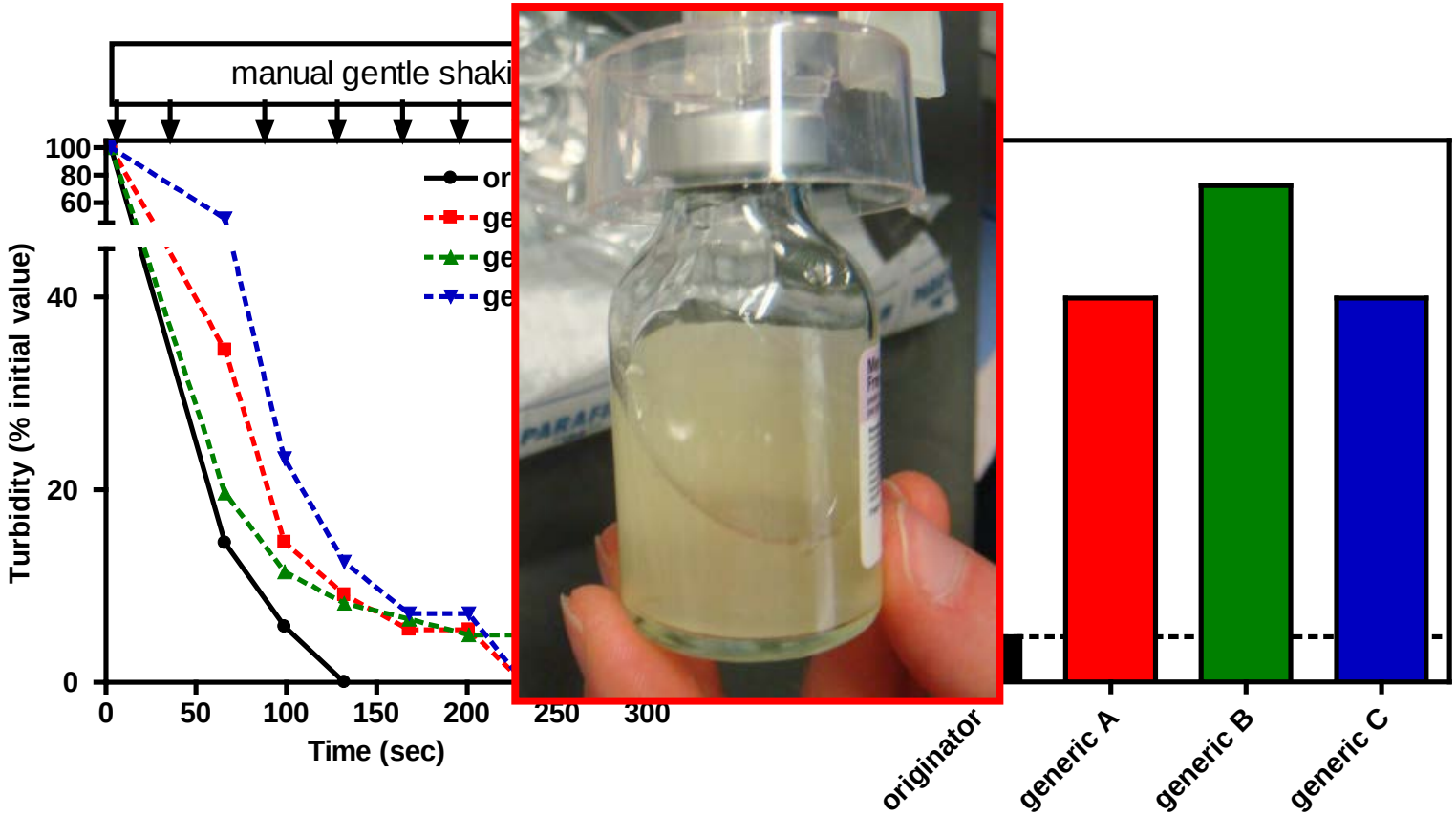




Delattre et al. 30th International Congress of Chemotherapy, Taipei, Taiwan – poster #724 (to be presented)

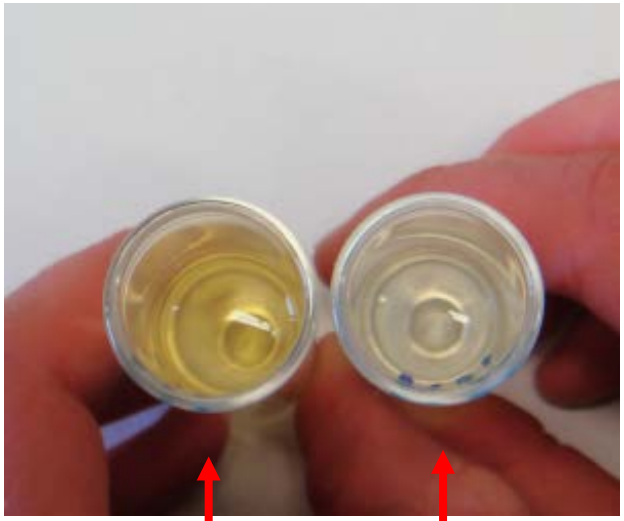
Dissolution of meropenem in Belgium

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



Delattre et al. 30th International Congress of Chemotherapy, Taipei, Taiwan – poster #724 (to be presented)

Impurities in meropenem: coloured compounds

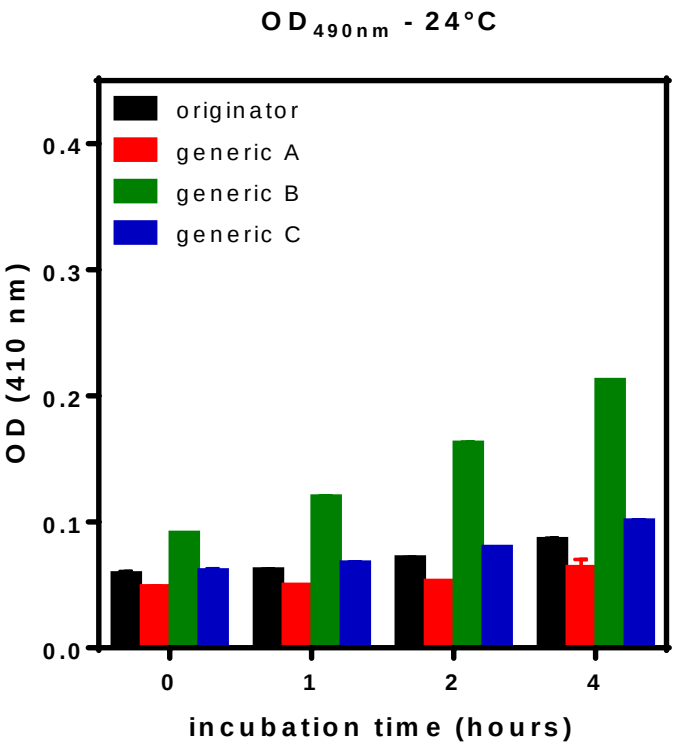


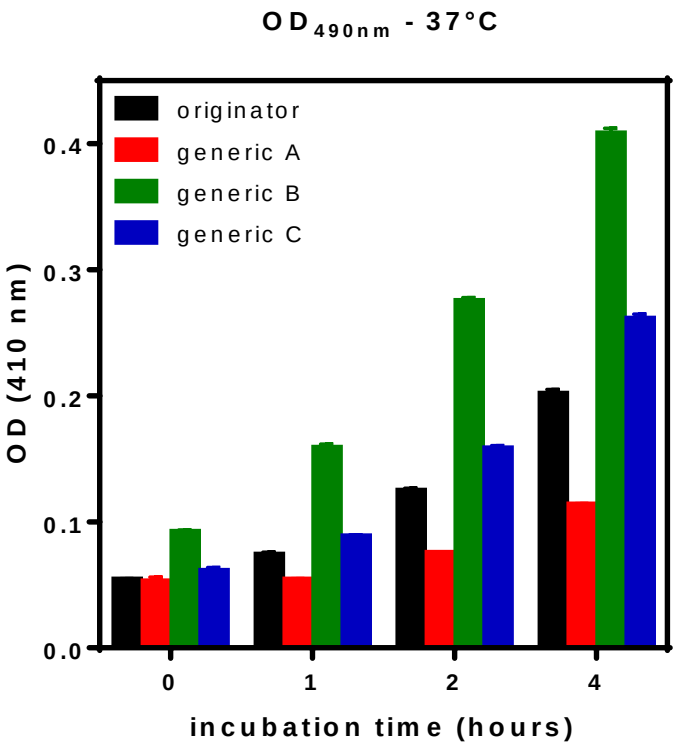
generic B **originator**

are you happy with the colour?

Delattre et al. 30th International Congress of Chemotherapy, Taipei, Taiwan – poster #724 (to be presented)

Impurities in meropenem: coloured compounds





Delattre et al. 30th International Congress of Chemotherapy, Taipei, Taiwan – poster #724 (to be presented)

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

Trefi *et al.* J Pharm Biomed Anal 2007;44:743-754 - PMID 17446031

Impurities in ciprofloxacin

This is a synthesis precursor !

