Effect of generic antibiotic introduction: key learnings

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  – Belgian Science Foundation (F.R.S.-FNRS), Ministry of Health (SPF), and Walloon and Brussels Regions

• Speaking fees
  – Bayer, GSK, Sanofi, Johnson & Johnson, OM-Pharma

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

Slides: http://www.facm.ucl.ac.be → Lectures
You said "generics": the recent story of a well known antibiotic

Before patent expiration

<table>
<thead>
<tr>
<th>Generic (PI-Pharme)</th>
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<tbody>
<tr>
<td>Lévofloxacine</td>
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<tr>
<td>compr. (sec.)</td>
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<tr>
<td>10 x 500mg</td>
<td>Rx</td>
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<tr>
<td>(importation parallèle)</td>
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<table>
<thead>
<tr>
<th>Generic (Sanofi-Aventis)</th>
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<tbody>
<tr>
<td>Lévofloxacine</td>
<td></td>
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<tr>
<td>compr. (sec.)</td>
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<tr>
<td>10 x 250mg</td>
<td>Rx</td>
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<tr>
<td>10 x 500mg</td>
<td>Rx</td>
</tr>
<tr>
<td>Flacon perf.</td>
<td></td>
</tr>
<tr>
<td>1 x 500mg / 100ml</td>
<td>U.H.</td>
</tr>
</tbody>
</table>

http://www.cbip.be/GGR/Index.cfm?ggrWelk=/nIndex/GGR/Stof/IN_L.cfm
# A well known antibiotic in Belgium

1. **Levofloxacin Actavis (Actavis)**
   - sac perf.
   - € 5 x 500 mg / 100 ml U.H. [€63]

2. **Levofloxacin BG (Eurogenerics)**
   - compr. (séc.)
   - € 10 x 250 mg
   - € 30 x 500 mg
   - € 1 x 500 mg / 100 ml
   - U.H. [€21]

3. **Levofloxacin Fresenius Kabi (Fresenius Kabi)**
   - flacon perf.
   - € 1 x 500 mg / 100 ml
   - U.H. [€27]

4. **Levofloxacin Hospira (Hospira)**
   - sac perf.
   - € 1 x 500 mg / 100 ml
   - U.H. [€27]

5. **Levofloxacin Mylan (Mylan)**
   - compr. (séc.)
   - € 10 x 250 mg
   - € 14 x 250 mg
   - € 10 x 500 mg
   - € 14 x 500 mg
   - flacon perf.
   - € 10 x 500 mg / 100 ml
   - U.H. [€270]

6. **Levofloxacin Sanchez (Sanchez)**
   - compr. (séc.)
   - € 10 x 250 mg
   - € 10 x 500 mg
   - € 30 x 500 mg
   - b

7. **Levofloxacin Teva (Teva)**
   - compr. (séc.)
   - € 10 x 250 mg
   - € 10 x 500 mg
   - € 30 x 500 mg
   - b

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http://www.cbip.be/GGR/Index.cfm?ggrWelk=/nIndex/GGR/Stof/IN_L.cfm
But why would you choose 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
6. All of the above

Please, give your FIRST choice (1-5) OR choose 6
I guess the real and only justifiable answer is...
What shall we discuss?

1. The US and the EU laws
2. Approach to PK bioequivalence
3. Approach to microbiological equivalence
   - MIC, MPC, heteroresistance …
4. Approach to pharmacodynamic equivalence
   - PK/PD animal models and clinical data
5. Problems related to dissolution and stability
6. Impurities and falcified medicines
7. The hidden risk of "low cost" antibiotics
What shall we discuss?

1. The US and the EU laws

http://vlpmaricopa.org/vlp/clc/Aboutus.htm
Last visited: 25 March 2014
The US Law

• 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

US "Abbreviated New Drug Application"

Abbreviated New Drug Application (ANDA): Generics

An Abbreviated New Drug Application (ANDA) contains data which when submitted to FDA’s Center for Drug Evaluation and Research, Office of Generic Drugs, provides for the review and ultimate approval of a generic drug product. Once approved, an applicant may manufacture and market the generic drug product to provide a safe, effective, low cost alternative to the American public.

