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

Paul M. Tulkens, MD, PhD

Cellular and Molecular Pharmacology
Louvain Drug Research Institute
Université catholique de Louvain
Brussels, Belgium

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

• Research grants
  – Theravance, Astellas, Targanta, Cerexa/Forest, AstraZeneca, Bayer, GSK, Trius, Rib-X, Eumedica
  – Belgian Science Foundation (F.R.S.-FNRS), Ministry of Health (SPF), and Walloon and Brussels Regions

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

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

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

Before patent expiration

<table>
<thead>
<tr>
<th>Tavanic (Pfizer)</th>
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<tr>
<td>[lévofloxacine]</td>
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<td>compr. (séc.)</td>
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<td>10 x 500mg</td>
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<td>(importation parallèle)</td>
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<table>
<thead>
<tr>
<th>Tavanic (Sanofi-Aventis)</th>
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<td>10 x 500mg</td>
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<td>flacon perf.</td>
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<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 500mg / 100ml U.H. [€35]

2. Levofloxacin BG (Eurogenerics)
   - Compr. (séc.)
     - 10 x 500mg R<sub>k</sub> b € 21.42
     - 30 x 500mg R<sub>k</sub> b € 57.66
   - Sac perf.
     - € 1 x 500mg / 100ml U.H. [€17]

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

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

5. Levofloxacin Mylan (Mylan)
   - Compr. (séc.)
     - 10 x 250mg R<sub>k</sub> b € 14.98
     - 14 x 250mg R<sub>k</sub> b € 24.43
     - 10 x 500mg R<sub>k</sub> b € 21.98
     - 14 x 500mg R<sub>k</sub> b € 35.13
   - Flacon perf.
     - € 10 x 500mg / 100ml U.H. [€170]

6. Levofloxacin Sandoz (Sandoz)
   - Compr. (séc.)
     - 10 x 250mg R<sub>k</sub> b € 14.42
     - 10 x 500mg R<sub>k</sub> b € 21.09
     - 30 x 500mg R<sub>k</sub> b € 58.15

7. Levofloxacin Teva (Teva)
   - Compr. (séc.)
     - 10 x 250mg R<sub>k</sub> b € 14.42
     - 10 x 500mg R<sub>k</sub> b € 21.09
     - 30 x 500mg R<sub>k</sub> b € 56.66
   - Sac perf.
     - 10 x 250mg / 50ml U.H. [€35]
     - 10 x 500mg / 100ml U.H. [€170]

Tavanic (PfPharma)
- Compr. (séc.)
  - 10 x 500mg R<sub>k</sub> b € 21.94
  (importation parallèle)

Tavanic (Sanofi-Aventis)
- Compr. (séc.)
  - 10 x 250mg R<sub>k</sub> b € 14.98
  - 10 x 500mg R<sub>k</sub> b € 21.97
  - Flacon perf.
    - € 1 x 500mg / 100ml U.H. [€17]
And also in Vietnam for all fluoroquinolones… coming from all over the world

Daiichi (Japan) is actually the originator!
And all over the world...
Why choosing a "generic" antibiotic?

1. Because it is like airlines: low cost is better
2. Because they have the same quality as the original ones
3. Because they can be produced locally (in my country) (as opposed to countries of "Big Pharma")
4. Because my patients / my hospital / my country has/have limited resources
5. Because "old antibiotics" (no longer under patent) cover most of my needs

Please, vote now (1 choice)
I guess the real and only justifiable answer is...

Your prescription, your choice.

$71
Thirty-day prescription of one brand name drug

$22
Thirty-day prescription of its generic equivalent

Much cheaper!
What shall we discuss?

1. A political choice (US and EU laws as an example)
2. Approach to PK bioequivalence
3. Approach to microbiological equivalence
4. Approach to pharmacodynamic equivalence
5. Problems related to dissolution and stability
6. Impurities and falsified medicines
7. The hidden risks of "low cost" antibiotics
The US Law

PUBLIC LAW 98-417—SEPT. 24, 1984

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 Restora-
tion 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)
In the European Union

 on the Community code relating to medicinal products for human use
 (OJ L 311, 28.11.2001, p. 67)

* Legislative act of the European Union that is then translated into country-specific laws for actual implementation, which may vary (in details) between countries (vs regulations that are self-executing and do not require local adaptations)

• …the applicant shall not be required to provide the results of pre-clinical tests and of clinical trials if he can demonstrate that the medicinal product is a generic of a reference medicinal product…

• …‘generic medicinal product’ shall mean a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies…

1st round of conclusions and discussions

• The decision to go for generics is a political decision

• It finds its origin and basis in
  – the limited duration of the patent protection
    (usually about 20 years post patent application), which makes generics possible after about 10 years of effective commercialisation)
  – the fact that drug production costs are usually very low
    (often only a very minor fraction of the total requested by the innovator at the time of initial commercialization)

• The main and only incentive in the promotion of the generics is, for governments, to acquire and provide drugs more cheaply to the population
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** \(^1\) (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?