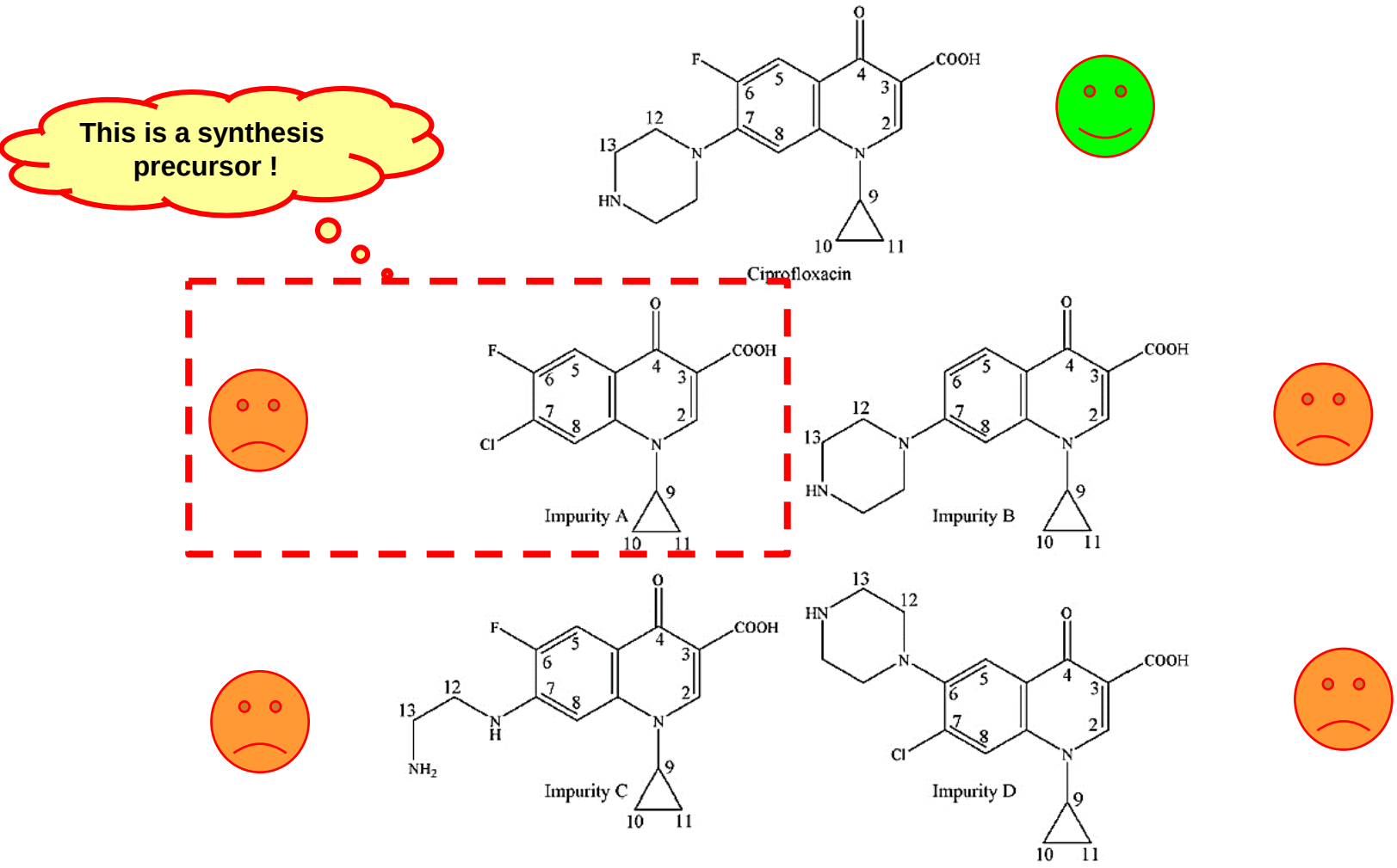


Fig. 1. Structure of ciprofloxacin and its main impurities.

Trefi *et al.* J Pharm Biomed Anal 2007;44:743-754 - PMID 17446031

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
Published 29 Feb 2015 - Last accessed 17 Oct 2017

MEDIPLANET

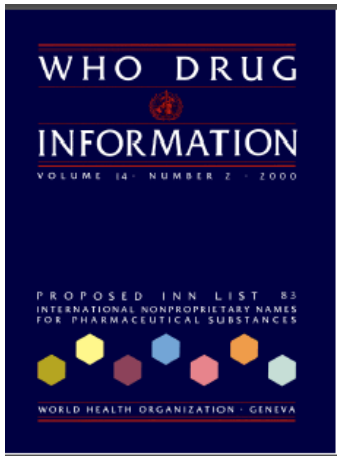
Génériques: 8 nouveaux médicaments retirés du marché en France

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 list makes 135 pages

And problems in the World known since 2000…



WHO Drug Information Vol. 14, No. 2, 2000

General Policy Issues

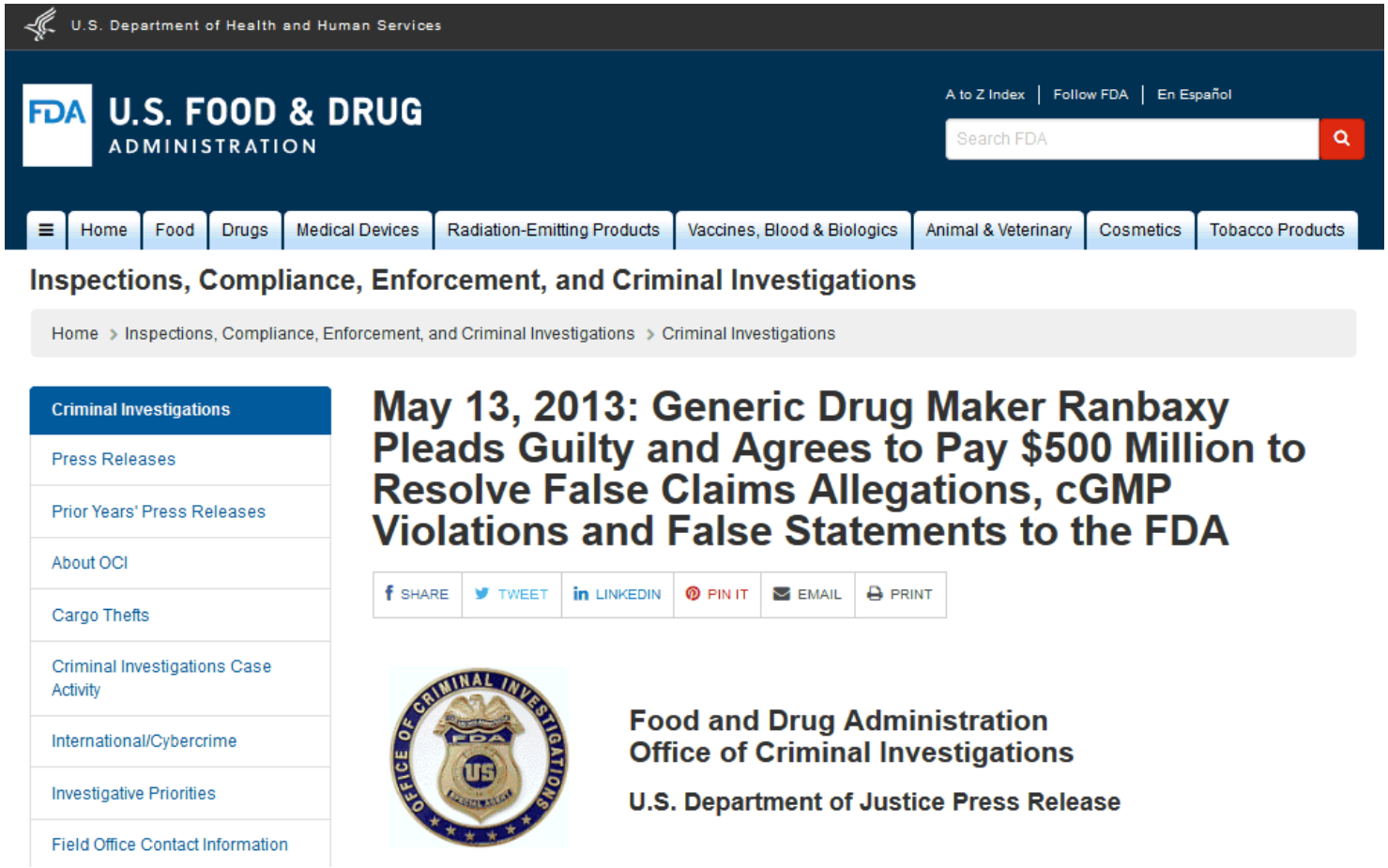
Generic drugs: the hidden issues of quality and cost

Jean-Yves Videau, General Manager, Centrale humanitaire médicopharmaceutique (CHMP), France, (http://www.chmp.org) in collaboration with Bonnie Fundafunda, Echo International Health Services, United Kingdom (http://www.echohealth.org.uk)

Available for download at http://apps.who.int/medicinedocs/pdf/h1463e/h1463e.pdf
Last accessed: 19 Oct 2017

Although the manufacture of generic essential drugs offers a practical way of [providing an acceptable level of health care at a reasonable cost], the quality of these products tends to be jeopardized by overriding considerations of cost.

and led to criminal investigations in the US…



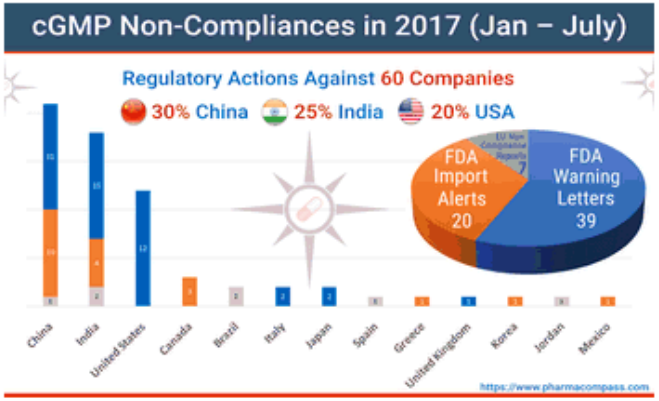
https://www.fda.gov/ICECI/CriminalInvestigations/ucm433761.htm
Last accessed: 19 Oct 2017

But the story continues…

PHARMACOMPASS
Grow Your Pharma Business Digitally

Mid-2017 Recap of FDA Warning Letters, Import Alerts & EU Non-Compliances

Created: 10 Aug 2017 View: 2774



Last year, data integrity was a hot topic of discussion in the pharmaceutical industry. According to a recent analysis by GMP (good manufacturing practices) intelligence expert, Barbara Unger, approximately 80 percent of all FDA warning letters in 2015 and 2016 included a data integrity component, and approximately 70 percent of the published European GMP non-compliance reports cited similar shortcomings.