A generic drug product is one that is comparable to an innovator drug product in dosage form, strength, route of administration, quality, performance characteristics and intended use. All approved products, both innovator and generic, are listed in FDA’s Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book).

Generic drug applications are termed "abbreviated" because they are generally not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness. Instead, generic applicants must scientifically demonstrate that their product is bioequivalent (i.e., performs in the same manner as the innovator drug). One way scientists demonstrate bioequivalence is to measure the time it takes the generic drug to reach the bloodstream in 24 to 36 healthy volunteers. This gives them the rate of absorption, or bioavailability, of the generic drug, which they can then compare to that of the innovator drug. The generic version must deliver the same amount of active ingredients into a patient’s bloodstream in the same amount of time as the innovator drug.

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)
  
FDA approved generic drugs: "Orange book" *

* http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm
FDA approved generic drugs: "Orange book" *

As in LEVAQUIN®

* http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm

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)*

<table>
<thead>
<tr>
<th>Amended by</th>
<th>Official Journal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
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</tbody>
</table>

* 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 EU Directive

• By way of derogation from Article 8(3)(i), and without prejudice to the law relating to the protection of industrial and commercial property, 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 which is or has been authorised under Article 6 for not less than eight years in a Member State or in the Community.

• ‘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. …

Bioavailability studies need not be required of the applicant if he can demonstrate that the generic medicinal product meets the relevant criteria as defined in the appropriate detailed guidelines.
What shall we discuss?

1. The US and the EU laws
2. Approach to PK bioequivalence

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

• Bioequivalence is an accepted surrogate for therapeutic equivalence (including for branded drugs when the marketed form differs from the form used in development…)

• Primary metrics are

  – **AUC** (area under the plasma concentration–time profile of the active substance)
    → extent of absorption
  – **$C_{\text{max}}$** (the maximum plasma concentration of the active substance)
    → extent and rate of absorption
  – **$T_{\text{max}}$** (the time when $C_{\text{max}}$ is reached)
    → rate of absorption

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

\[ C_{\text{max}} \]

\[ T_{\text{max}} \]
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**.

**Notes:**
1. If both AUC and $C_{\text{max}}$ are within range, the generic should have the same bioavailability than 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 "tightened acceptance intervals, Health Canada requires 0.9 – 1.12, but FDA accepts 0.8 – 1.25

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** Guidance for Industry (BIOEQUIVALENCE GUIDANCE) - Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations
But what about in Asia?

ASEAN GUIDELINES FOR THE CONDUCT OF BIOAVAILABILITY AND BIOEQUIVALENCE STUDIES

But what about in Asia?

2.4 Bioequivalence

Two medicinal products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and if their bioavailabilities after administration in the same molar dose are similar to such degree that their effects, with respect to both efficacy and safety, will be essentially the same.

Alternatively to classical bioavailability studies using pharmacokinetic end points to assess bioequivalence, other types of studies can be conducted, e.g. human studies with clinical or pharmacodynamic end points, studies using animal models or in vitro studies as long as they are appropriately justified and/or validated.

Is this enough?

1. The US / EU / Asian laws are sufficient and convince me to say that generics are like the original products.

2. While accepting the laws, I'm not convinced and would like to have additional information from the producers.

3. What is required by law is insufficient and the laws need to be changed.

Only ONE answer (1, 2 or 3), please!
What shall we discuss?

1. The EU and US laws
2. Approach to PK bioequivalence
3. Approach to microbiological and therapeutic equivalence
   - MIC, MPC, heteroresistance …
   - Approach to pharmacodynamic equivalence
   - PK/PD animal models and clinical data

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).

