Generics, copies, substandard drugs: How to assess quality of drugs?

Disclosure:

• Merck International Fellow in Clinical Pharmacology (past)
• Consultant to MSD (past)
• Consultant to Teva Pharmaceutical (past)
• Sanofi-Aventis Advisory board on biosimilars (present)
• Consultant to Neuroderm. (present)
• Consultant to Boehringer Ingelheim (present)
Global Drug Expenditure

IMF, November 2013, The global use of medicines: Outlook through 2017
Annual New Drug Launches

IMS, April 2014. Medicine use and shifting cost of health care.
US Spending on Drugs - 2013

Drug Expenditure by Medical Discipline

 IMS, November 2013, The global use of medicines: Outlook through 2017
Generic Medicines

- Significant decrease in cost (70-90%)
- 1.2 trillions over the last 10 years

Diagram:
- Generic
- Brand
- 86% Volume of Prescriptions
- 100%

Graph:
- $\$\$
- $250$
- $200$
- Percent (%)
- Volume of Prescriptions
Approval of Generic Drugs

- Active ingredient
- Dosage form
- Strength
- Route of administration

Similar:
- Extent of absorption ($C_{max}$)
- Rate of elimination (AUC)
Approval of Generic Drugs

- Pharmaceutical Equivalence
- Bioequivalence
  
Exemption from long and expensive Phase III studies
## Efficacy & Safety of Generic Medicines

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Studies</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-Blockers</td>
<td>6</td>
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</tr>
<tr>
<td>Diuretics</td>
<td>10</td>
<td>135</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>4</td>
<td>242</td>
</tr>
<tr>
<td>Antiplatelet</td>
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</tr>
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<td>ACE Inhibitors</td>
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<td>138</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td><strong>30</strong></td>
<td><strong>847</strong></td>
</tr>
</tbody>
</table>

## Efficacy & Safety of Generic Medicines

### Table: Effect Size and Favors

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Studies</th>
<th>Subjects</th>
<th>Effect Size (95% CI)</th>
<th>Favors</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-Blockers</td>
<td>6</td>
<td>135</td>
<td>0.00 (−0.24 to 0.25)</td>
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<tr>
<td>Diuretics</td>
<td>10</td>
<td>135</td>
<td>−0.03 (−0.28 to 0.22)</td>
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<tr>
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<td>242</td>
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<tr>
<td>Antiplatelet agents</td>
<td>2</td>
<td>50</td>
<td>0.21 (−0.19 to 0.61)</td>
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<tr>
<td>ACE inhibitors</td>
<td>1</td>
<td>23</td>
<td>−0.09 (−0.68 to 0.50)</td>
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**Overall** 30 847

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Low Adoption Rate

- Negative editorials
- Patient’s fear from low quality drugs
- Lack of knowledge regarding the approval process
- Switching without explanation
- Low quality “copies” (substandard)
The Imatinib Revolution

IRIS Study - 8 Years Follow-Up Data

- Overall survival 85%
- Overall Survival* 93% (CML related only)
- Event free survival 81%

Disappointing low (~30%) penetration rate

Approval of Generic Imatinib
Imatinib Response Failure

- The emergence of mutations/duplications
- Inconsistent adherence
- Severity of disease at presentation
- Pharmacokinetic variability

Through imatinib concentrations:
- Higher levels = better response
- Threshold levels of 1,000 ng/ml
Imatinib Through Threshold

Through imatinib > 1000 ng/ml:

• Better clinical response
• Better molecular response
• Better Cytogenetic response
CCyR & Imatinib Through

CCyR & Imatinib Through

Approval of Generic Imatinib

Single Dose Pharmacokinetics
- Similar Cmax
- Similar AUC
- Similar Through Concentration?
Clinical Experience with Copies of Imatinib

- No data on EMA or Health Canada approved generics
- Relapse after switching from Gleevec to copies:

  **Limited Value**
  - Single anecdotal case reports
  - No data on the quality of the copy drug

- Observational studies
Clinical Experience with Copies of Imatinib

Generic Formulation Used in Turkey (N=145)

- Switched to generic (N=80)
- Remained on Gleevec (N=65)

Median follow up – 12 months

- MMR: 75% vs. 77%
- Dose/w: 2814 mg vs. 2744 mg

Clinical Experience with Copies of Imatinib

Generic Formulation Used in Japur India (N=213)

Treated by generic (N=76)
Treated by Gleevec (N=137)

Lower socioeconomic status of patients in the Gleevec arm

CMR 47% 32%
Clinical Response 96% 88%

Cost of Imatinib Therapy

Approval of Generic Imatinib

Expected Changes

• Substantial cost reduction
• Enhanced penetration
• Improved adherence
Approval of Generic Imatinib

Ensuring Quality

• Approval in accordance with guidelines
• Mandatory post-switching intense clinical and laboratory monitoring
• Empowerment of medical staff and patients