Thoughts on generic product properties that might impact the clinical effect: what are the downsides?

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Are they equal?

Your prescription,
your choice.

Thirty-day prescription of one brand name drug: £71
Thirty-day prescription of its generic equivalent: £22

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.

A well known antibiotic in Belgium...

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

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

2. **Levofloxacin BG (Eurogenerics)**
   - [levofloxacin]
   - compr. (séc.)
   - 10 x 500mg  Rk  b  € 21,42
   - 30 x 500mg  Rk  b  € 57,66
   - sac perf.
   - 1 x 500mg / 100ml  U.H.  [€17]

3. **Levofloxacin Fresenius Kabi (Fresenius Kabi)**
   - [levofloxacin]
   - flacon perf.
   - 1 x 500mg / 100ml  U.H.  [€17]

4. **Levofloxacin Hospira (Hospira)**
   - [levofloxacin]
   - sac perf.
   - 1 x 500mg / 100ml  U.H.  [€17]

5. **Levofloxacin Mylan (Mylan)**
   - [levofloxacin]
   - compr. (séc.)
   - 10 x 250mg  Rk  b  € 14,98
   - 14 x 250mg  Rk  b  € 24,43
   - 10 x 500mg  Rk  b  € 21,98
   - 14 x 500mg  Rk  b  € 35,13
   - flacon perf.
   - 10 x 500mg / 100ml  U.H.  [€17]

6. **Levofloxacin Sandez (Sandoz)**
   - [levofloxacin]
   - compr. (séc.)
   - 10 x 250mg  Rk  b  € 14,42
   - 10 x 500mg  Rk  b  € 21,03
   - 30 x 500mg  Rk  b  € 56,15

7. **Levofloxacin Teva (Teva)**
   - [levofloxacin]
   - compr. (séc.)
   - 10 x 250mg  Rk  b  € 14,42
   - 10 x 500mg  Rk  b  € 21,03
   - 30 x 500mg  Rk  b  € 56,16
   - sac perf.
   - 10 x 250mg / 50ml  U.H.  [€17]
   - 10 x 500mg / 100ml  U.H.  [€17]

8. **Tavanic (PI-Pharma)**
   - [levofloxacin]
   - compr. (séc.)
   - 30 x 500mg  Rk  b  € 21,14
   - (importation parallèle)

9. **Tavanic (Sanofi-Aventis)**
   - [levofloxacin]
   - compr. (séc.)
   - 10 x 250mg  Rk  b  € 14,98
   - 10 x 500mg  Rk  b  € 21,97
   - flacon perf.
   - 1 x 500mg / 100ml  U.H.  [€17]

What shall we discuss?

1. The EU and US regulations
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. True content and impurities
7. The hidden risk of "low cost" antibiotics
What shall we discuss?

1. The EU and US regulations (6 slides)
2. Approach to PK bioequivalence
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## EU regulations

**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>
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<tbody>
<tr>
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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)

EU regulations

• 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.
EU regulations: what needs to be supplied for non-biological product

- Data for Modules 1, 2 and 3 *
- **together** with data showing **bioavailability and bio-equivalence** with the original medicinal product

Special attention needs to be paid to:
- the grounds for claiming essential similarity;
- a summary of **impurities** (with an evaluation of these);
- an evaluation of the **bio-equivalence studies** or a justification why studies were not performed;
- an **update of published literature** relevant to the substance and the present application;
- every claim not known from or inferred from the properties of the medicinal product should be discussed and substantiated by published literature and/or additional studies.
- **equivalence of safety and efficacy properties of different salts, esters or derivatives** of an authorised active when he claiming essential similarity.

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* Module 1 = administrative information; Module 2 = Summaries; Module 3 = Chemical, pharmaceutical and biological information for medicinal products containing chemical and/or biological active substances; Module 4 = non-clinical reports; Module 5 = clinical reports
US regulations

- 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"

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" *

FDA approved generic drugs: "Orange book" *

[Image of FDA website]

<table>
<thead>
<tr>
<th>App No</th>
<th>TE Code</th>
<th>RLD</th>
<th>Active Ingredient</th>
<th>Dosage Form; Route</th>
<th>Strength</th>
<th>Proprietary Name</th>
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<td>INJECTABLE; INJECTION</td>
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<td>LEVOFLOXACIN</td>
<td>INJECTABLE; INJECTION</td>
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<td>LEVOFLOXACIN</td>
<td>AKORN</td>
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<td>No</td>
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<td>AURIBINDO PHARMA LTD</td>
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<td>A202328</td>
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<td>INJECTABLE; INJECTION</td>
<td>EQ 750MG/30ML (EQ 25MG/ML)</td>
<td>LEVOFLOXACIN</td>
<td>AURIBINDO PHARMA LTD</td>
</tr>
</tbody>
</table>


As in LEVAQUIN®

http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm
What shall we discuss?