G.J. Moet et al. / Diagnostic Microbiology and Infectious Disease 65 (2009) 319–322

-6

-19

-16

-35

-42

RLOT replicates

Zosyn® lots

Generic lots (23; 4/2008)

Generic lots (23; this report)

Potency variations (%)

●=RLOT, X=average variation, —=range of results

Fig. 1. Extent of potency variations among 4 groups of experiments with piperacillin/tazobactam intravenous injection lots.
MIC values (vancomycin)

Table 1 Comparison of antimicrobial activity against various clinical isolates in a brand name and generic antibiotics

<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></td>
<td></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 higher than for the reference product...
MIC values (meropenem)

MICs determined by arithmetic dilutions for strains displaying MICs ranging from 0.125 to 128 mg/L (geometric values)

Susceptible strains (MIC ≤ 2 mg/L)

Intermediate strains (2 ≤ MIC < 8 mg/L)

Resistant strains (MIC > 8 mg/L)

Van Bambeke et al., in preparation

MERONEM® = meropenem commercialized by AstraZeneca
Killing curves and hetero-resistance (vancomycin)

FIG 1 Vancomycin population analysis profile of S. aureus GRP-0109 after being isolated from a patient with persistent bacteremia and unsuccessful generic treatment, indicating altered susceptibility in comparison with strain ATCC 29213: 10 times more cells were able to grow at 1 mg/liter of vancomycin, 4 times more grew at 2 mg/liter, and 2.5 times more grew at 3 mg/liter (resistance frequency data at right).

Killing curves and hetero-resistance (vancomycin)

**FIG 1** Vancomycin population analysis profile of *S. aureus* GRP-0109 after being isolated from a patient with persistent bacteremia and unsuccessful generic treatment, indicating altered susceptibility in comparison with strain ATCC 29213: 10 times more cells were able to grow at 1 mg/liter of vancomycin, 4 times more grew at 2 mg/liter, and 2.5 times more grew at 3 mg/liter (resistance frequency data at right).

**FIG 3** Pre- and postexposure PAP of *S. aureus* GRP-0109 (AUC in parentheses). Values for the initial isolate are plotted. Treatment with innovator vancomycin (Lilly) caused a down and left curve shift, indicating a reduction in the less susceptible subpopulations, which is sharply different from three generics, which had higher AUCs and up and/or right displacement of the curve, (especially Proclin), due to resistant subpopulation enrichment. The control saline group exhibited a down and left displacement, consistent with reversion of unstable resistance associated with reduced fitness. The limit of detection for all of the postexposure isolates was 10 CFU/ml, and for the GRP-0109 initial strain the limit was 0 CFU/ml.

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

Neutropenic thigh mouse 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 ineffectve 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

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.

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

Neutropenic thigh mouse model

Figure 3. Unpredictability of therapeutic equivalence from pharmaceutical equivalence. The graph illustrates the dose-response curves of gentamicin made by three well-reputed makers: Abbott, Sigma and S. Plough. Abbott and Sigma were indistinguishable from S Plough in terms of concentration and potency of the active pharmaceutical ingredient, MIC, MBC, MBC/MIC ratios but significantly different in terms of therapeutic efficacy, although the same batch of each product was tested in vitro and in vivo.

doi:10.1371/journal.pone.0010744.g003

Gentamicin: evidence of non-equivalence for survival in animals

Neutropenic thigh mouse model

Figure 4. Results from survival experiments. Log-rank test curves obtained from neutropenic mice infected in the thighs with *P. aeruginosa* GRP-0019 and treated during 4 days with placebo (n = 5), GNT-Recipe (n = 10), or the innovator of gentamicin (n = 10) at the dose required for maximal effect (768 mg/kg per day divided q6h), starting 2 h (panel A) or 6 h (panel B) post-infection. Uninfected neutropenic mice serving as toxicity controls received the same treatment and were identical to the other animals but, instead of *P. aeruginosa*, were mock-inoculated in the thighs with sterile saline (n = 5 mice per gentamicin product). No significant impact on survival was detected between both gentamicin products. doi:10.1371/journal.pone.0010744.g004

Clinical alerts (efficacy and safety) ?