With a little over half the year gone, *PharmaCompass* analyzed the regulatory action for current GMP (cGMP) non-compliance to evaluate how things are looking so far in 2017.

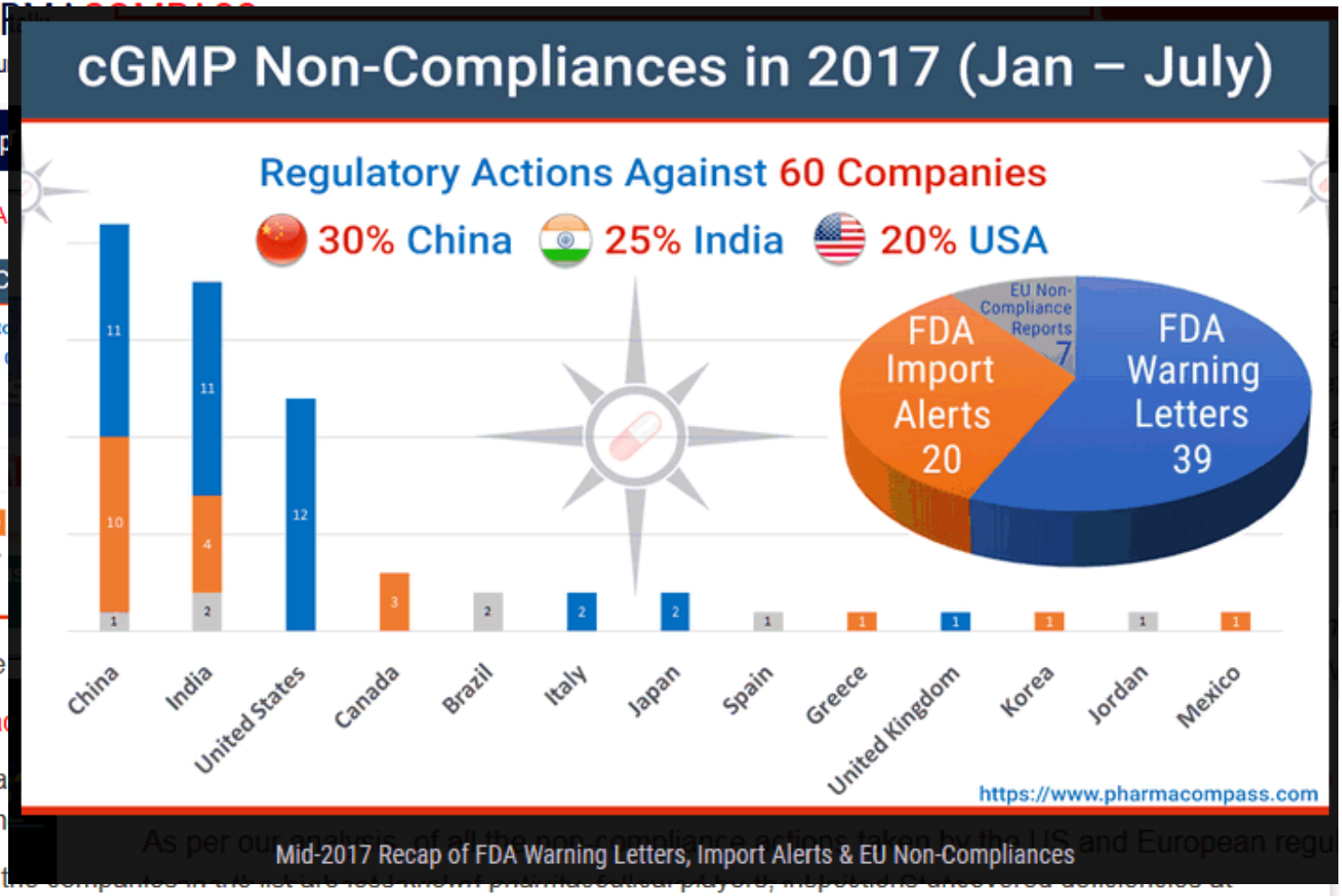
Click here to access the compilation of all 2017 non-compliances (Excel version available) for FREE!

As per our analysis, of all the non-compliance actions taken by the US and European regulators, India and China continue to see the highest level of activity, followed by the United States.

While most of the companies in the list are less known pharmaceutical players, inspections uncovered deficiencies at leading companies like Pfizer, Teva, Mylan and B Braun.

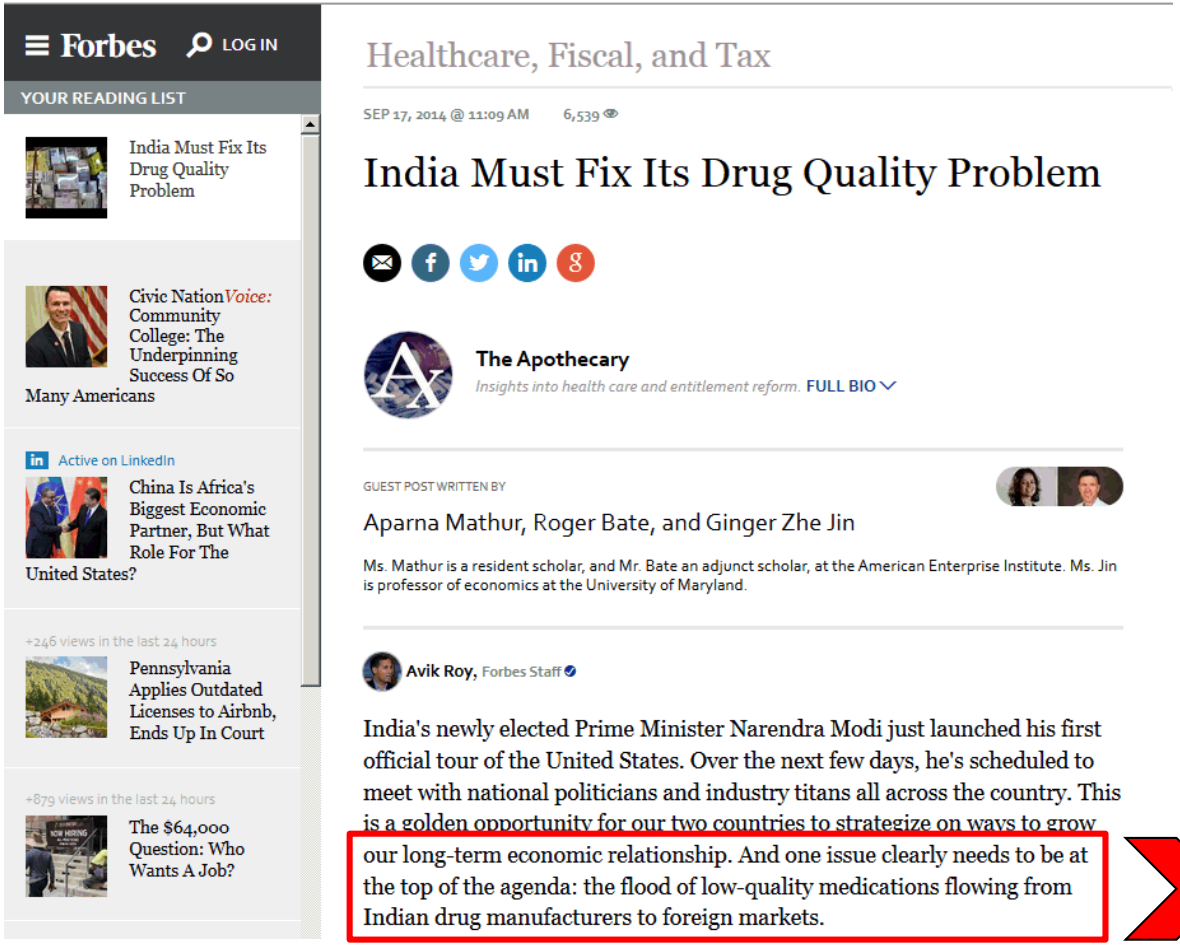
https://www.pharmacompass.com/radio-compass-blog/mid-2017-recap-of-fda-warning-letters-import-alerts-eu-non-compliances
Last accessed: 19 Oct 2017

But the story continues…



https://www.pharmacompass.com/radio-compass-blog/mid-2017-recap-of-fda-warning-letters-import-alerts-eu-non-compliances
Last accessed: 19 Oct 2017

And we know the origins…



Forbes LOG IN

YOUR READING LIST

India Must Fix Its Drug Quality Problem

Civic Nation *Voice:* Community College: The Underpinning Success Of So Many Americans

Active on LinkedIn

China Is Africa's Biggest Economic Partner, But What Role For The United States?

+246 views in the last 24 hours

Pennsylvania Applies Outdated Licenses to Airbnb, Ends Up In Court

+879 views in the last 24 hours

The $64,000 Question: Who Wants A Job?

