Economy of rare (orphan) technologies

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In the world
- Theme of rare (orphan) technologies appeared in USA in 1983
- In Europe there are pan-European documents
- European List of Orphan Drugs has 440 positions

Main groups of orphan medical technologies
- Hereditary diseases of cell’s metabolism
- Central nervous system diseases
- Hematology
- Oncology
- Thrombophilies
- Transplantology
- Cardiovascular, lung and mixed diseases
- Rheumatic diseases

In Russia
- List of orphan medical technologies appeared in 2005
- Nowadays it contains 40 technologies
- There is no special legislation and regulation in Russia

Orphan diseases and orphan technologies
- Affect small number of people – from several to 10 000 in Russia
- There is a treatment with a dramatic effect available
- Target therapy
- Changes in diseases classifications
- There is need for different diagnostic approach
- Rarity makes it impossible:
  - To conduct common clinical studies
  - To register across the world
  - Sell from drugstores
  - Sell for prices, based on a prime cost

Patients’ registry – new methodology of investigation becomes available
- Investigating “typical practice” or “real world”
- There is a need for simple, automatic, standardized process. Both doctors and patients take part in the development and management of registries
- Time-consuming (for rare diseases)
- Should be international (especially for rare diseases), always multicentered
- Can lead to unexpected results, that contradicts to existing stereotypes and practice
- Should include economics issues
Antibodies to antihemophilic factor VIII as an example of orphan technologies

- Patients appeared after introducing of VIII factor in 2005 (10-times increasing consumption, in 2008 2,5-times increasing)
- Number of patients with antibodies – 150 people, should be about 600
- Antibodies are detected only in 4-5 regions of Russia
- Cost of treatment:
  - To stop bleeding - 120 000 USD per year for the whole life
  - To remove antibodies - up to 8 mln. USD per year, then – standard treatment (not always helps!)

Issues of orphan diseases diagnosing

- High-specialized molecular-biologic methods – expensive equipment, trained personnel
- In the world – diagnostics is concentrated in specialized centres, in Russia – is made by pharmaceutical companies
- There is no practice of obtaining and post delivery of biologic material
- There is neither scientific nor managing program of development

Professional Service for Rare (Orphan) Diseases of Formulary Committee of Russian Academy of Medical Sciences

- Standards and protocols of medical care
- Public monitoring of governmental program of drug supply for 7 rare diseases
- Proposals for regulating documents
- Collaboration of different target groups – doctors, patients, manufacturers, distributors, managers
- Assessment of quality of life and economics of program
- Creation of state policy and governmental program for rare diseases, including diagnostic issues

Orphan diseases and orphan drugs

- Hypophysial nanism: Somatropin
- Multiple sclerosis: Glatiramer acetate, Interferon beta-1a, Interferon beta-1b
- Myeloid leukemia and other hemoblastosis:
  Bortezomib, Imatinib, Rituximab, Fludarabine
- Gaucher’s disease: Imiglucerase
- Cystic fibrosis: Dornase alfa
- Transplantation:
  Mycophenolic acid, Mycophenolate mofetil, Tacrolimus, Ciclosporin
- Hemophilia: Antihemophilic factor VIII, Octocog alfa, Antihemophilic factor IX, Eptacog alfa (activated)

Regulating documents of centralized supply of drugs from federal budget

Распоряжение Правительства РФ от 2 октября 2007 г. №1328-р – об утверждении перечня централизованно закупаемых за счет федерального бюджета ЛС, предназначенных для лечения «дорогостоящих» заболеваний.

Постановление Правительства РФ от 17 октября 2007 г. № 682 – о централизованной закупке в 2008 и 2009 гг. лекарственных средств, предназначенных для лечения больных гемофилией, муковисцидозом, гипофизарным нанисмом, болезнью Гоше, миелолейкозом, рассеянным склерозом, а также после трансплантации органов и (или) тканей.

Приказ Минздравсоцразвития РФ от 19 октября 2007 г. № 650 – о формах заявок на поставку ЛС.

Приказ Минздравсоцразвития РФ от 28 ноября 2007 г. № 727 – об органе, осуществляющем ведение Федерального регистра больных.