Safety and efficacy of generic drugs with respect to brand formulation

Luca Gallelli¹, Caterina Palleria¹, Antonio De Vuono², Laura Mumoli¹, Piero Vasapollo², Brunella Piro³, Emilio Russo³

¹Department of Health Science, Regional Center on drug information, Mater Domini University Hospital, Italy and Chair of Pharmacology, School of Medicine, University of Catanzaro, ²Department of General Medicine, ASP Cosenza, ³Department of Pharmacovigilance, ASP Cosenza, Italy


In this case-review, we report the lack of efficacy during treatment with generic formulations of fluoroquinolones and discuss the relative reasons also considering the limitations of this legal approach.
Clinical alerts (efficacy and safety)?

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.
And what about pharmaceutical quality?

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, give your FIRST choice (1, 2 OR 3) OR choose 4 OR 5
What shall we discuss?

1. The EU and US laws
2. Approach to PK bioequivalence
3. Approach to microbiological and therapeutic equivalence
   - MIC, MPC, heteroresistance …
   - Approach to pharmacodynamic equivalence
   - PK/PD animal models and clinical data
4. Dissolution, stability, impurities
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

Brand name meropenem

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

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

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

Van Bambeke et al., in preparation
Are Primary Health Care Professionals (nurses) happy? (meropenem)

**dissolution time**

Repeated Measures ANOVA
- P value: 0.1136
- P value summary: ns

**questionnaire - solubilisation**

Repeated Measures ANOVA
- P value: 0.3084
- P value summary: ns

Van Bambeke et al., in preparation
Impurities in meropenem: coloured compounds

Van Bambeke et al., in preparation
Impurities in meropenem: coloured compounds

Van Bambeke et al., in preparation
Substandard (wrong) drugs in the world?

Figure 1.

Figure 1. Examples of recent accounts of substandard drugs around the world

Falsified Medicines: An EU reaction

DIRECTIVE 2011/62/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 8 June 2011
amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products
(Text with EEA relevance)


with an immediate follow-up from the Industry

http://www.egagenerics.com/index.php/publications
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
   2. lack of innovative research …
      and research for those who pay …
"Low cost antibiotics" and "prudent use" …

The sour Danish experience

Figure 1. (a) Comparison of the number of ciprofloxacin trade names for oral use (thick line) and the median price per DDD registered monthly in PHC in Denmark (thin line), and the influence of the introduction of generics. The arrow marks the time of introduction of generic versions of ciprofloxacin. (b) The influence of removal of 50% reimbursement and of the introduction of generics on the total use of ciprofloxacin and median price per DDD registered monthly in PHC in Denmark (thin line). Consumption (thick line) is expressed in terms of DDDs per 1000 inhabitants per day. The arrows mark the times of removal of reimbursement of ciprofloxacin and the introduction of generic versions, respectively. 100 DDK≈13 EUR.

Innovative antibiotic development is abandoned

Innovative antibiotic development is abandoned

May 22, 2013: HHS forms strategic alliance to develop new antibiotics

**Date:** May 22, 2013

**Company:** GlaxoSmithKline of North Carolina

**Contract amount:** This agreement is not a contract; other transactional authority was used to create a strategic alliance. BARDA will contribute $40 million over 18-months. The agreement can be extended up to five years and up to a total of $200 million

**About the contract:** The agreement is the first in which BARDA has taken a portfolio approach with a private sector company instead of contracting to develop a single medical countermeasure. The agreement is flexible, allowing drug candidates to be moved in or out of the portfolio, based on advanced development stage and technical considerations, during joint semi-annual portfolio reviews. Under the agreement, GSK researchers will conduct safety and toxicity testing, clinical pharmacology studies, clinical studies, and non-clinical studies to support approval to treat illnesses caused by bioterrorism agents like anthrax, plague and tularemia, as well as address antibiotic resistance. One of the antibiotics to be further developed under this agreement is GSK‘944, the first in class of drugs that targets bacterial DNA replication in a unique fashion. GSK has conducted studies in which GSK‘944 protected or successfully treated animals suffering from anthrax, plague, or tularemia.

**Additional information:** The partnership with GSK is funded by BARDA’s Broad Spectrum Antimicrobials Program. BARDA is seeking additional proposals for broad-spectrum antimicrobials that could potentially treat or prevent illnesses due to biological threat agents. Proposals are accepted through the Broad Agency Announcement BARDA-EAA-12-100-SOL-00011 at www.fbo.gov.