Healthcare, Fiscal, and Tax

SEP 17, 2014 @ 11:09 AM 6,539

India Must Fix Its Drug Quality Problem

The Apothecary

Insights into health care and entitlement reform. FULL BIO

GUEST POST WRITTEN BY

Aparna Mathur, Roger Bate, and Ginger Zhe Jin

Ms. Mathur is a resident scholar, and Mr. Bate an adjunct scholar, at the American Enterprise Institute. Ms. Jin is professor of economics at the University of Maryland.

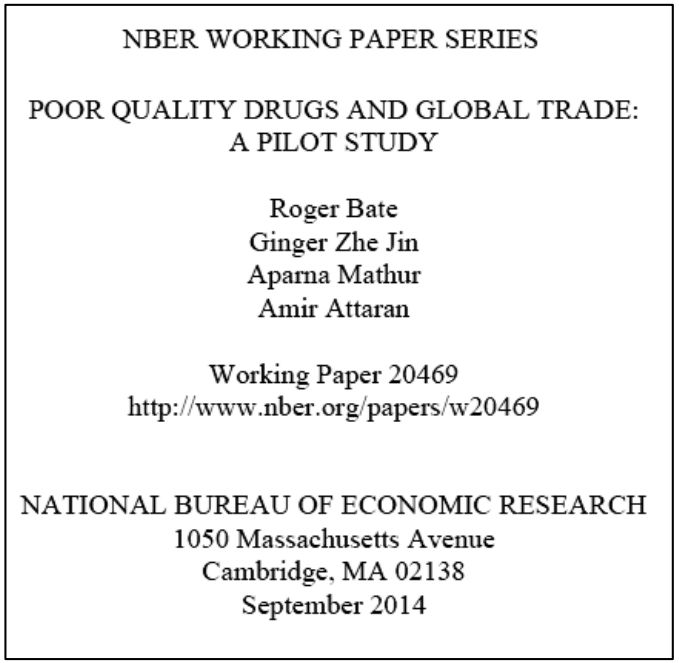
Avik Roy, Forbes Staff

India's newly elected Prime Minister Narendra Modi just launched his first official tour of the United States. Over the next few days, he's scheduled to meet with national politicians and industry titans all across the country. This is a golden opportunity for our two countries to strategize on ways to grow our long-term economic relationship. And one issue clearly needs to be at the top of the agenda: the flood of low-quality medications flowing from Indian drug manufacturers to foreign markets.

https://www.forbes.com/sites/theapothecary/2014/09/17/india-must-fix-its-drug-quality-problem/#5ebd4e0e70b3
Last accessed: 19 Oct 2017

And one issue clearly needs to be at the top of the agenda: **the flood of low-quality medications flowing from Indian drug manufacturers to foreign markets.**

Drug quality may vary according to whom the drugs are sold …



NBER WORKING PAPER SERIES

POOR QUALITY DRUGS AND GLOBAL TRADE:
A PILOT STUDY

Roger Bate
Ginger Zhe Jin
Aparna Mathur
Amir Attaran

Working Paper 20469
http://www.nber.org/papers/w20469

NATIONAL BUREAU OF ECONOMIC RESEARCH
1050 Massachusetts Avenue
Cambridge, MA 02138
September 2014

Available from http://www.nber.org/papers/w20469
Last accessed: 19 Oct 2017

Pharmaceutical experts anecdotally have observed that some Indian manufacturers sell inferior medicines to markets where drug regulatory oversight is weak, and better medicines to markets where oversight is more effective.

US and EU common actions for drug quality…


U.S. Department of Health and Human Services

FDA U.S. FOOD & DRUG ADMINISTRATION

FDA takes unprecedented step toward more efficient global pharmaceutical manufacturing inspections

Agency completes eight capability assessments as part of the Mutual Recognition Agreement between the U.S. and European Union

https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm583057.htm
Last accessed: 6 Nov 2017


31 October 2017
EMA/662403/2017
Media and Public Relations

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Press release

EU-US mutual recognition of inspections of medicines manufacturers enters operational phase

Major milestone is a testimony to mutual trust

http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2017/10/WC500237909.pdf
Last accessed: 6 Nov 2017

The U.S. Food and Drug Administration has determined the agency will recognize eight European drug regulatory authorities as capable of conducting inspections of manufacturing facilities that meet FDA requirements.

"At a time in which medical product manufacturing is truly a global enterprise, there is much to be gained by partnering with regulatory counterparts to reduce duplicative efforts and maximize global resources while realizing the greatest bang for our collective inspectional buck," said FDA Commissioner Scott Gottlieb, M.D.

why do you think they must act together ?

We should also address the CRIMINAL 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 & Attaran A. Lancet. 2010;376(9751):1446-1448 - PMID 21036261

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

Johnston & Holt Br J Clin Pharmacol. 2014;78:218-243 - PMID 24286459

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.

An European action is ongoing … but is costly

COUNCIL OF EUROPE
CONSEIL DE L'EUROPE

COUNCIL OF EUROPE

edqm
European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé

Home | About us | European Pharmacopoeia | Reference Standards | Certification of Suitability | OMCL Network | Transfusion & Transplantation | Patient & Consumer Health Protection

Home > Patient & Consumer Health Protection > Anti-counterfeiting activities > The MEDICRIME Convention

The MEDICRIME Convention

Background and scope

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

- the manufacturing of falsified medical products.
- supplying, offering to supply and trafficking in falsified 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.

Map of Countries

that have signed the MEDICRIME Convention

Latest update: ratification of Turkey (21/09/17)

https://www.edqm.eu/en/medicrime-convention-0
Last accessed: 18 Oct 2016

An European action is ongoing … but is costly

COUNCIL OF EUROPE
CONSEIL DE L'EUROPE

COUNCIL OF EUROPE

edqm
European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé

Home | About us | European Pharmacopoeia | Reference Standards | Certification of Suitability | OMCL Network | Transfusion & Transplantation | Patient & Consumer Health Protection

Home > Patient & Consumer Health Protection > Anti-counterfeiting activities > The MEDICRIME Convention

The MEDICRIME Convention

Background and scope

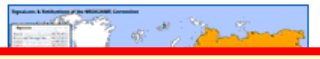
The Council of Europe has drawn up the first international treaty against counterfeit medical products and similar crimes involving threats to public health, the MEDICRIME Convention, to establish as offences:

- the manufacturing of falsified medical products.

Map of Countries

that have signed the MEDICRIME Convention

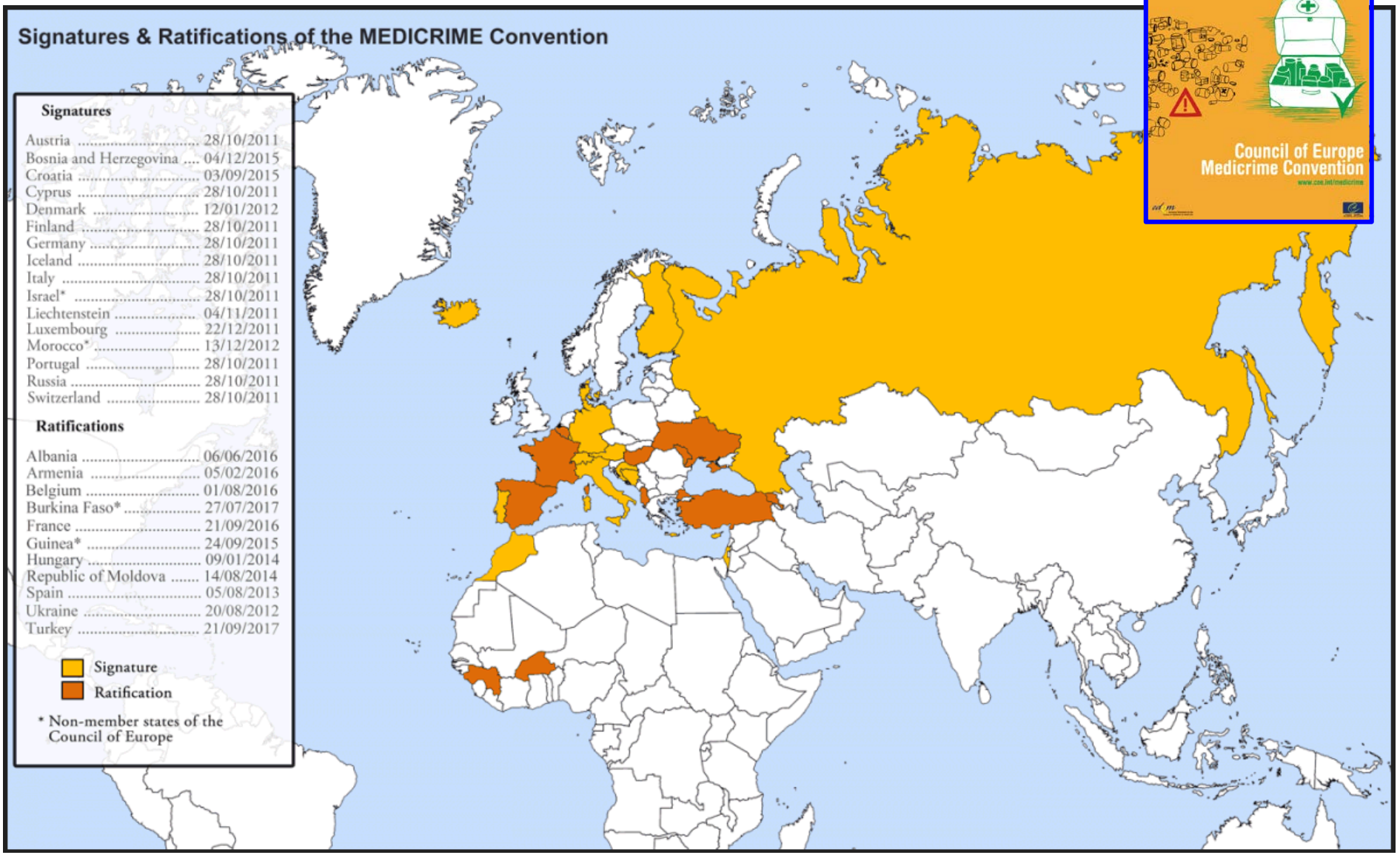
Latest update: ratification of Turkey (21/09/17)



