Branded vs. generic of antibiotics: Evidence-based approach

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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…
Would you prefer to see there originals or copies?

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 …

Generics volume share of the unprotected market by country in 2003, 2008 and 2013

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

Last visited: 15 Oct 2017
### Global Spending, 2012 and 2017

<table>
<thead>
<tr>
<th>Region</th>
<th>2012</th>
<th>2017</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Developed</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brand</td>
<td>72%</td>
<td>67%</td>
</tr>
<tr>
<td>Generic</td>
<td>16%</td>
<td>21%</td>
</tr>
<tr>
<td>Other</td>
<td>12%</td>
<td>12%</td>
</tr>
<tr>
<td>Total</td>
<td>$622Bn</td>
<td>$650-680Bn</td>
</tr>
<tr>
<td><strong>Pharmerging</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brand</td>
<td>31%</td>
<td>26%</td>
</tr>
<tr>
<td>Generic</td>
<td>58%</td>
<td>63%</td>
</tr>
<tr>
<td>Other</td>
<td>11%</td>
<td>11%</td>
</tr>
<tr>
<td>Total</td>
<td>$224Bn</td>
<td>$370-400Bn</td>
</tr>
<tr>
<td><strong>Rest of the world</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brand</td>
<td>57%</td>
<td>52%</td>
</tr>
<tr>
<td>Generic</td>
<td>27%</td>
<td>31%</td>
</tr>
<tr>
<td>Other</td>
<td>16%</td>
<td>17%</td>
</tr>
<tr>
<td>Total</td>
<td>$120Bn</td>
<td>$125-155Bn</td>
</tr>
<tr>
<td><strong>World</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brand</td>
<td>61%</td>
<td>52%</td>
</tr>
<tr>
<td>Generic</td>
<td>27%</td>
<td>36%</td>
</tr>
<tr>
<td>Other</td>
<td>12%</td>
<td>12%</td>
</tr>
<tr>
<td>Total</td>
<td>$965Bn</td>
<td>$1,170-1,200Bn</td>
</tr>
</tbody>
</table>

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: IMS Health Thought Leadership, September 2013

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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
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.

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".

TITLE I—ABBREVIATED NEW DRUG APPLICATIONS

- 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)
  Last accessed: 17 Oct 2017
- Product-Specific Guidances for Generic Drug Development:
  Last accessed: 20 Oct 2017
In the European Union

**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)

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• …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 marketed form differs from the form used in development…\(^2\))

- Primary metrics are \(^1,^3\)
  - \(\text{AUC}\) (area under the plasma concentration–time profile of the active substance)
    \(\rightarrow\) extent of absorption
  - \(C_{\text{max}}\) (the maximum plasma concentration of the active substance)
    \(\rightarrow\) extent and rate of absorption
  - \(T_{\text{max}}\) (the time when \(C_{\text{max}}\) is reached)
    \(\rightarrow\) rate of absorption

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AUC – $C_{\text{max}}$ – $T_{\text{max}}$
What if the absorption is decreased?

![Graph showing changes in concentration over time with annotations for $C_{\text{max}}$ and AUC.]
What if absorption is delayed?

![Graph showing concentration over time with peaks at C_{max} and T_{max}.]
Criteria of bioequivalence (EMA* / FDA**)

• Calculate the **90% confidence interval** around the **geometric mean ratios** of both AUC and $C_{\text{max}}$ for Test (generic) and Reference (innovator).

• The 90% confidence intervals should, in most cases, be **within the 0.80 – 1.25 acceptance limits**.

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** Guidance for Industry (BIOEQUIVALENCE GUIDANCE) - Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations
Criteria of bioequivalence (EMA / FDA)

- Calculate the **90% confidence interval** around the **geometric mean ratios** of both AUC and $C_{\text{max}}$ 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 $C_{\text{max}}$ are within range, the generic should have the same bioavailability as the reference.
2. Statistical evaluation of $T_{\text{max}}$ 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 "tightly" 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 $^{1-3}$