1. The EU and US regulations (6 slides)

2. Approach to PK bioequivalence (9 slides)

3. Approach to microbiological equivalence
   - MIC, MPC, heteroresistance …

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5. Dissolution and stability

6. True content and impurities

7. The hidden risk of "low cost" antibiotics
Bioequivalence: principles

• Bioequivalence is an accepted surrogate for therapeutic equivalence¹ (including for branded drugs when the marketed form differs from the form used in development…)²

• Primary metrics are¹,³
  – **AUC** (area under the plasma concentration-time profile of the active substance)
    → **extent of absorption**
  – **Cₘₐₓ** (the maximum plasma concentration of the active substance)
    → **extent and rate of absorption**
  – **Tₘₐₓ** (the time at which **Cₘₐₓ** is reached)
    → **rate of absorption**

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

$\downarrow C_{\text{max}}$

$\uparrow \text{AUC}$
What if absorption is delayed?

What if absorption is delayed?

What if absorption is delayed?

What if absorption is delayed?

What if absorption is delayed?

What if absorption is delayed?

What if absorption is delayed?

What if absorption is delayed?

What if absorption is delayed?
If absorption is markedly delayed, you also have a lower initial AUC.
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  
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 \textit{PK equivalence} leading to \textit{pharmacological equivalence}?
  - \textit{in vitro} testing (MIC, MPC, impact on hetero-resistance) …
  - PK/PD models (animals)
  - Clinical studies (?)

- What about \textit{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?)
  - …
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Potency (piperacillin)

Using the incremental MIC assay (Jones et al. Diagn Microbiol Infect Dis 61:76–79).

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

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

Moet et al. Diagnostic Microbiology and Infectious Disease 2009;65: 319–322
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
# 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></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></td>
<td>12.70 ± 4.77</td>
<td>–</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td><em>Pseudomonas aeruginosa</em> (100)</td>
<td></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*¹

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.

MIC values (meropenem)

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

Van Bambeke et al., in preparation
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)

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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 of 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.

Killing curves and hetero-resistance (vancomycin)

FIG 5 Changes in resistance frequencies (RFs) to 1, 2, and 3 mg/liter of vancomycin after in vivo exposure to innovator vancomycin (Lilly), generic versions (APP, Abbott, and Proclin), or sterile saline. At 1 mg/liter, compared to initial values (GRP-0109), Lilly reduced the RFs by almost 10-fold, while generics induced no significant change. At 2 mg/liter Lilly also reduced the RFs, but generic products significantly increased them 10- to 1,000-fold. At 3 mg/liter, again Lilly reduced the RFs, APP and Abbott did not change the baseline RF, and Proclin significantly increased it by 1 order of magnitude. In the saline group RFs were reduced about 1 log_{10} at all concentrations. The asterisk indicates that the postexposure value is significantly different from the preexposure value (Student’s t test); P values of 0.0002 and 0.0005 for Lilly and saline at 1 mg/liter, respectively; P values of 0.0258, 0.0012, 0.0002, <0.0001, and 0.0029 for Lilly, APP, Abbott, Proclin, and saline at 2 mg/liter, respectively; P values of 0.0140, 0.0152, and 0.0094 for Lilly, Proclin, and saline at 3 mg/liter, respectively. CFU counts at 4 mg/liter and higher were below the limit of detection.
Production of mutant (piperacillin/tezobactam)

Table 17 Spontaneous mutant production in the diffusion gel assay for Piperacillin/Tazobactam

<table>
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<th>Sample</th>
<th>(A.\ b. \ 189)</th>
<th>(P.\ a. \ 54)</th>
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<tr>
<td></td>
<td>Median</td>
<td>(\delta)</td>
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<tr>
<td>Standard</td>
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<tr>
<td>M1</td>
<td>127.00</td>
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<tr>
<td>M9</td>
<td>123.67</td>
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<td>M18</td>
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<td>1.528</td>
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<td>M6</td>
<td>125.67</td>
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<td>M10</td>
<td>127.67</td>
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<td>M16</td>
<td>128.33</td>
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<tr>
<td>M5</td>
<td>128.00</td>
<td>1.000</td>
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<tr>
<td>M14</td>
<td>124.33</td>
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<td>F</td>
<td>2.657</td>
<td>1.898</td>
</tr>
<tr>
<td>prob.</td>
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<td>0.045</td>
</tr>
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Figure 8 Diffusion gel assay testing the production of spontaneous Meropenem resistant mutants, with A. baumanii 147 as a control strain and K. pneumoniae 63 as a mutant-producing strain.

Conclusions

All the samples analyzed by standardized microbiological methods fulfill the requirements for content according to USP XXVII. They all show the same antimicrobial behavior because they have similar MIC, MLC and CC values and produce similar numbers of mutants.
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4. Approach to pharmacodynamic equivalence
   - PK/PD (animal models) and clinical data … (8 slides)
5. Dissolution and stability
6. True content and impurities
7. The hidden risk of "low cost" antibiotics
**Vancomycin: evidence of non-equivalence**

Neutropenic tight mouse model

![Graph](image)

**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

Neutropenic tight mouse 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 vivo

Neutropenic tight 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 in vivo

Neutropenic tight 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

Metronidazole: complete equivalence

**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.

But what about clinical effectiveness?