- the manufacturing of falsified medical products.
- supplying, offering to supply and trafficking in falsified medical products

https://www.edqm.eu/en/medicrime-convention-0
Last accessed: 18 Oct 2016

MEDICRIME: which countries ?



https://www.edqm.eu/sites/default/files/medicrime-world-map-en.png
Last accessed: 18 Oct 2017

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 !
    3. **Drug shortages …**
    4. **Price increases…**

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
Published Sep 2013 - Last accessed: 17 Oct 2017

But see what happens with “Low cost antibiotics“…
The sour Danish Experience

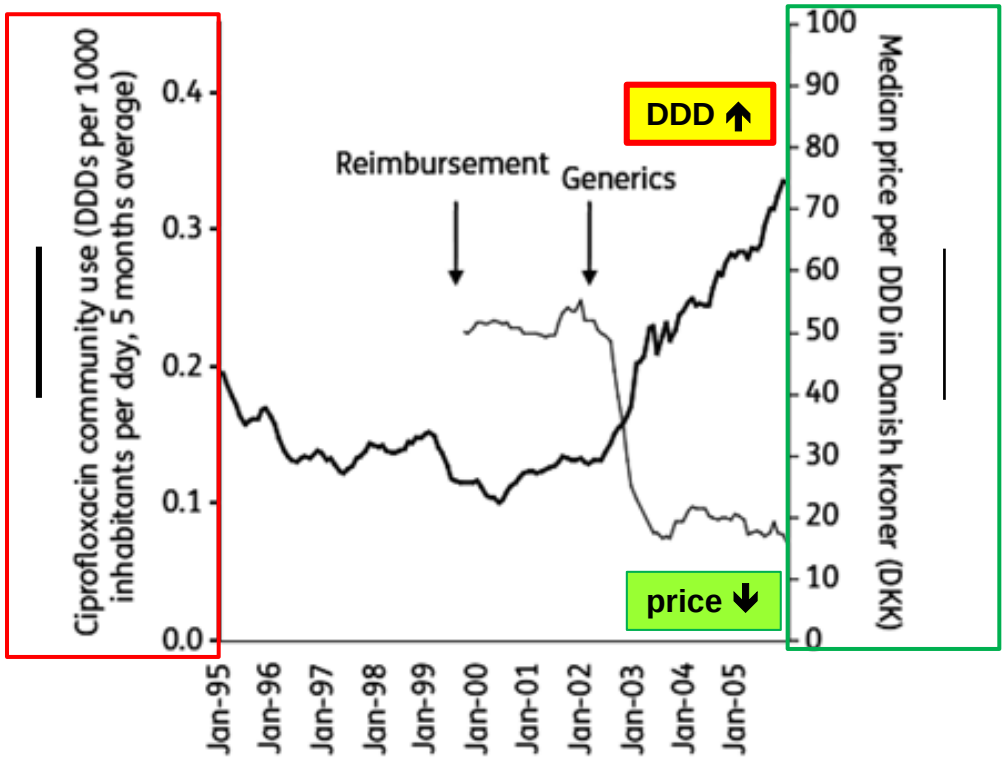
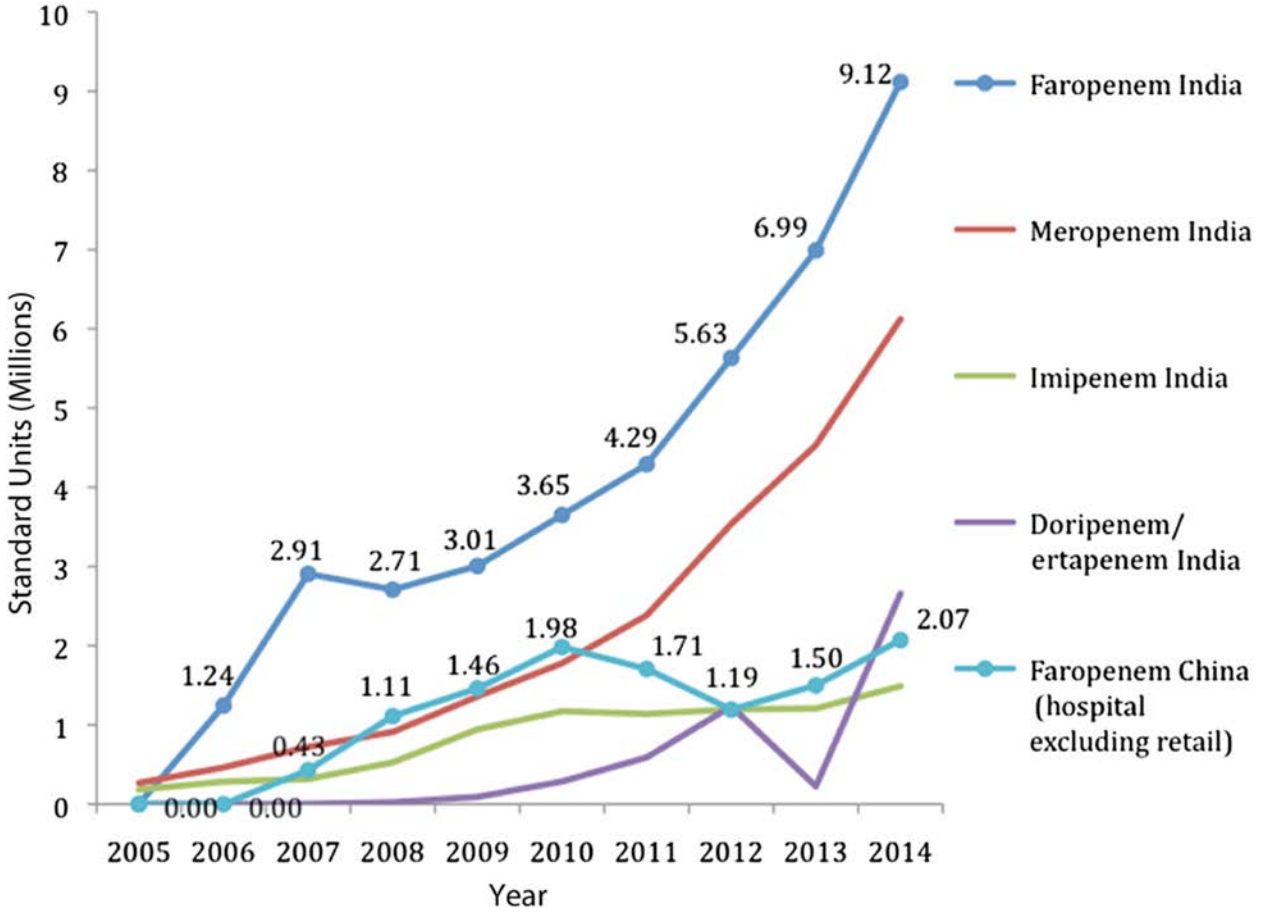


Figure 1.

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.

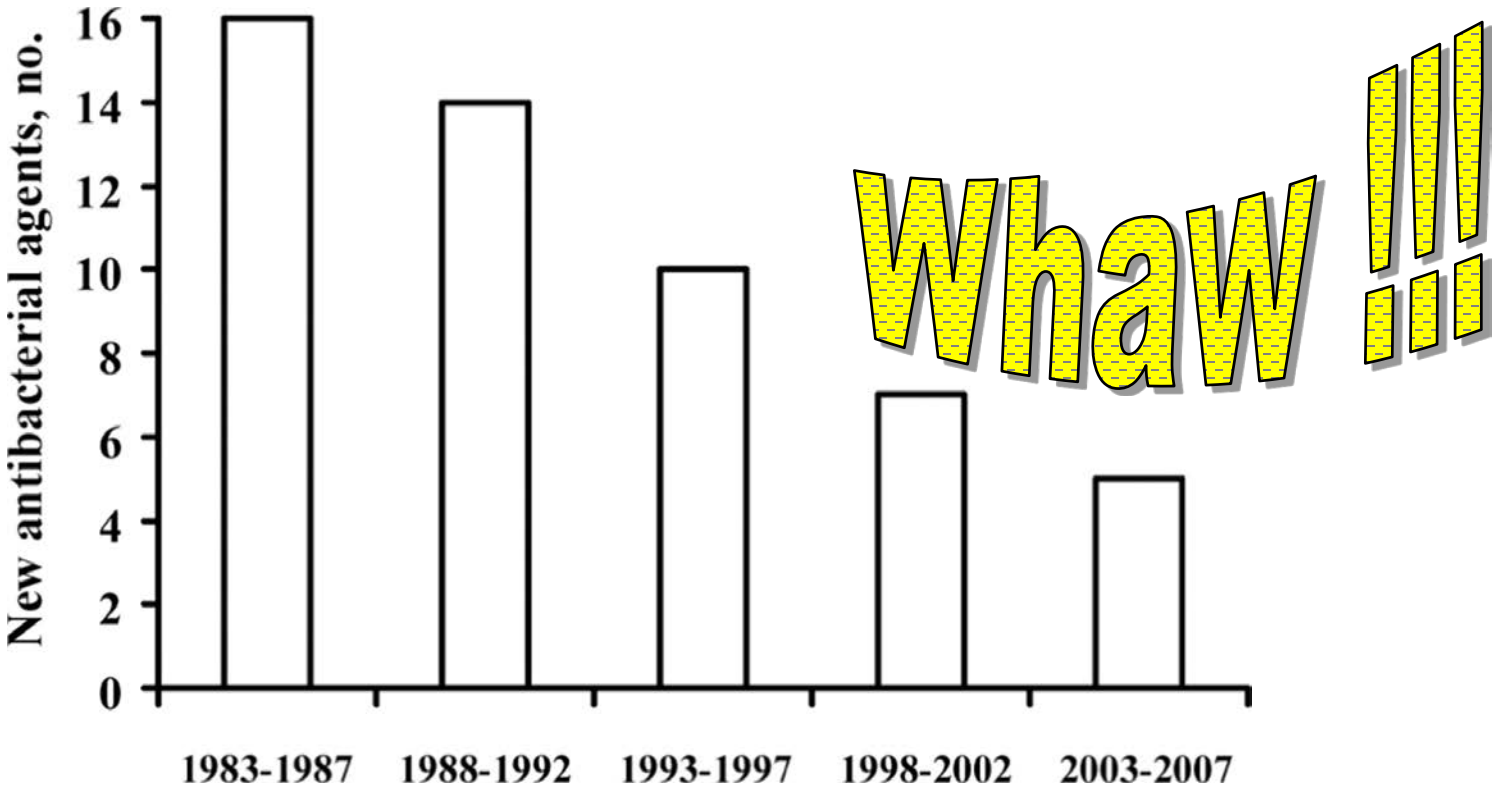
Jensen *et al.* J Antimicrob Chemother 2010; 65:1286–1291 – PMID 20363806