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

Last accessed: 29 March 2014

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

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Pathogen (no.)</th>
<th>No. of generic markers</th>
<th>Nonidentical rate of the MIC value of all generics (mean ± SD)</th>
<th>MIC distribution (%) of the most different generic versus brand name drug</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1/8</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>MRSA (90)</td>
<td>5</td>
<td>25.00 ± 15.52</td>
<td>–</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>MRSA (147)</td>
<td>7</td>
<td>28.09 ± 10.29</td>
<td>–</td>
</tr>
<tr>
<td>Cefotiam</td>
<td><em>Staphylococcus aureus</em> (100)</td>
<td>7</td>
<td>8.71 ± 3.04</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td><em>Escherichia coli</em> (100)</td>
<td>7</td>
<td>12.00 ± 5.89</td>
<td>–</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td><em>Streptococcus pneumoniae</em> (126)</td>
<td>6</td>
<td>12.70 ± 4.77</td>
<td>–</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td><em>Pseudomonas aeruginosa</em> (100)</td>
<td>2</td>
<td>3.00 ± 2.83</td>
<td>–</td>
</tr>
<tr>
<td>Meropenem</td>
<td><em>P. aeruginosa</em> (100)</td>
<td>7</td>
<td>18.57 ± 3.46</td>
<td>–</td>
</tr>
<tr>
<td>Imipenem</td>
<td><em>P. aeruginosa</em> (100)</td>
<td>4</td>
<td>9.00 ± 2.58</td>
<td>–</td>
</tr>
</tbody>
</table>

*MRSA* methicillin-resistant *Staphylococcus aureus*. 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.


**MICs were often 2 x higher than for the reference product...**
MIC values (meropenem) in Belgium

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

susceptible strains (MIC ≤ 2 mg/L)

Van Bambeke et al., 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 (fAUC/MIC, 267 h) because this product was discontinued and the remaining amount was insufficient for the highest doses.

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.

A series of other papers raising questions...

**International Journal of Antimicrobial Agents**

Short Communication

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

Livia L.S. de Mattos 1, Fausto K. Ferraris 1, Tiago S.C. Machado 2, Thais M. de Brito 2, Amanda S. Chaves 2, Hélia M. Pereira 2, Douglas P. Pinto 2, Diego M.D. da Silva 2, Fabio C. Amendoeira 1, 2

1 Instituto Nacional de Controle de Qualidade em Saúde, Fundação Oswaldo Cruz (INSS-Fiocruz); Av. Brasil, 4315—Mangueiras, Rio de Janeiro, RJ 21045-002, Brazil
2 Laboratório de Farmacognosia, Fundação Oswaldo Cruz (Fiocruz); Mangueiras, Rio de Janeiro, RJ, Brazil

**Diagnostic Microbiology and Infectious Disease**

Antimicrobial Susceptibility Studies

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

Hsin-Yun Sun 1, Hsiao-Wei Liao 2, Meng-Huei Sheng 3, Hui-Min Tai 4, Ching-Hua Kuo 1, 2, Wang-Huei Sheng 1, 4

1 Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan
2 School of Pharmacy, College of Medicine, National Taiwan University, Taipei, Taiwan
3 Jia-Nan University of Pharmacy and Science, Taichung, Taiwan
4 Department of Pharmacy, National Taiwan University Hospital, Taipei, Taiwan

**Pharmaceutics**

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

Moawia M. Al-Tabakha 1, 2, Khairi M. S. Fahelelbom 2, Dana E. 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@aua.ac.ae (K.M.S.F.); dana.obaid@aua.ac.ae (D.E.E.O.);
sadik.sayed@aua.ac.ae (S.S.)

* Correspondence: sphmaa@hotmail.com; Tel.: +971-6-705-6208

**Journal of Infection and Public Health**

Letter to the Editor

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

**International Journal of Antimicrobial Agents**

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

Carlos A. Rodriguez 3, María Agudelo 1, 2, Andres F. Zuluaga 3, Omar Vesga 1, 2, 3, 4

3 GRIFE (Grupo Investigador de Problemas en Enfermedades Infecciosas), Facultad de Medicina, Universidad de Antioquia, Medellín, Antioquia, Colombia
4 Infecciones Infecciosas Unit, Hospital Universitario San Vicente Fundación, Medellín, Colombia
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.
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

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

Carlos A. Rodríguez, a,b Maria Agudelo, a,b,d t 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, Medellín, Colombia; Infectious Diseases Unit, Hospital Universitario San Vicente Fundación, Medellin, Colombia d

But pharmacodynamics equivalence can also be demonstrated.

Impact on Resistance of the Use of Generic Products: the Case of Ciprofloxacin

Carlos A. Rodriguez, a,b Maria Agudelo, a,b,d Andres F. Zuluaga
GRIF: Grupo Investigador de Problemas en Enfermedades Infecciosas, a Department of Biology, University of Antioquia, Medellin, Colombia; b Infectious Diseases Unit, Hospital Universitario San Juan de Dios, Bogota, Colombia; c Laboratory of Microbiology, Padre Hurtado Institute, Bogota, Colombia; d Laboratory of Microbiology, Departamento de Microbiologia, Facultad de Medicina, Universidad de Antioquia, Medellin, Colombia.

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

“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.”
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.