Cost-effectiveness of empirical prescribing of antimicrobials in community-acquired pneumonia in three countries in the presence of resistance.


![Figure 2. Calculated clinical failure rates with first-line therapy in CAP due to susceptible pathogens and antimicrobial-resistant pathogens (rounded). MXF, moxifloxacin; CLR, clarithromycin; AMX, amoxicillin; AMC, co-amoxiclav; AZM, azithromycin; DOX, doxycycline; ROX, roxithromycin; CXM, cefuroxime axetil.]

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26 June 2013 Bayer Anti-infectives Advisory Board, Beijing, China
But what about clinical effectiveness?

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Figure 2. Calculated clinical failure rates with first-line therapy in CAP due to susceptible pathogens and antimicrobial-resistant pathogens (rounded). MXF, moxifloxacin; CLR, clarithromycin; AMX, amoxicillin; AMC, co-amoxiclav; AZM, azithromycin; DOX, doxycycline; ROX, roxithromycin; CXM, cefuroxime axetil.
What shall we discuss?

1. The EU and US regulations (6 slides)
2. Approach to PK bioequivalence (6 slides)
3. Approach to microbiological equivalence
   - MIC, MPC, killing curves … (8 slides)
4. Approach to pharmacodynamic equivalence
   - PK/PD animal models … (8 slides)
5. Dissolution and stability (5 slides)
6. True content and impurities
7. The hidden risk of "low cost" antibiotics
Dissolution in Japan (meropenem)...

*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

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 in Belgium (meropenem)...

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 in Belgium (meropenem)...

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
What shall we discuss?

1. The EU and US regulations (6 slides)
2. Approach to PK bioequivalence (6 slides)
3. Approach to microbiological equivalence
   - MIC, MPC, killing curves … (8 slides)
4. Approach to pharmacodynamic equivalence
   - PK/PD animal models … (8 slides)
5. Dissolution and stability (6 slides)
6. True content and impurities (4 slides)
7. The hidden risk of "low cost" antibiotics
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 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

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

Impurities in meropenem: coloured compounds

are you happy with the colour?

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

Van Bambbeke et al., in preparation
What shall we discuss?

1. The EU and US regulations (6 slides)
2. Approach to PK bioequivalence (6 slides)
3. Approach to microbiological equivalence
   - MIC, MPC, killing curves … (8 slides)
4. Approach to pharmacodynamic equivalence
   - PK/PD animal models … (8 slides)
5. Dissolution and stability (6 slides)
6. True content and impurities (6 slides)
7. The hidden risk of "low cost" antibiotics (1 slide)
"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.

Summary / Discussion

- 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.

- Antibiotics might be a good starting point to modify the current legislative framework concerning generics at the level of the EU-Parliament and the US Congress … or another "World Power"…
Back-up
Are generic really comparable?

### Arithmetic Comparison

<table>
<thead>
<tr>
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<th>Generic A</th>
<th>Reference</th>
<th>Generic B</th>
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<tr>
<td>25% Percentile</td>
<td>19.50</td>
<td>32.00</td>
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<tr>
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<td>32.50</td>
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<td>75% Percentile</td>
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### Geometric Comparison

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<td>Upper 90% CI</td>
<td>1.473</td>
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## Are generic really comparable?

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<td>0.89</td>
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<td>39.00</td>
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<td>0.38</td>
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</table>

**arithmetic mean**
- 25.92
- 34.92
- 31.17
- 0.76
- 0.89

**SD**
- 8.26
- 4.54
- 4.06
- 0.26
- 0.06

**geometric mean**
- 24.49
- 34.63
- 30.90
- 0.71
- 0.89

**CI 90**
- 0.12
- 0.03

**lower 90**
- 0.58
- 0.86

**higher 110**
- 0.83
- 0.92
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>
<tr>
<td>Number of values</td>
<td>12</td>
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<tr>
<td>Minimum</td>
<td>0.2900</td>
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</tr>
<tr>
<td>25% Percentile</td>
<td>0.6200</td>
<td>0.8700</td>
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<tr>
<td>Median</td>
<td>0.7350</td>
<td>0.8850</td>
</tr>
<tr>
<td>75% Percentile</td>
<td>0.9600</td>
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<tr>
<td>Maximum</td>
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<tr>
<td>Mean</td>
<td>0.7583</td>
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<tr>
<td>Std. Deviation</td>
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<td>0.05726</td>
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<td>Std. Error</td>
<td>0.07565</td>
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<tr>
<td>Geomean</td>
<td><strong>0.7072</strong></td>
<td><strong>0.8924</strong></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>
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</thead>
<tbody>
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<td>80.00</td>
<td>125.00</td>
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<td>35</td>
<td>77.23</td>
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<td>40</td>
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<tr>
<td>45</td>
<td>72.15</td>
<td>138.59</td>
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<tr>
<td>≥50</td>
<td>69.84</td>
<td>143.19</td>
</tr>
</tbody>
</table>

* $CV(\%) = 100\sqrt{e^{\frac{sWR^2}{2}}} - 1$