And a dramatic Indian experience…



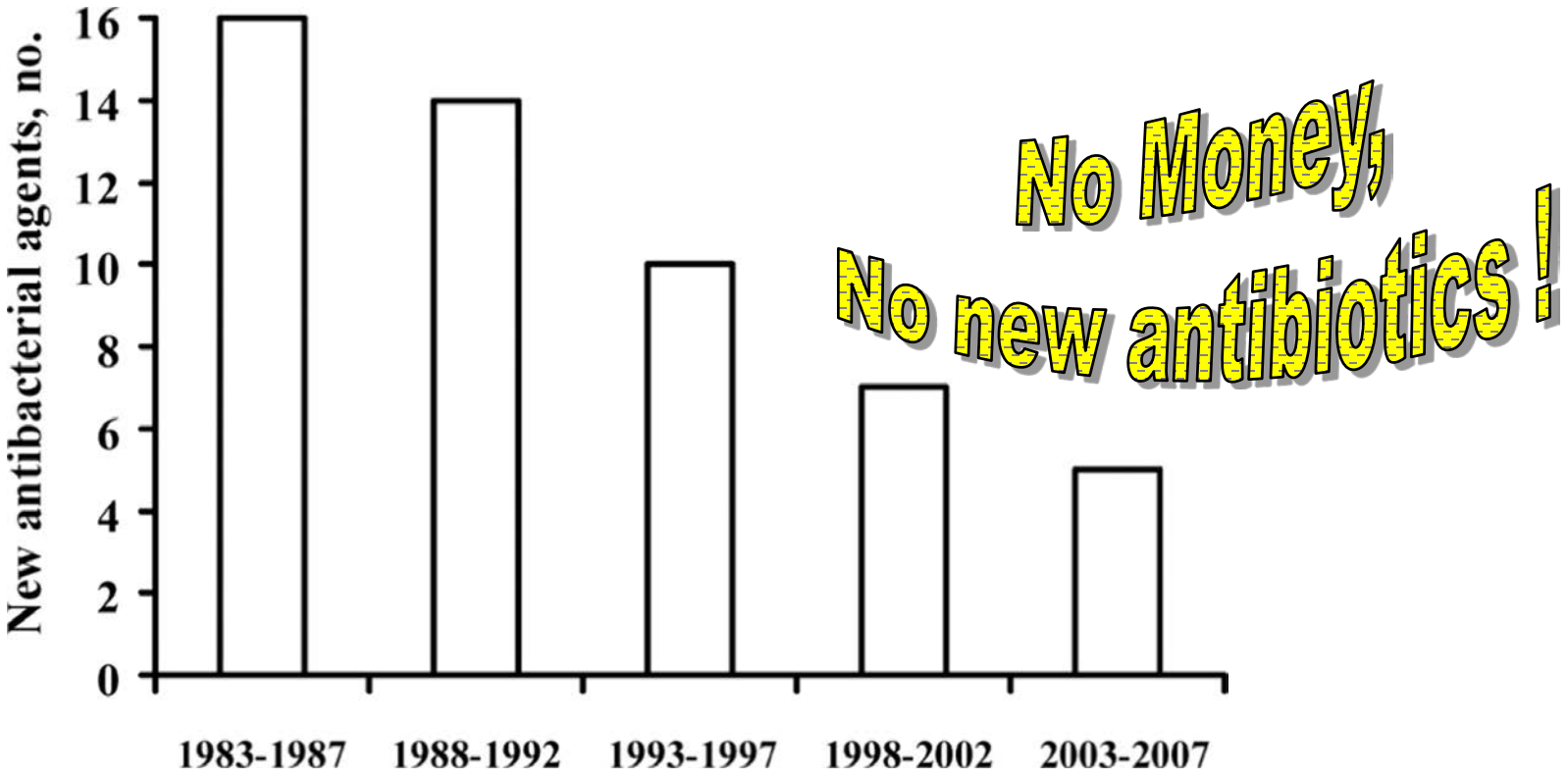
Gandra *et al.* Clin Infect Dis. 2016;62:1050-1052 - PMID 26908807

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 …

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 investme… earmarked for biomedical research and public healt… surveillance agains… …ificantly reinforce the nation's campaign to stop …

https://www.asm.org/i…
Last accessed: 08/0…

The tax-payer will pay for this !

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

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

Drug shortages …

a nightmare for pharmacists

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

Pauwels *et al*. PLoS One. 2015;10:e0119322 - PMID 25775406

Drug shortages …

PLOS ONE

RESEARCH ARTICLE

Insights into European Drug Shortages: A Survey of Hospital Pharmacists

a recent paper … (2015…)

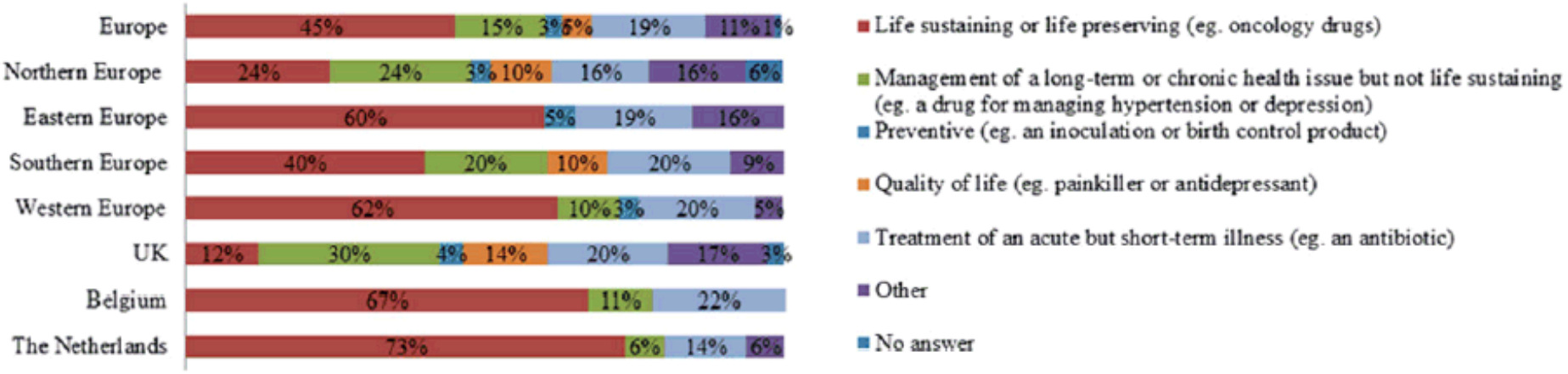
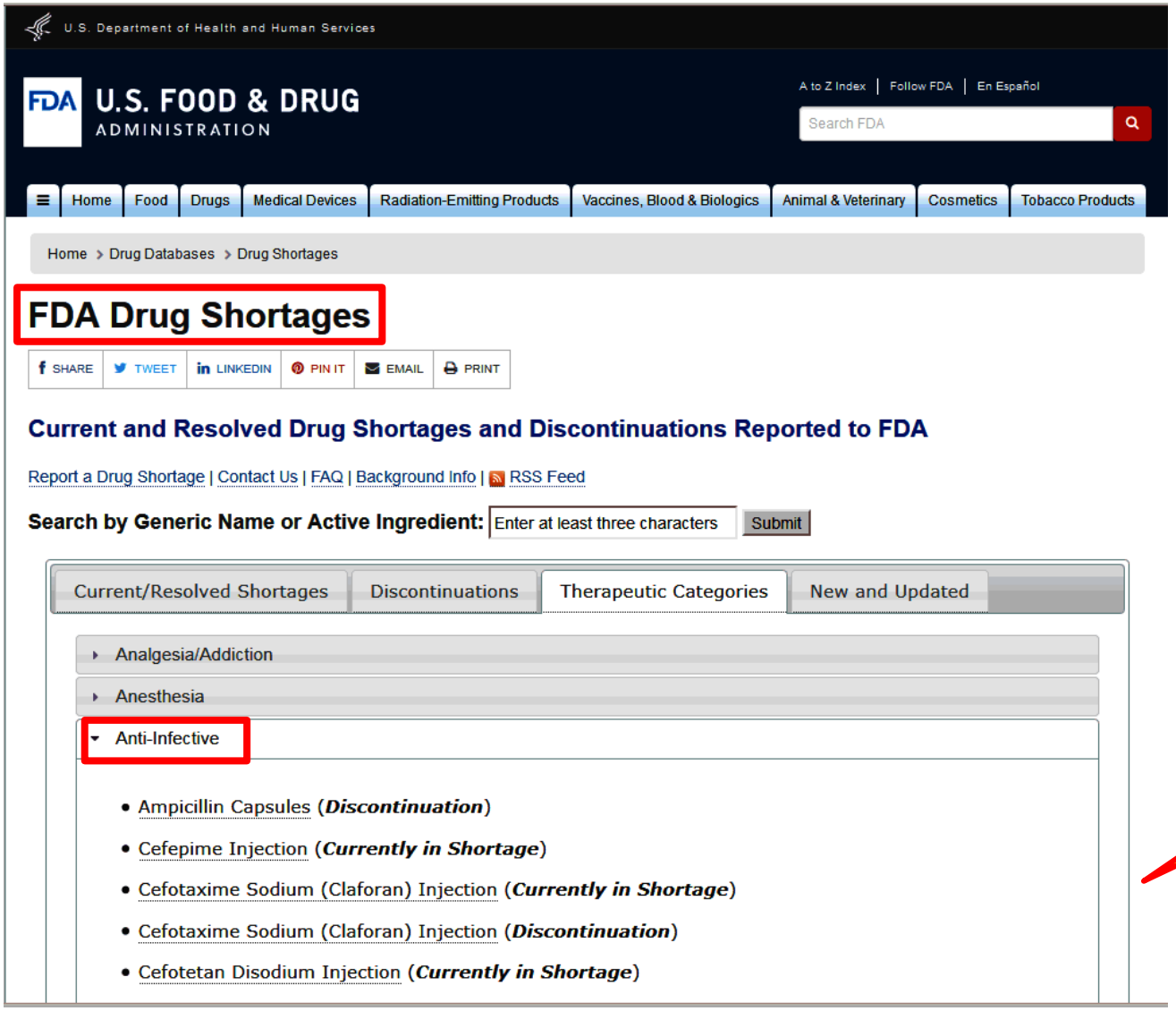