- $C_{\text{max}}$
- AUC

Graph showing concentration over time.
What if absorption is delayed?

![Graph showing time (h) vs. concentration (mg/L) with annotations for C_max and T_max.]

7/03/2015 9th RTI Forum, Ho-Chi-Minh City, Vietnam
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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**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 “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  
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 \(^1-^3\)

Is this enough? What do you think?

1. The US / EU laws (or the law of my country) are sufficient and convince me to say that generics are like the original products

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

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

Please, vote now (1 choice)
What shall we discuss?

1. A political decision (US and EU laws as an example)
2. Approach and limits to PK bioequivalence studies
3. Approach to microbiological and therapeutic equivalence
   - MIC
   - PK/PD animal models
   - clinical data (case reports)

http://www.umu.se/english/research/research-excellence/strong-research/Infection+Biology
Last visited: 25 March 2014

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).

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

Moet *et al.* Diagnostic Microbiology and Infectious Disease 2009;65: 319–322
MIC values (vancomycin)

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

<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>54.4</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>MRSA (147)</td>
<td>7</td>
<td>28.09 ± 10.29</td>
<td>59.2</td>
</tr>
<tr>
<td>Cefotiam</td>
<td>Staphylococcus aureus (100)</td>
<td>7</td>
<td>8.71 ± 3.04</td>
<td>87.0</td>
</tr>
<tr>
<td></td>
<td>Escherichia coli (100)</td>
<td>7</td>
<td>12.00 ± 5.89</td>
<td>77.0</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>Streptococcus pneumoniae (126)</td>
<td>6</td>
<td>12.70 ± 4.77</td>
<td>81.7</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>Pseudomonas aeruginosa (100)</td>
<td>2</td>
<td>3.00 ± 2.83</td>
<td>95.0</td>
</tr>
<tr>
<td>Meropenem</td>
<td>P. aeruginosa (100)</td>
<td>7</td>
<td>18.57 ± 3.46</td>
<td>78.0</td>
</tr>
<tr>
<td>Imipenem</td>
<td>P. aeruginosa (100)</td>
<td>4</td>
<td>9.00 ± 2.58</td>
<td>88.0</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 Bambake et al., in preparation
Vancomycin: evidence of non-therapeutic equivalence revealed by a PK/PD animal model

Neutropenic mouse thigh infection model

FIG. 1. In vivo efficacy against *S. aureus* GRP-0057 (years 2002 and 2003) at a low inoculum (4.30 ± 0.05 log$_{10}$ CFU per thigh when subcutaneous treatment q1h started). Vancomycin generic products are compared with the innovator (VAN-Lilly) in dose-effect experiments (2.34 to 1,200 mg/kg per day) using the neutropenic mouse thigh infection model (each data point represents the mean CFU/g of both thighs from a single mouse). (A) Pharmacodynamic patterns of VAN-Abbott US and VAN-Lilly fitted to the Hill model. Despite containing a significantly greater concentration of API (125%), VAN-Abbott US was completely ineffective in vivo. VAN-Abbott US is shown in a separate graph because of its greater AUC/MIC ratio than that of VAN-Lilly (123%; their dosing regimens were identical). (B) VAN-APP and VAN-Proclin were both pharmacologically 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.

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.”
Safety and efficacy of generic fluoroquinolones compared to brand formulation

Luca Gallelli1, Caterina Palleria1, Antonio De Vuono2, Lisa Fuso1, Emilio Russo1

1Department of Health Science, Regional Center on drug information, Maltese School of Medicine, University of Catanzaro, 2Department of General Medicine and Infectious Disease, Catanzaro Hospital, Catanzaro, 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.

CONCLUSION

In conclusion, the use of generic drugs could be related with an increased days of disease (time to relapse) or might lead to a therapeutic failure; on the other hand, a higher drug concentration might expose patients to an increased risk of dose-dependent side-effects. Overall, it is advisable to well evaluate the effects of generic formulations during the therapeutic treatment.

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

ACKNOWLEDGMENTS

The Italian Drug Agency (Agenzia Italiana del Farmaco) is kindly acknowledged for its financial and technical support.
2nd round of conclusions and discussions

• There are contradictory observations about the **pharmacodynamic and therapeutic equivalence** of generic antibiotics, (even from the same investigators when comparing different products!)

• The reasons for a non-equivalence remain often obscure but may be related to **differences in biophysical properties** that will impact on the inter- and intra-organ bioavailability, which **cannot be detected by simple measurements of serum levels**

• This needs to be further studied, but, at this point, is beyond the clinician’s grip!