Постановление Правительства РФ от 4 декабря 2007 г. № 840 – о предоставлении субсидий из федерального бюджета бюджетам субъектов РФ на осуществление организационных мероприятий по обеспечению граждан ЛС.

Number of patients with 7 orphan diseases

(Federal Agency for Health Care and Social Development, January 1, 2008)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Federal privileged persons</th>
<th>Regional privileged persons</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemophilia</td>
<td>5733</td>
<td>1376</td>
<td>7109</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>1313</td>
<td>67</td>
<td>1380</td>
</tr>
<tr>
<td>Hypophysial nanism</td>
<td>1474</td>
<td>780</td>
<td>2254</td>
</tr>
<tr>
<td>Gaucher’s disease</td>
<td>119</td>
<td>32</td>
<td>151</td>
</tr>
<tr>
<td>Myeloleukemia and other hemoblastosis</td>
<td>11935</td>
<td>1648</td>
<td>13583</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>9272</td>
<td>2056</td>
<td>11328</td>
</tr>
<tr>
<td>Transplantation</td>
<td>9688</td>
<td>390</td>
<td>10088</td>
</tr>
<tr>
<td><strong>TOTAL:</strong></td>
<td><strong>39544</strong></td>
<td><strong>6349</strong></td>
<td><strong>45893</strong></td>
</tr>
</tbody>
</table>
Main challenges

• To investigate quality of life in patients suffering from 7 orphan diseases
• To investigate correlation of quality of life with treatment
• To determine cost of QALY

Governmental program for orphan diseases

• Diagnostic in diagnostic centres for orphan diseases (3-4 across Russia)
• Centres for orphan diseases in all regions of Russia
• Responsible for orphan diseases doctors in each region and territory
• Address delivery of drugs
• Home treatment
• Centres for drug infusion and injection in one-day hospitals
• Registers with participation of primary care doctors

Volume of purchase (1st and 2d half years 2008)
(Federal Agency for Health Care and Social Development, March 2008)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Volume of purchase (RUB.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemophilia</td>
<td>3 969 670 814.62</td>
</tr>
<tr>
<td></td>
<td>5 849 364 646.85</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>271 497 655.17</td>
</tr>
<tr>
<td></td>
<td>344 961 828.93</td>
</tr>
<tr>
<td>Hypophysial nainm</td>
<td>449 937 989.52</td>
</tr>
<tr>
<td></td>
<td>48 932 337.65</td>
</tr>
<tr>
<td>Gaucher’s disease</td>
<td>575 486 740.14</td>
</tr>
<tr>
<td></td>
<td>564 851 929.39</td>
</tr>
<tr>
<td>Myelo-leukemia and other hemoblastosis</td>
<td>6 721 133 408.04</td>
</tr>
<tr>
<td></td>
<td>5 769 122 684.81</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>2 791 076 199.21</td>
</tr>
<tr>
<td></td>
<td>2 791 076 199.21</td>
</tr>
<tr>
<td>Transplantation</td>
<td>658 481 380.41</td>
</tr>
<tr>
<td></td>
<td>861 505 590.09</td>
</tr>
<tr>
<td>TOTAL:</td>
<td>15 359 648 197.87 ????</td>
</tr>
<tr>
<td>There is lack of coincidence in official data</td>
<td>15 767 699 672.85 ????</td>
</tr>
</tbody>
</table>
We began to treat orphan diseases in Russia

- Since 2008 patients with hemophilia, cystic fibrosis, hypophysial nanism, Gauche disease, myeloleukemia and other hemoblastosis, disseminated sclerosis, condition after transplantation have more access to treatment
- Complex diagnostic studies is a key element for detecting diseases, initiating and changing treatment
- All diagnostic studies are included into standards of medical care
- There are NO DISEASES and NO PATIENTS without modern diagnostics

We get money for treatment, but not for diagnostics. We get money for nothing...

