Biosimilars: general issues, approaches to regulation in Europe

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Main topics of presentation
- What is biological product?
- What are their differences from conventional chemical compounds?
- Why biosimilars can not be considered as generics, and then how to compare them?
- Regulation of biosimilars circulation in Europe (EMEA experience)
- Interchangeability of biotech analogues?

Biological products
- Immunobiological drugs;
- Medicines produced in terms of biotechnological processes:
  - Recombinant DNA technology;
  - Controlled expression of genes coding the production of biologically active proteins;
  - Hybrid methods and monoclonal antibodies
- Genotherapeutic and somatotherapeutic drugs
- Including: insulin, somatotropin, interferons, colony-stimulating factors, erythropoietins, heparin, coagulation factors
- Essential medicines
- Expensive drugs (2010 – up to 50% of the total circulation of medicines in the world)

Differences of biological products from chemical agents
- More complex structure (significantly higher molecular weight - aspirin (850 Da), interferon (19000 Da); three-dimensional structure (as a rule, chemicals have one-dimensional structure)
- Its formula is not definitely determined (but it is always exactly determined in chemicals)
- Interact ion with a large number of receptors (up to 100; chemicals – with 4-5 receptors)
- It is less stable during storage
- Biological drugs are more complex drugs than chemicals

Biosimilars
- Similarity
  - Identical molecule (molecular weight, a set of amino acids)
  - Same origin
- Differences
  - Different technological cycles – it is impossible to exclude changes in properties and in effect
  - Irreproducible up to 100%
- Erythropoietins – the same set and sequence of amino acids, but they differ in the parameters of glycosylation
- Granulocyte colony-stimulating factors – differ in their terminal amino acid and parameters of glycosylation

We need biotech analogues for the same purpose as generics – to provide greater availability of treatment due to lower prices of reproduced products

Why biosimilars can not be considered as generics, and then how to compare them?
- Biosimilar drug = generic?
- Differences biologicals and chemical agents, presented above, require special approach to the registration of biologicals and organization of post-marketing studies
- Searching in Medline for keywords “Drug, Generic”, we found 2270 articles
- Searching in Medline for keyword “Biological Products”, we found 313 381 articles
- Searching for combination of generics and biological products we found only 47 articles
Table 1 and Table 2

Do You see the difference?

Registration of biosimilars in Europe (EMEA)

<table>
<thead>
<tr>
<th>TOPIC</th>
<th>TITLE</th>
<th>APPLICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overarching</strong></td>
<td>Guideline on Similar Biological Medical Products</td>
<td>General, Applies to all biosimilars</td>
</tr>
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<td><strong>Quality</strong></td>
<td>Guideline on Similar Nonclinical Medical Products Containing Biotechnology-Derived Proteins as Active Substance: Quality Issues</td>
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<tr>
<td><strong>Nonclinical &amp; Clinical</strong></td>
<td>Guideline on Similar Biological Medical Products Containing Biotechnology-Derived Proteins as Active Substance: Nonclinical &amp; Clinical Issues</td>
<td></td>
</tr>
<tr>
<td><strong>Annexes</strong></td>
<td>Recombinant Human Erythropoietin</td>
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<td></td>
<td>Recombinant Human Insulin Human</td>
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<td></td>
<td>Recombinant Human Growth Hormone</td>
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<td>Recombinant Human Granulocyte Colony-Stimulating Factors</td>
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<td>Studies in vitro</td>
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Studying new biosimilars (EMEA)

It is necessary to prove the similarity with the original product in terms of quality, safety and efficiency

- Pharmacotherapeutic group, changes in the analogue compared with the original drug, observed or potential differences between drugs, clinical application should be studied
- Insignificant changes in the molecular structure of the product are permitted
- The research plan, individual criteria of effectiveness for each group of drugs
- 1 “reference” drug is chosen for comparison
- Objective: to detect differences from the original drug
- Solutions - always individual

Studying new biosimilars (EMEA) (2)

Studies in vitro

- Studies in vivo (evaluation of specific parameters, toxicological observations)
- Pharmacokinetic and pharmacodynamic studies (change in pharmacodynamics, Pharmacokinetics)
- Separate evaluation of immunogenecity
- Clinical trials (at least two, randomized, double-blind, crossover or parallel design). You can use surrogate point, but only if you have accurate information about dependence of the surrogate point from the end result (hemoglobin, reticulocytes, and others)
- Post-marketing study is compulsory

Registration of biosimilars in Europe (EMEA)(2)

- General Guides
  - Comparability of biological products (2003)
  - Similar biological products (2005)
  - Comparison of biological products after changing production conditions (2007)
  - Evaluation of immunogenecity (2008)
    - Special manuals
      - Comparison of recombinant insulin (2006)
      - Comparison of somatotropin (2006)
      - Comparison of recombinant granulocyte colony-stimulating factors (2006)
      - Comparison of recombinant erythropoietin (2006)
      - Comparison of low molecular weight heparin (2007, 2009)
      - Comparison of recombinant interferon-alpha (2009)
  - Specific Product data requirements


Example of EMEA registration requirements for erythropoietins

Preclinical
- In vitro: comparative biological studies (binding to the receptor, cell proliferation)
- In vivo: evaluation of erythropoietic effect on mice, 4-week study of repeated dose toxicity in rats
  - Clinical
- Pharmacokinetic and pharmacodynamic studies (in healthy people). Evaluation of the following parameters: AUC, C_max, T1/2, reticulocyte count
- Clinical trials (at least two)

Example of EMEA registration requirements for erythropoietins (2)

Clinical
- 2 - randomized, 2-blind studies
- Population: patients with chronic renal failure, patients on dialysis and without it should not be confused
- For different ways of administration – individual studies
- Phase of dose correction (untreated patients or 3-month break in treatment)
- Maintenance-dose phase (selected treatment for patients with good effect)
- Duration of the study - 6 months
- Endpoints: the number of patients who reached a certain level of hemoglobin, change in hemoglobin, the number of patients maintaining hemoglobin at a certain level, general appointed dose of erythropoietin, the number of transfusions

Example of EMEA registration requirements for erythropoietins (3)

Study of immunogenicity
- In terms of clinical trial
- Duration - not less than 12 months
- Post-marketing studies
- The manufacturer submits a plan of observation
- Particular attention should be paid to rare adverse reactions and immunogenicity

Example of EMEA registration requirements for erythropoietins (4)

Registration and circulation of biotech analogues are not discussed in Russia
- The lack of regulation in Russia will lead to new problems (Maysept / Cellcept, Eprex / Epocrin)
- Prescription, replacement of biological products during distribution is a separate topic
- Regulatory documents appeared recently in the U.S.A. (because patents in the U.S. ends later than in Europe)
- In Europe regulatory rules are adopted in EMEA (for centralized registration), but only a few EU countries have national rules in this area