**Press Release:** HHS forms strategic alliance to develop new antibiotics

http://www.piersystem.com/go/doc/3803/1863406/
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)

• Improved criteria for anti-infective drugs (MIC, MPC, animal PK/PD, …) are probably necessary (but are not yet implemented)

• Antibiotics are cheap (compared to other chemotherapeutic agents), making discussion about costs largely irrelevant … while savings in this area may cause HUGE expenses now and later…

• Antibiotics might be a good starting point to modify the current legislative framework concerning generics at the level of the EU-Parliament, the US Congress, and Asian Countries Authorities …
Back-up
You said "generics"

Lead generic companies resort to multiple strategies for growth. These include:

- applying for **generic approvals** with Food and Drug Administration (FDA) and European Medicines Agency (EMA);
- **merger and acquisitions**;
- developing a strong and innovative **generic drug pipeline**;
- **improving infrastructure** to enhance manufacturing and R&D capabilities;
- **new product launches**, and geographic expansion.

If absorption is markedly delayed, you also have a lower initial AUC.
Additional criteria for early AUC (EMA) *

- Use the partial **AUC truncated** at the population median of $T_{\text{max}}$ for the reference formulation for products where rapid absorption is of importance

Unsolved problems with PK-based bioequivalence … (application to antibiotics)

- Is **PK equivalence** leading to **pharmacological equivalence**?
  - *in vitro* testing (MIC, MPC, impact on hetero-resistance) …
  - PK/PD models (animals)
  - Clinical studies (?)

- What about **intravenous forms**?
  (that, by definition, are not amenable to conventional bioequivalence studies)

- What about
  - dissolution times (critical in a nursing environment)
  - stability (penems, e.g.)
  - impurities (do you like them?)
  - …
Are generic really comparable?

<table>
<thead>
<tr>
<th></th>
<th>generic A</th>
<th>reference</th>
<th>generic B</th>
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<tbody>
<tr>
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<tr>
<td>Minimum</td>
<td>12.00</td>
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<tr>
<td>25% Percentile</td>
<td>19.50</td>
<td>32.00</td>
<td>29.00</td>
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<tr>
<td>Median</td>
<td>26.50</td>
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<tr>
<td>75% Percentile</td>
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<tr>
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<td>36.00</td>
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<tr>
<td>Mean</td>
<td>25.92</td>
<td>34.92</td>
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<tr>
<td>Std. Deviation</td>
<td>8.262</td>
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<tr>
<td>Lower 90% CI</td>
<td>21.63</td>
<td>32.56</td>
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<tr>
<td>Upper 90% CI</td>
<td>30.20</td>
<td>37.27</td>
<td>33.27</td>
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</table>

**AUC (mg x L⁻¹ x h)**

<table>
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<th>generic a</th>
<th>reference</th>
<th>generic B</th>
</tr>
</thead>
<tbody>
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<tr>
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<td>1.307</td>
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<tr>
<td>Upper 90% CI</td>
<td>1.473</td>
<td>1.570</td>
<td>1.523</td>
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Are generic really comparable?

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<td>34.92</td>
<td>31.17</td>
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<td>geometric mean</td>
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<td>30.90</td>
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<td>0.89</td>
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<tr>
<td>higher 110</td>
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<td>0.83</td>
<td>0.92</td>
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Are generic really comparable?