Diagnostic of hemophilia with antibodies to antihemophilic factor (1)

- Number of patients: 136
- Number on high-dose ITI-therapy: 21 patients
- Cost of treatment of 1 patient per year: 58 mln. RUB
- Diagnostic examination to diagnose: test for inhibitor to antihemophilic factors VIII and IX activity
- Standardized laboratories in 10-11 cities (sometimes are out of order): Moscow, Saint-Petersburg, Kirov, Barnaul, Ekaterinburg, Samara, Rostov-on-Don etc.
- Other laboratories: divergence with reference-laboratory, lack of reagents and equipment
- Diagnostic examination is free of charge for patients

Diagnostic of von Willebrand's disease (1)

- Number of patients: 3800, including 141 with sever and extreme form
- Cost of treatment of 1 patient per year: 490 000 – 5 mln. RUB
- There should be 1.5 mln. patients in Russia (all forms, including mild)
- Number of patients that should receive treatment is about 6000
- Diagnostic examination to diagnose:
  ✓ Test for activity and properties of von Willebrand's factor in blood,
  ✓ Test of level of antigen of von Willebrand's factor,
  ✓ Detection of von Willebrand's factor in platelets,
  ✓ Analyses of von Willebrand's factor multimeres in plasma,
  ✓ Specific test for binding of von Willebrand's factor with clotting factor VIII
Diagnostic of von Willebrand's disease (2)
• Whole complex of analyses is needed for diagnose
• Complex analyses are available only in Moscow and Saint-Petersburg, partly – in Barnaul and Kirov
• In other centers – lack of reagents, equipment, trained personnel
• Mail sending of samples is not possible
• Diagnostic studies are free of charge for patients

Diagnostic of chronic myeloleukemia (1)
• Number of patients: 4800
• Number treated with Glivek: 2800
• Cost of treatment of 1 patient per year: 1 mln. RUB.
• Diagnostic examination to diagnose:
  ✓ Cytogenetic investigation of bone marrow (detecting specific Philadelphian chromosome) OR
  ✓ Method of qualitative PCR (detecting specific protein bcr/abl – producing by Philadelphian chromosome)

Diagnostic of chronic myeloleukemia (2)
• After confirming of chronic myeloleukemia diagnosis patient starts treatment with Glivek (targeted therapy).
• Cytogenetic and molecular monitoring should be made for control of effectiveness
• Cytogenetic monitoring every 6 months
• Molecular monitoring every 3 months

Diagnostic of chronic myeloleukemia (3)
• Only clinical blood analyses and biochemical blood analyses are covered by insurance. Neither cytogenetic, no molecular studies are covered by government
• That studies are essential for assessment of therapy effectiveness, changing dose of Glivek, shifting to other therapy
• There is no state financing for cytogenetic and molecular studies

Diagnostic of chronic myeloleukemia (4)
Novartis company (manufacture of Glivek) supports laboratories in Russia:
• 13 cytogenetic laboratories – diagnosis and monitoring of chronic myeloleukemia
• 4 laboratories for molecular diagnostic - detecting protein bcr/abl by RT-PCR
• 4 preparing to start molecular diagnostic in the nearest time
• Support of laboratories includes: acquisition of equipment, reagents, training of personnel, mailing blood and bone marrow samples, logistics

Diagnostic of chronic myeloleukemia (5)
• Nowadays 100% patients (diagnosis, monitoring) are covered by diagnostic studies
• Diagnostic studies are free of charge for patients (thanks to Novartis)
Diagnostic of chronic B-cell lymphatic leukemia (1)

• Number of patients: about 5000
• Cost of treatment of 1 patient per year: 650 000 RUB
• Diagnostic examination to diagnose:
  ✓ immune marker analysis – for all patients
  ✓ cytogenetic investigation (deletion 17p etc.) – for all patients, preparing for therapy (about 40% of patients)

Diagnostic of chronic B-cell lymphatic leukemia (2)

• Immune marker analyses is available in all big regional cities
• Cytogenetic investigation is available in 5 cities: Moscow, Novosibirsk, Yekaterinburg, Khabarovsk, Saint-Petersburg
• Cost of immune marker analyses is 1000 – 4000 RUB
• Cost of cytogenetic investigation is 3000 – 15000 RUB

Diagnostic of chronic B-cell lymphatic leukemia (3)

• Nowadays 70% of needy patients are covered by immune marker analyses
• Cytogenetic investigation is accessible for very low number of patients (no data)

Therapeutic monitoring of levels of cytostatic agent in blood after kidney, liver, heart transplantation (1)