Fig 1. Drug types affected by drug shortages according to the respondents. Respondents who indicated that particular types of medicines suffered more from shortages than others were considered. The relative number of respondents per answer was shown for Europe (n = 128), Northern Europe (n = 8), Eastern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

Pauwels *et al*. PLoS One. 2015;10:e0119322 - PMID 25775406

Drug shortages are not only in Belgium…



The list is 24 items long !

https://www.accessdata.fda.gov/scripts/drugshortages/
Last accessed: 20 Oct 2017

But the situation was known years ago …

IMS INSTITUTE FOR HEALTHCARE INFORMATICS

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

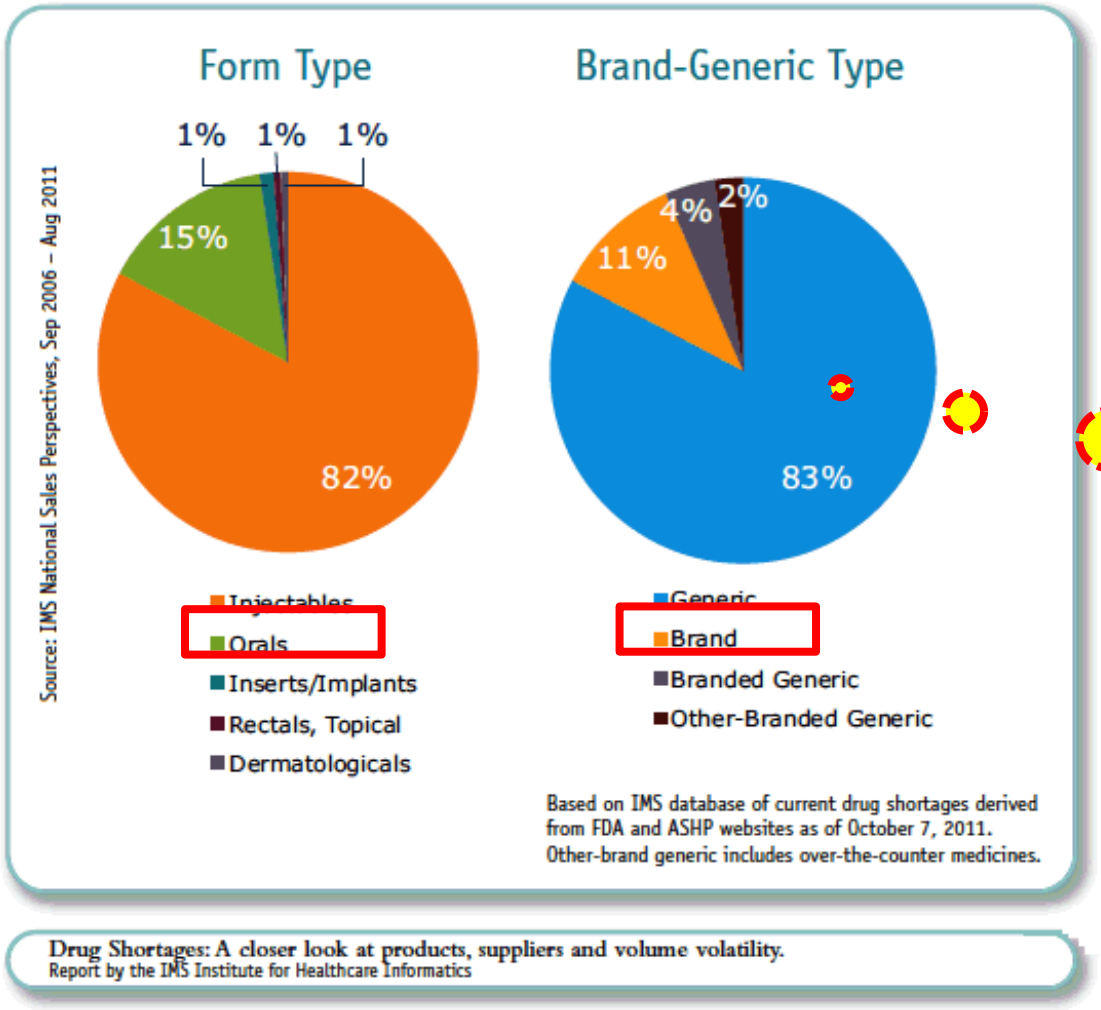
November 2011

Report by the IMS Institute for Healthcare Informatics

https://www.imshealth.com/files/web/IMSH%20Institute/Reports/Drug%20Shortages%20A%20closer%20look/IHII_Drug_Shortage_Report.pdf
Last accessed: 18 Oct 2017

… 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"

https://www.imshealth.com/files/web/IMSH%20Institute/Reports/Drug%20Shortages%20A%20closer%20look/IHII_Drug_Shortage_Report.pdf
Last accessed: 18 Oct 2017

Price increases !

News

Some Generic Drugs See Huge Price Increases

Ken Terry

September 15, 2016

> The prices of generic drugs covered under the Medicare Part D program dropped overall from 2010 to 2015, but a group of 315 drugs saw extraordinary price increases during that period, according to a new report from the US Government Accountability Office (GAO). The study was requested by members of Congress who were concerned about reports of spiking generic drug prices.

https://www.medscape.com/viewarticle/868812
Last accessed: 19 Oct 2017

Price increases !

Medscape Infectious Diseases

NEWS & PERSPECTIVE

News

Some Gen

Ken Terry

September 15, 2016

The prices
dropped o
price increa
Governmer
members c
drug prices

https://www.medscape.com
Last accessed: 19 Oct 201

United States Government Accountability Office

GAO

Report to Congressional Requesters

August 2016

GENERIC DRUGS UNDER MEDICARE

Part D Generic Drug Prices Declined Overall, but Some Had Extraordinary Price Increases

GAO-16-706

http://www.gao.gov/assets/680/679022.pdf
Last accessed: 19 Oct 2017

Observed for:

- cefuroxime axetil
- cephalexin
- ciprofloxacin
- clarithromycin
- clindamycin
- doxycycline
- erythromycin
- gentamicin
- metronidazole
- ofloxacin
- tobramycin

Why do prices increase ?

Clinical Infectious Diseases

MAJOR ARTICLE

Trends in Pricing and Generic Competition Within the Oral Antibiotic Drug Market in the United States

Jonathan D. Alpern,[1] Lei Zhang,[2] William M. Stauffer,[1] and Aaron S. Kesselheim[3]

[1]Division of Infectious Disease and International Medicine, Department of Internal Medicine and [2]Clinical and Translational Science Institute, University of Minnesota, Minneapolis; and [3]Program on Regulation, Therapeutics, and Law, Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts

Alpern et al. Clin Infect Dis 2017;[Epub ahead of print] - PMID 29020146

Why do prices increase ?

Clinical Infectious Diseases

MAJOR ARTICLE

Trends in Pricing and Generic C
Oral Antibiotic Drug Market in

Jonathan D. Alpern,[1] Lei Zhang,[2] William M. Stauffer,[1] and Aaron S. Kesselheim[3]

[1]Division of Infectious Disease and International Medicine, Department of Internal Medicine and [2]Clinical a
on Regulation, Therapeutics, and Law, Division of Pharmacoepidemiology and Pharmacoeconomics, Departm
Massachusetts

Alpern et al. Clin Infect Dis 2017;[Epub ahead of print] - PMID 29020146

It all depends from the competition !