Ratio of AUCs with calculation of the geometric means (point estimates)

<table>
<thead>
<tr>
<th></th>
<th>ratio A/ref</th>
<th>ratio B/ref</th>
</tr>
</thead>
<tbody>
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<td>Number of values</td>
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<tr>
<td>Median</td>
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<tr>
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<tr>
<td>Maximum</td>
<td>1.1300</td>
<td>1.0600</td>
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<tr>
<td>Mean</td>
<td>0.7583</td>
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<tr>
<td>Std. Deviation</td>
<td>0.2620</td>
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<tr>
<td>Std. Error</td>
<td>0.07565</td>
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<tr>
<td>Geomean</td>
<td>0.7072</td>
<td>0.8924</td>
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</table>

90% CI around point estimate (0.58-0.83)

90% CI around point estimate (0.86-0.92)
Special situations (EU)

Narrow therapeutic index drugs

- In specific cases of products with a narrow therapeutic index, the acceptance interval for AUC should be tightened to 90.00-111.11%. Where Cmax is of particular importance for safety, efficacy or drug level monitoring the 90.00-111.11% acceptance interval should also be applied for this parameter. It is not possible to define a set of criteria to categorise drugs as narrow therapeutic index drugs (NTIDs) and it must be decided case by case if an active substance is an NTID based on clinical considerations.

Highly variable drugs or drug products

- The extent of the *widening* is defined based upon the within-subject variability seen in the bioequivalence study using scaled-average-bioequivalence according to \([U, L] = \exp[\pm k \cdot sWR]\), where \(U\) is the upper limit of the acceptance range, \(L\) is the lower limit of the acceptance range, \(k\) is the regulatory constant set to 0.760 and \(sWR\) is the within-subject standard deviation of the log-transformed values of Cmax of the reference product (Important: this applies to \(C_{\text{max}}\) only, NOT to AUC)

<table>
<thead>
<tr>
<th>Within-subject CV (%)*</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>80.00</td>
<td>125.00</td>
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<tr>
<td>35</td>
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<td>40</td>
<td>74.62</td>
<td>134.02</td>
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<tr>
<td>45</td>
<td>72.15</td>
<td>138.59</td>
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<tr>
<td>(\geq 50)</td>
<td>69.84</td>
<td>143.19</td>
</tr>
</tbody>
</table>

* \(CV(\%) = 100\sqrt{e^{\frac{s^2}{2}} - 1}\)
Potency (oxacillin)

Figure 1 Concentration-response relationship of innovator and generic products of oxacillin in the microbiological assay. A. The slopes and intercepts of OXA-BLA, OXA-COL, OXA-OPH, OXA-PEN, and OXA-SCA were not statistically different from those of OXA-BMS (innovator), thus confirming their pharmaceutical equivalence (P = 0.1165). The standard curves of all products are better described by a single linear regression, shown here with the 95% confidence interval. B. The slopes and intercepts of OXA-CAR, OXA-EXP, OXA-MEM and OXA-VIT were significantly different to the innovator’s (P < 0.03458), thus failing pharmaceutical equivalence. As generic products belong to populations different to that of the innovator, each is described by an independent linear regression with their respective coefficient of determination (r²).

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

**C<sub>max</sub>/MIC**

![Graph showing C<sub>max</sub>/MIC relationship](image)

- **P=0.06** (CFA)
- **AdjR<sup>2</sup> = 0.808**

**Time>MIC**

![Graph showing Time>MIC relationship](image)

- **P=0.249** (CFA)
- **AdjR<sup>2</sup> = 0.796**

**AUC/MIC**

![Graph showing AUC/MIC relationship](image)

- **P=0.102** (CFA)
- **AdjR<sup>2</sup> = 0.846**

FIG 5 Influence of pharmacodynamic indices on the antimicrobial effect of metronidazole on *B. fragilis* in a neutropenic mouse thigh anaerobic infection model. Only one curve is depicted because the data belong to a single population despite the fact that they were obtained after treatments of different groups of animals with a generic product or the innovator. The AUC/MIC ratio drives the antibacterial efficacy of metronidazole.

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 SPMCIB (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 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.

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

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

A Journey to the statins ....

Do all those patients really need a statin?

Very good for the budget

Source: INAMI / RIZIV
"Low cost antibiotics" and Internet

http://antidotum.org/index.php?showtopic=424075
"Low cost antibiotics" and Internet

www.buygeneric24.org

Friendly support - acceptable prices

24/7 LIVE SUPPORT

YOUR SHOPPING CART, PLEASE SEND US YOUR ENQUIRY FOR GETTING PRICES.