• Number of patients: more than 5000
• Transplantation allowed in 53 Russian hospitals: 16 in Moscow and Saint-Petersburg, 39 – in other cities
• Transplantation is allowed by is not made everywhere
• Obligatory tests after transplantation: therapeutic monitoring level of cytostatic agent (Tacrolimus, Ciclosporin) in blood
• This studies are really available in 10 centers

Therapeutic monitoring of levels of Ciclosporin in blood

• Therapeutic monitoring is made only in 10 transplantation centers, covered by state financing
• In the first year after transplantation patient should receive up to 12 monitoring investigations!
• Method is well known – test C0 (basic monitoring)
• More precise test C2 is not available (patient takes Ciclosporin at 2 hours before investigation)
• Mail sending of samples is not possible.

Diagnostic of Gaucher’s disease (1)

• Number of patients: 217
• Total number treated with Imiglucerase: 130 patients
• Diagnostic examination to diagnose:
  ✓ Biochemical investigation of enzyme deficiency (diagnosis, initiation of treatment)
  ✓ Molecular-genetic investigation (differential diagnosis, for all children)
Diagnostic of Gaucher's disease (2)
- Biochemical investigation is available in 4 cities: Moscow, Saint-Petersburg, Novosibirsk, Rostov-on-Don
- Molecular-genetic investigation is available only in Moscow and Rostov-on-Don
- Low application of methods due to rarity of disease

Diagnostic of Gaucher's disease (3)
- Mail sending of samples is possible
- Up to 90% of patients visited centers in order to make an investigation! But some of them also take clinical examination
- Monitoring of enzyme marker is essential for changing dose of Imiglucerase – up to 3 time per year

Diagnostic of Gaucher's disease (4)
- Total cost of both studies is about 1400 RUB
- Biochemical investigation made by Genzyme company (manufacture of Imiglucerase)
- Patients pay for molecular-genetic investigation
- Nowadays all needy patients (diagnosis, monitoring) are covered by diagnostic studies

Diagnostic abroad
- Diagnostic examination abroad became complex after prohibition of coming-out of biologic tissues and specimens since 28 of May 2007 by Federal Custom Authority
- In 2007 about 28 000 Russian patients participated in international clinical studies, part of them – in the studies of rare (orphan) drugs

Contribution to diagnostic of orphan diseases by pharmaceutical companies
- Hiring personnel
- Training of personnel
- Acquisition equipment
- Acquisition reagents
- Maintaining mail and messenger services
- Mail sending of samples and specimens

Some issues of company-sponsored diagnostics
- Such diagnostic services are disconnected with health care system
- Probably some services are not licensed
- Probably some methods and equipments are not registered in Russia

Without this contribution diagnosis and treatment of rare curable diseases are impossible

Manufactures of drugs replace state functions and activity in diagnostics and monitoring of rare expensive diseases!

When crisis crash out: tomorrow or today already?
A question:

What will happen with patients if pharmaceutical companies stop diagnostics?

Why we should worrying about it?..

Expensive treatment (total sum is about – 1 bill. EURO) depends on diagnosis, based on formally absent in Russian health care system services

Moreover...

Diagnostic tests for rare diseases are obligatory and present in standards of medical care

At the same time...

- Since 2008 state programs of screening of working population has started in Russia
  - Mammography
  - Oncology markers of breast cancer
  - Prostate-specific antigen
- Are we ready to manage patients «discovered» by screening?
- How much does it cost?

Clinical effectiveness and efficiency of these screening methods are not determined

Problem solving

- Scientific, evidence-based and cost-effectiveness approach to logistics of diagnostic technologies
- Creation of state centers for diagnosing rare diseases
- Training, accreditation of personnel, quality management

Today’s Russian state policy in rare diseases

«NO for diagnostic», means:
«NO patient – NO problems…»
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Economy of rare surgical technologies

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Causes of slow development of rare (orphan) surgical technologies in Russia
- Lack of patient registers
- Lack of diagnostic in regions
- Lack of specialized centers
- No governmental program of financing
- Lack of standards and protocols of care

Examples of rare surgical technologies
- Treatment of hyperlipidemia
- Transplantation
- Orthopedic treatment of patients, suffering from hemophilia with antibodies to antihemophilic factor