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, 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 !
And this brings me to **pharmaceutical quality**…
What is your opinion?

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

Please, think about what YOU would choose!
Dissolution of meropenem in Japan

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

Crystals size in meropenem in Japan

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

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

Delattre et al. 30th International Congress of Chemotherapy, Taipei, Taiwan – poster #724 (to be presented)
Impurities in meropenem: coloured compounds

**OD$_{490\text{nm}}$ - 24°C**

- originator
- generic A
- generic B
- generic C

**OD$_{490\text{nm}}$ - 37°C**

- originator
- generic A
- generic B
- generic C

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

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

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

Groupe de RMN Biomédicale, Laboratoire SPCMB (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 ± 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 Pharmacopoeia. 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.

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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.

Problems appearing in Europe!

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

http://www.medioplanet.be/fr/content/la-belgique-retire-4-medicaments-commercialises-par-la-societe-indienne-gvk-biosciences
Last accessed: 08/02/2015

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

http://ansm.sante.fr/fr-informer/Actualites/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!

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.


The list makes 135 pages
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…

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

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.
But the story continues…

[Chart showing cGMP Non-Compliances in 2017 (Jan – July) with data on regulatory actions against 60 companies, distribution of non-compliances by country (30% China, 25% India, 20% USA), and FDA import alerts and warning letters.

As per our analysis, China leads in cGMP non-compliances, followed by India, the United States, Canada, Brazil, Italy, Japan, Spain, Greece, United Kingdom, Korea, and Jordan. EM

Last accessed: 19 Oct 2017
And we know the origins...

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.

Last accessed: 19 Oct 2017
Drug quality may vary according to whom the drugs are sold …

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.
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
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 detection and prevention of substandard medicines and the need for ongoing efforts to address this global public health issue.

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

The 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.

https://www.edqm.eu/en/medicrime-convention-0

An European action is ongoing … but is costly

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MEDICRIME: which countries?

Signatures & Ratifications of the MEDICRIME Convention

**Signatures**
- Austria: 28/10/2011
- Bosnia and Herzegovina: 04/12/2015
- Croatia: 03/09/2015
- Cyprus: 28/10/2011
- Denmark: 12/01/2012
- Finland: 28/10/2011
- Germany: 28/10/2011
- Iceland: 28/10/2011
- Italy: 28/10/2011
- Israel*: 28/10/2011
- Liechtenstein: 04/11/2011
- Luxembourg: 22/12/2011
- Morocco*: 13/12/2012
- Portugal: 28/10/2011
- Russia: 28/10/2011
- Switzerland: 28/10/2011

**Ratifications**
- Albania: 06/06/2016
- Armenia: 05/02/2016
- Belgium: 01/08/2016
- Burkina Faso*: 27/07/2017
- France: 21/09/2016
- Guinea*: 24/09/2015
- Hungary: 19/01/2014
- Republic of Moldova: 14/08/2014
- Spain: 05/08/2013
- Ukraine: 20/08/2012
- Turkey: 21/09/2017

* Non-member states of the Council of Europe

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 levofloxacinS in Belgium
What shall we discuss?

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

Developing the first national antimicrobial prescribing and stewardship competences

D. Ashiru-Oredope1*, B. Cookson2 and C. Fry3 on behalf of the Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection Professional Education Subgroup†


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†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
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.
And a dramatic Indian experience...

Innovative antibiotic development is abandoned by Industry

Why do they abandon it?

No Money, No new antibiotics!

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

Last accessed: 08/02/2015

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

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 investments. Significant, significantly reinforce the nation's surveillance against campaign to stop.

Last accessed: 08/07/2016

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

Drug shortages ...

a nightmare for pharmacists

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

Drug shortages ...

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


![Image of a recent paper (2015...)]
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 …

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

Report by the IMS Institute for Healthcare Informatics


Last accessed: 18 Oct 2017
... and the main affected products were known

Most products are injectables and generics

and the main reason is "market volatility"
Price increases!

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.

Last accessed: 19 Oct 2017
Price increases!

Some Generics Were Hit Particularly Hard

The prices of selected generic drugs dropped overall, but some had extraordinary price increases.

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

GAO-16-706

Last accessed: 19 Oct 2017

Observed for:

- cefuroxime axetil
- cephalexin
- ciprofloxacin
- clarithromycin
- clindamycin
- doxycycline
- erythromycin
- gentamicin
- metronidazole
- ofloxacin
- tobramycin
Why do prices increase?

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. Kesselheim3

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

Why do prices increase?

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?

FDA, EMA, your approval body...

Pharmacy

Ministry of health

Company

Laboratory
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

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!