<table>
<thead>
<tr>
<th>US BRAND NAME</th>
<th>GENERIC NAME</th>
<th>INDIAN BRAND</th>
<th>COMPANY</th>
<th>PACKING</th>
<th>FORM</th>
<th>STRENGTH</th>
<th>QUANTITY</th>
<th>REMOVE</th>
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<tr>
<td>Levofloxacin</td>
<td>Levofloxacin</td>
<td>LEVOFLOX/Levaquin</td>
<td>PROTEC/pia</td>
<td>30</td>
<td>Tab</td>
<td>250 mg</td>
<td>1</td>
<td></td>
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</table>

PLEASE, COMPLETE INFO BELOW (REQUIRED) FOR ENQUIRY PRICE:

First Name:  
Last Name:  
E-mail:  
Country:  
Discount code:  

Your Message:  

NEW YEAR OFFERS

FREE REGISTERED MAIL SHIPPING FOR ORDERS MORE THAN $100
FREE COURIER SHIPPING FOR ORDERS MORE THAN $150

A recent economic US study

A "natural experiment" in which Meijer, a popular Midwestern retail chain, offered 14-day supplies of certain generic oral antibiotics free of charge to customers with prescriptions from October 2006 (about 2 millions prescriptions analysed from 2004 trough 2008)

- We find that the program increased the filled prescriptions of covered (free) antibiotics while reducing those of not-covered (paid) antibiotics, with an increase in overall antibiotic prescriptions.
The situation may be worse in veterinary medicine

The consequences of generic marketing on antibiotic consumption and the spread of microbial resistance: the need for new antibiotics

P.-L. TOUTAIN & A. BOUSQUET-MELOU

UMR 1331 Toxalim INRA, INPT- Ecole Nationale Vétérinaire de Toulouse, Toulouse Cedex, France
The situation may be worse in veterinary medicine

The consequences of generic marketing on antibiotic consumption and the spread of resistance

- In France, introduction of generic fluoroquinolones increased their use by 30% in turkey (n=5500) production and 50% in chicken broiler (n=7000) production.

- The level of resistance in Spain where cheap generics are available is associated with a higher use of fluoroquinolones in poultry and pigs vs Germany, UK or Denmark where prices are higher and practice better controlled.

⇒ Generic drug promotion in veterinary medicine is not consistent with the general objective of Public Health authorities to restrict the use of antibiotics in veterinary medicine…
A spiral to death (in Belgium)?

• For antibiotics and antifungals, if a medical doctor or a dentist prescribes for an acute treatment:
  – under the name of the active compound: the rules of prescription under INN (*) are of application (delivery of the cheapest preparation available)
  – under a trade name: as from 1st May 2012, the pharmacist must deliver the product available in the group of « the cheapest drugs ».

• The drug acquisition cost for the treatment of a community-acquired pneumonia following the recommendations of BAPCOC (**) (amoxicillin [3 g / day in 3 administrations for 5 to 7 days] is only 13-14 € … (ex-factory price: ~7 €)

* INN: International International Nonproprietary Name
** BAPCOC: Belgian Antibiotic Policy Coordination Committee
A spiral to death (in Belgium)?

- For **antibiotics** and **antifungals**, if a medical doctor or a dentist prescribes for an **acute treatment**:
  - under the name of the active compound: the rules of prescription under INN (*) are of application (delivery of the cheapest preparation available)
  - under a trade name: as from 1<sup>st</sup> **May 2012**, the pharmacist must deliver the product available in the group of « the cheapest drugs ».


- The drug acquisition cost for the treatment of a **community-acquired pneumonia** following the **recommendations of BAPCOC (**)** (amoxicillin [3 g / day in 3 to 7 days] is only **13-14 €** … (ex-factory price: ~7 €)


This infernal spiral (to low prices) explains why innovators leave the field

* INN: International Nonproprietary Name
** BAPCOC: Belgian Antibiotic Policy Coordination Committee
Unless Big Brother comes to your help…

Collaborations

Harvard University - Anti-Pseudomonas Antibody Technology
Aridis is collaborating with the Laboratory of Dr. Gerald Pier on the preclinical development of Aerucin. This work is being funded by a National Institute of Health NIAID grant.