Treatment of hyperlipidemia
- Should be about 100,000 patients in Russia
- 120 patients were found, now receive treatment
- All patients are treated in Moscow and Saint-Petersburg
- Treatment – LDL aphaeresis once in a week
- There is no more than 6000 procedures per year in Russia
- One procedure of aphaeresis costs about 1000 USD

Transplantation in Russia
- No register of patients needing transplantation
- Problems with tissue banks and tissue typing
- No clear and valid information about patients after transplantation
- No information about success and effectiveness of transplantation
- No planning of number of transplantation and total expenditures
- Weak legislation

Why treatment of hemophilia is successful?
- Valid register of patients
- Standard and protocol of medical care
- Governmental program of financing
- Appropriate supply with drugs
- Several centers with trained specialists
- Clarity of accounts
Register of patients with hereditary coagulopathy

There is data on 7374 patients (1761 under 18 years old)
Number of patients with antibodies to antihemophilic factor - 140

Features of clinical course in patients with antibodies to antihemophilic factor

In patients 6-18 years old, bones are affected 15 times more often, mostly pseudotumor is seen.

82% of patients are hospitalized with purulent and septic complications.

The table below shows the types of surgical interventions performed in patients with antibodies to antihemophilic factor:

<table>
<thead>
<tr>
<th>Surgical interventions on joint</th>
<th>Number</th>
<th>Extrarticular surgical interventions</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synovectomy of knee-joint</td>
<td>13</td>
<td>Pseudotumor extirpation</td>
<td>10</td>
</tr>
<tr>
<td>Synovectomy of elbow joint</td>
<td>3</td>
<td>Open arthroscopy</td>
<td>2</td>
</tr>
<tr>
<td>Arthroplasty of knee-joint</td>
<td>1</td>
<td>Life-saving surgery</td>
<td>4</td>
</tr>
<tr>
<td>Arthroplasty of hip-joint</td>
<td>4</td>
<td>Total arthroplasty</td>
<td>2</td>
</tr>
<tr>
<td>Impost etc. of knee-joint</td>
<td>6</td>
<td>Partial arthroplasty</td>
<td>3</td>
</tr>
<tr>
<td>Impost etc. of hip-joint</td>
<td>1</td>
<td>Synovectomy</td>
<td>2</td>
</tr>
<tr>
<td>Amputation</td>
<td>1</td>
<td>Intersurgical bone graft removal</td>
<td>3</td>
</tr>
<tr>
<td>Amputation</td>
<td>1</td>
<td>Anterior cruciate ligament repair</td>
<td>2</td>
</tr>
<tr>
<td>Amputation</td>
<td>1</td>
<td>Anti-infectious surgical refinement</td>
<td>12</td>
</tr>
</tbody>
</table>

TOTAL: 36

82% of patients had high titre of antibodies.

Hemostatic regimens during surgical treatment of patients with antibodies to antihemophilic factor

- High-dose therapy with antihemophilic factor VIII
- Drugs consisting of activated prothrombin complex
- Recombinant activated antihemophilic factor VII

Types of surgical interventions in patients with antibodies to antihemophilic factor

Endoprosthesis of knee-joint and hip joint

95% - good clinical results
There were 151 endoprosthesis procedures of knee-joint and 32 - of hip joint made since 1992 (includes 91 procedures of knee-joint endoprosthesis and 17 procedures of hip joint endoprosthesis since 2005).

6 procedures of knee-joint endoprosthesis were made in patients with antibodies to antihemophilic factor.

All surgical interventions in patients with antibodies to antihemophilic factor were made in Hematological Scientific Centre of Russian Academy of Medical Sciences.

Medication during surgical intervention and after that:
- Eptacog alfa (activated) 120 mcg/kg every 2 hours, than interval extension to 3 and 4 hours.
- OR
- Drugs consisting of activated prothrombin complex (FEIBA) 100 units/kg every 12 hours.

How many units of drugs are needed for surgical interventions in patients with antibodies to antihemophilic factor? How much does it cost?
- About 250 vials of NovoSeven 2,4 mg are necessary.
- It costs about ≈ 650 000 USD

Thank you for attention!