Proof of interchangeability of pharmaceutical products and assurance of their quality in Ukraine

Olga Baula
State Pharmacological Center MoH Ukraine

e-mail: baula@pharma-center.kiev.ua
site: www.pharma-center.kiev.ua
phone: +38 (044) 498 4303

ICDRA
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The geographical center of Europe is situated on the territory of Ukraine.

Population = 46.3 million

- Area – 603,700 km² (5.7% area of Europe)
- 2nd in Europe by area size

Situated in the South-East of East-European Valley (Central-Eastern Europe)
Pharmaceutical Sector of Ukraine

Registration certificates
12972

Finished pharmaceutical products (FPP)
10869
Domestic – 3322 (25.6%)
Imported – 7547 (58.1%)

FFP packaging from in bulk
872
Domestic – 101 (0.8%)
Imported – 761 (5.9%)

Active pharmaceutical ingredients (API)
1241
Doemstic – 192 (1.5%)
Imported – 1049 (8.1%)

Share in money
– $2 billion

Increase of market share
– at least 20% per year

Manufacture
– 147 domestic enterprises
1993 – registration process for pharmaceuticals was launched in Ukraine


2001 – alignment of rules governing pharmaceuticals in Ukraine with EU principles

2005 – adoption of a set of regulations related to generic interchangeability
Regulatory requirements for equivalence assessment of generic products in Ukraine

- Decree of the Cabinet of Ministers of Ukraine of May 26, 2005 № 376 (as amended)
- Order of the Ministry of Health of Ukraine of 26.08.2005 №426 (as amended)
- Order of the Ministry of Health of Ukraine of 17.04.2007 №190
Harmonization

Regulatory requirements adopted in Ukraine concerning bioavailability and bioequivalence studies of generic products have been developed in compliance with EMEA guidelines and WHO recommendations.
Pharmaceuticals are

Innovator (13% in Ukraine)

- Has reliable evidence of efficacy, safety and quality, is originally registered based on full registration dossier and is/was under the patent protection

Generic (73% in Ukraine)

- Meets the same quality, efficacy and safety standards as an innovation product, designed for its therapeutic interchangeability and marketed after expiry of the patent or exclusivity right to an innovation product

Interchangeability of Pharmaceuticals

- Equivalent (therapeutically interchangeable)

Quality

Efficacy

Safety
Interchangeability
Main feature of generic is a therapeutic interchangeability

Pharmaceutical equivalence
- Identity of qualitative and quantitative parameters of active ingredient
- Identity of dosage form
- Identity or similarity of excipient’s content
- Equivalence of pharmaceutical development
- Equivalence of quality specifications and requirements to manufacture (GMP)

Bioequivalence

Pharmaceutical alternatives
- Same molar amount of the same active pharmaceutical moiety
- Active pharmaceutical ingredient has different chemical form (other salts or ethers)
- Different pharmaceutical form (tablets, capsules)
- Equivalence of pharmaceutical development
- Equivalence of quality specifications and requirements to manufacture (GMP)

Two products are bioequivalent if they are:
- Pharmaceutically equivalent or pharmaceutically alternatives
- Have similar bioavailability
- Provide the same efficacy and safety after administration in the same molar dose
**Structure of pharmaceuticals registered in Ukraine**

- Solid oral: 2%
- Parenteral: 3%
- Topical: 5%
- Liquid oral: 5%
- Nasal, ophthalmic, aerosol: 9%
- Biological: 19%
- Homeopathic: 57%

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**About 5500 generic products which interchangeability to be justified including:**

- **35%** - registered based on BE/BA documented evidence

**About 1,5%** - pharmaceutical products registered for «historical reasons»

**63% - generic products ???**
Equivalence assessment procedure

**Comparator**
- At least 3 bathes from which one with interim results of dissolution testing is selected

**Generic**
- At least 1/10 manufacturing batch or manufacturing batch (<100,000 items)

- Pharmaceutical equivalence or alternatives
  - In vitro comparative studies using dissolution testing
    - In vivo comparative studies
      - In vitro/in vivo correlation (IVIVC)
In vitro comparative studies

**Biowaiver** – is a procedure for registration of solid dosage forms based on Biopharmaceutics Classification System (BCS) and results of in vitro comparative studies using dissolution testing.

**Products registered through biowaiver procedure**

- Diazepam
- ASA
- Letrozole

**FPP dissolution** (FPP)

**API permeability** (API)

**API solubility** (API)
Applications for registration rejected

In 2007 each fifth application for registration was rejected

- Lack of pharmaceutical equivalence
- Inadequate quality of API
- Improper selection of a comparator product
- Non-evident BE/BA
Example of comparative pharmacokinetic studies of Fluconazole

Mean values of plasma concentration (R and T)
Substance – Fluconazole

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Lower 90%</th>
<th>Upper 90%</th>
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<tr>
<td>$C_{\text{max}}$</td>
<td>89.5639</td>
<td>98.6740</td>
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<tr>
<td>$\text{AUC}_{\text{last}}$</td>
<td>96.6373</td>
<td>109.7870</td>
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<tr>
<td>$\text{AUC}_{\text{inf}}$</td>
<td>98.3170</td>
<td>112.8023</td>
</tr>
</tbody>
</table>

Interchangeability of Pharmaceuticals
Example of comparative pharmacokinetic studies of Riluzole

Mean values of plasma concentration (R and T)
Substance – Riluzole

<table>
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<tr>
<th>Parameter</th>
<th>Lower 90%</th>
<th>Upper 90%</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>70.5435</td>
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<td>86.5047</td>
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Stages of quality assurance of generic product

- Established and justified during pharmaceutical development
- Justified by the bioequivalence assessment using in vivo and/or in vitro methods
- Provision at manufacturing process
- Evaluation and improvement throughout the product lifecycle
Next steps

- Ensuring GMP of pharmaceutical production of finished and investigational products prior to registration
- Conducting all clinical trials only in compliance with GCP
- Enforcement of post-marketing drug monitoring
WHO External assessment of regulatory functions in Ukraine

To address medium term update of BE/BA status of previously registered

Improved coordination of regulatory functions

Capacity building
Thank you for attention!

Olga Baula

e-mail: baula@pharma-center.kiev.ua
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