Biomedical Advanced Research and Development Authority (BARDA), US Dept. Health & Human Services - Aridis formulation technology
Aridis is working with BARDA and PATH to develop advanced stabilization formulation for influenza vaccines.

U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID, Ft. Detrick) - Gallium based anti-infective for biodefense (Panaecin)
Panaecin and new generation of gallium based complexes are being evaluated as post-exposure prophylactic anti-infectives for inhalational anthrax, tularemia, glanders, and plague.

Walter Reed Army Institute of Research (Washington, DC) - Gallium based anti-infective for wound healing (Panaecin)
Topical formulations of Panaecin are being evaluated as a topical anti-bacterial with wound healing properties.
Unless Big Brother comes to your help…

Achaogen Awarded $60M Contract Option by BARDA for the Clinical Development of Plazomicin

Achaogen, Inc. today announced the award of a $60M contract option from the Biomedical Advanced Research and Development Authority (BARDA). The option supports the conduct of a global Phase 3 superiority study that will evaluate the efficacy and safety of plazomicin in treating patients with serious gram-negative bacterial infections due to CRE. This pathogen-specific clinical study represents a new development approach to address unmet medical needs for multi-drug resistant bacterial infections. The study is expected to start in fourth quarter of 2013.

"We are excited and honored to continue the development of plazomicin in partnership with BARDA," said Kenneth J. Hillen, M.B. Ch.B., Chief Executive Officer and Chief Medical Officer of Achaogen. "The growing prevalence of CRE infections poses a substantial public health threat, given the high mortality rates associated with CRE infections. Plazomicin's strong potential to address this public health issue and to contribute to the global effort to guard against bacterial biothreats makes it a critically important agent in the antibacterial pipeline."

Plazomicin is a next-generation aminoglycoside antibiotic that Achaogen engineered to overcome key aminoglycoside resistance mechanisms. It has potent bactericidal activity against
Unless Big Brother comes to your help…

MCM Procurements and Grants

Medical Countermeasures Advanced Research, Development and Acquisition Contract and Grant Awards

October 23, 2013: New blood test would provide fast results for medical care after anthrax attack
September 26, 2013: BARDA boosts global ability to respond to pandemics
September 20, 2013: HHS funds development of freeze-dried plutonio for disaster response
September 19, 2013: BARDA funds development of drug to aid burn patients in disasters
September 19, 2013: HHS replenishes nation’s supply of anthrax antitoxin
September 18, 2013: HHS explores new emergency response use for approved steroid
September 17, 2013: BARDA funds study of therapy for thermal burns
September 16, 2013: BARDA evaluates burn dressing for radiation, sulfur mustard burns
August 23, 2013: BARDA Contract Supports Evaluation of Therapy for Severe Thermal Burns
August 22, 2013: BARDA Supports Proof-Of-Concept Studies for Small Molecule Development
July 30, 2013: BARDA contract supports development of a more effective skin graft to help burn patients after a radiologic event
June 25, 2013: BARDA supports new broad-spectrum antibiotic against glanders, melioidosis
May 24, 2013: BARDA supports new broad-spectrum antibiotic to treat anthrax, tularemia
May 22, 2013: HHS forms strategic alliance to develop new antibiotics
April 3, 2013: HHS awards contract to create test to identify resistant influenza viruses

http://www.phe.gov/newsroom/Pages/mcm-procurements.aspx
But EU is not too bad either

EU taxpayer funding: $83 \times 10^6$ euros

http://www.imi.europa.eu/
How can you COMBACTE?

CLIN-Net Network Participants

As of April 2013, 281 clinical sites in 32 countries have expressed an interest in joining CLIN-Net. In the third quarter of 2013, these sites will be approached with an explorative questionnaire to establish their current experience with clinical trials, their facilities to conduct trials and their need for (additional) GCP training.

Further auditing, site visits and certification will start in 2014.

https://www.combacte.com/?q=node/32