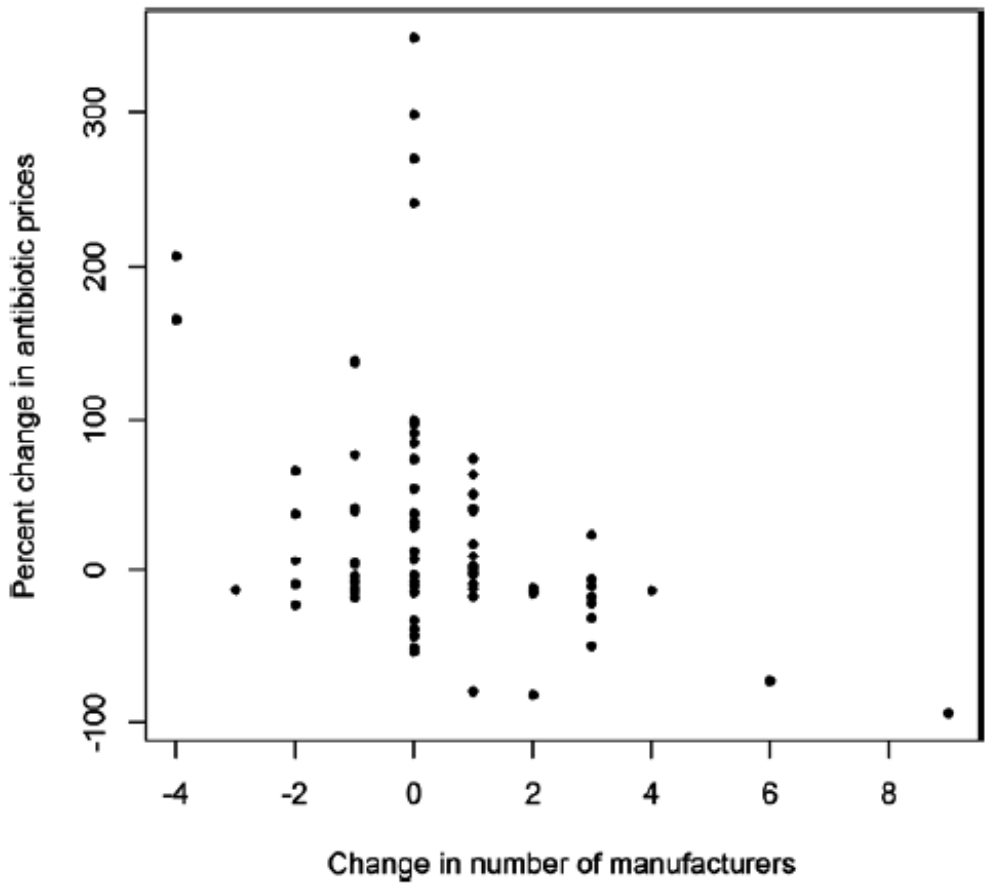
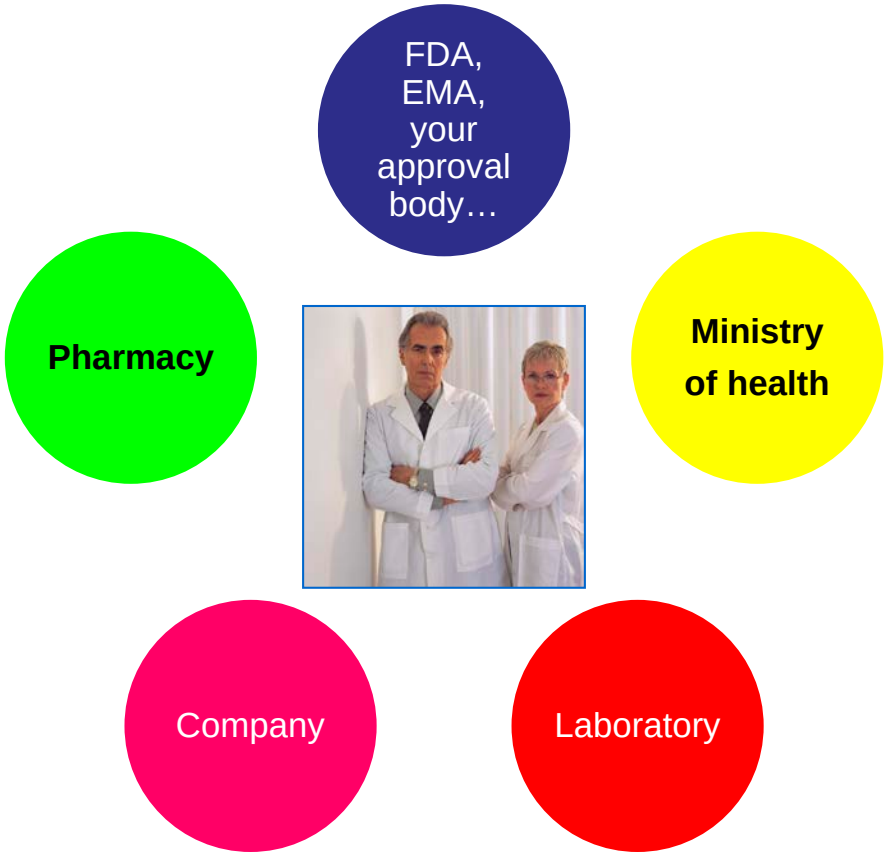


Figure 1. Association between the change in number of manufacturers and the change in antibiotic prices.

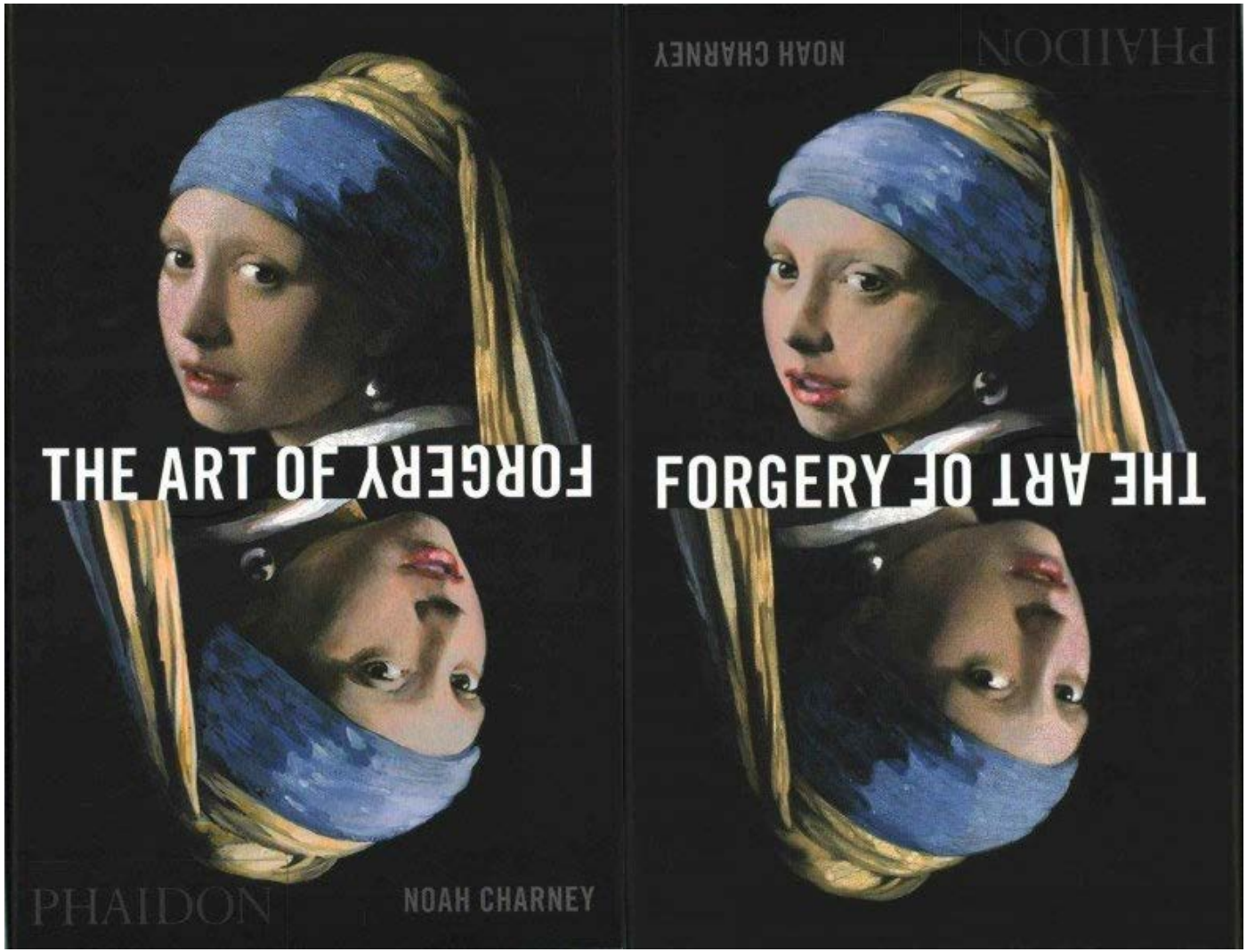
Now, what can I do as a clinician ?



Summary / Suggestions

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

Remember: a true copy must be a piece of art



https://www.npr.org/2015/06/23/412244490/could-the-masterpiece-be-a-fake-profit-revenge-and-the-art-of-forgery
Last visited: 8 Nov 2017

Thank you for your attention!

And ask questions

Here are questions…

Are you happy about the law(s) ?

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

Please, think about what YOU would choose !

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 !