Who can we really trust?
And this brings me to **pharmaceutical quality**…

What is your opinion?

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

Please, vote now (1 choice)
Dissolution of meropenem in Japan

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

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

Van Bambeke et al., in preparation

7/03/2015 9th RTI Forum, Ho-Chi-Minh City, Vietnam
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
Impurities in meropenem: coloured compounds

Van Bambeke et al., in preparation

are you happy with the colour?

generic B  originator
Impurities in meropenem: coloured compounds

**OD$_{490\text{nm}}$ - 24°C**

- **OD$_{490\text{nm}}$ - 37°C**

**Van Bambeke et al., in preparation**
Impurities in ciprofloxacin...

Available online at www.sciencedirect.com


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 ± 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

This is a synthesis precursor!

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

Substandard (wrong) drugs in the world?

A concerted effort is required on the part of governments, drug manufacturers, charities and healthcare providers to ensure that only drugs of acceptable quality reach the patient.
Problems appearing in Europe!

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

http://www.mediplanet.be/fr/content/la-belgique-retire-4-m%C3%A9dicaments-commercialis%C3%A9s-par-la-soci%C3%A9t%C3%A9-indienne-gvk-biosciences
Last accessed: 08/02/2015

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/8-informer/Ackualite/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!

http://www.mediplanet.be/fr/content/la-belgique-retire-4-m%C3%A9dicaments-commercialis%C3%A9s-par-la-soci%C3%A9t%C3%A9-indienne-gvk-biosciences
Last accessed: 08/02/2015

Last accessed: 08/02/2015

The lists makes 135 pages
We also have the problem of the counterfeited drugs

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

- 25% of drugs sold worldwide are substandard and 50% in some Countries...
- It hurts low and middle income countries the most...

Slide kindly communicated by S. Opal

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 counterfeit medical products.
- supplying, offering to supply and trafficking in counterfeit 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.

Important information

- Information document on the Medicrime Convention
  This document is multilingual: English, Spanish, Russian, French
- Fact sheet: Counterfeit Medicines (October 2013)

Map of Countries

that have signed the MEDICRIME Convention

Latest update: Ratification of Moldova

Last accessed: 20/02/2015
An European action is ongoing … but is costly

Last accessed: 20/02/2015

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MEDICRIME: which countries?

Signatures & Ratifications of the Medicrime Convention

**Signatures**
- Armenia: 20/09/2012
- Austria: 28/10/2011
- Belgium: 24/07/2012
- Cyprus: 28/10/2011
- Denmark: 12/01/2012
- Finland: 28/10/2011
- France: 28/10/2011
- Germany: 28/10/2011
- Hungary: 26/09/2011
- Iceland: 28/10/2011
- Italy: 28/10/2011
- Liechtenstein: 07/11/2013
- Luxembourg: 22/12/2011
- Moldova: 20/09/2012
- Portugal: 28/10/2011
- Russia: 28/10/2011
- Spain: 08/10/2012
- Switzerland: 28/10/2011
- Turkey: 29/06/2012
- Ukraine: 28/10/2011
- Guinea: 10/12/2012
- Israel: 28/10/2011
- Morocco: 13/12/2012

**Ratifications**
- Moldova: 14/08/2014
- Hungary: 09/01/2014
- Spain: 05/08/2013
- Ukraine: 20/08/2012

https://www.edqm.eu/medias/images/medicrime_world_map_with_list_english.jpg
Last accessed: 20/02/2015
3rd round of conclusions and discussion

• Generic drugs **may or may not** be of the same pharmaceutical quality as the original products

• The reasons for lower quality are
  – difficulties in **correctly reproducing the manufacturing and purifications procedures** of the originator (often more a “know how” than patentable matters)
  – the **race to low prices**
  – the fact that **controls may be insufficient** (after first registration)

• Only **stringent and continuous controls by public authorities** can help avoiding the flood of low quality products (but this may be difficult in face of the number of producers)

---

Do you remember how many **levofloxacin**S we now have in Belgium
What shall we discuss?

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

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.

Innovative antibiotic development is abandoned by Industry

Why do they abandon it?

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

Summary / Suggestions

• The decision to "go for generics" is a political one that may need revision (at political level) to avoid over-use of antibiotics

• **Pharmacokinetic criteria** are, so far, the (nearly) only ones adopted and accepted by the Regulatory Authorities (EMA / FDA / others…)

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

• The **control of the quality of the generics** (and of all antibiotics in general) is critical and should go beyond simple declarations and initial lot analysis…

• **Antibiotics are a precious commodity** that should not be lost. Misuse through low prices may cause **HUGE expenses in the future**…
Thank you for your attention!

And ask questions