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Biopharmaceuticals in the Russian Federation: A snapshot of policies for registration, reimbursement and use

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1. Background

Global biopharmaceutical industry is entering a new area. The first biopharmaceuticals, released 20–25 years ago are out of patent protection already. The top selling biopharmaceuticals with a market volume of tens of billions of US dollars will be out of patent by 2010. And the process will go on and on. Transnational corporations are sounding alarm: by producing bio-generics new biotechnologies, mostly of India and China, threaten multibillion profits of Big Pharma, the phrase often used to refer to companies with revenue in excess of $3 billion, and/or R&D expenditure in excess of $500 million. The largest transnational companies launched huge PR campaigns against bio-generic producers under the cover of safety concerns for the public. Though there is a scientific basis for some concern due to the fact that bio-generics are not absolute copies of originator brands, and thus differ from chemical generics, patient safety care is definitely not the sole reason for their anxiety.

There are at least two major points among the other objectives on the agenda for biologics of Big Pharma. Firstly, they aim at not allowing bio-generics on established markets for as long as possible and specifically on the markets of those countries with weak biotechnological expertise. This PR campaign is aimed at the regulatory authorities of these countries. Thus limiting generic competition transnational companies keep for themselves sales at the desirable high level. For example, Johnson & Johnson received more than 25 billion dollars only for its erythropoietin over a period of less than 10 years. Sales of biopharmaceuticals of the so called "big four" consisting of erythropoietin, interferon alfa and beta, and filgrastim are still at the multibillion level.

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Secondly, by hampering the further development of the era of bio-generics Big Pharma aims at preventing sales of local companies and thus their investment in research and development. The major concern is that the new biotechnologies of China and India, with state provided bio-strategies, will present the real threat not only by producing bio-generics, but also by delivering new originators to be patented globally in the next decade. The situation with locally produced biologicals in the Russian Federation has not become yet a reason for concern for Big Pharma. The former Soviet biotechnology research has been almost completely lost and new biotechnology companies are just emerging. At the same time the pharmaceutical market in the Russian Federation has recently been expanding to an enormous level. More than 17,000 trade marks are registered. Principles and methods of protecting the population from aggression of medicines and medicines' promotion have not been worked out. After annihilation of the Soviet medicines regulatory system the new processes aimed at regulation are at various stages of restoration and development. Since 2005 the system of free medicines' provision for designated categories of citizens has been re-organized. The model of "Provision of Supplemental Medicines", a state reimbursement programme ('DLO') for low-income sectors of the population, was introduced in January 2005. A national, Federal-wide priority project "Health" was launched in 2006 which aims at improvement of the quality and accessibility of health care, specifically of medicines.

2. Purpose

The present overview was undertaken with the aim to describe the existing policies for registration, reimbursement and use of biopharmaceuticals. We selected only monoclonal antibodies and recombinant DNA preparations for our descriptive analysis; none of these medicines are listed in the Essential Medicines list of WHO. We also aimed at looking into some pharmacoeconomical aspects of the use of various biopharmaceuticals in the Russian Federation.

3. Methods

For this overview we searched the official database of registered medicines in the Russian Federation [5]: for information on: date of registration, registered uses and unit price. We compared the year of primary registration in the Russian Federation with corresponding FDA information (approval year) [18].

We used official policy documents: the Essential Medicines List [2] and the List of Medicines for Supplementary Medicines Supply ('DLO') for designated categories of citizens for the four consecutive years 2005–2008; standard treatment guidelines for out-patient care and for specialized care. We calculated treatment costs multiplying unit prices by recommended length of treatment in terms of the number of units used. We used the database of the Federal Fund for Obligatory Medical Insurance (FFOMI) for the year 2006 and retrieved information on amounts used and expenses for the chosen biopharmaceuticals. We applied the methodology of ABC analysis [4] for the evaluation of expenses for selected biopharmaceuticals in 2006. We also searched the Russian language websites for sales of medicines in order to retrieve information on all additional procurements of chosen biopharmaceuticals. This overview has become the very first attempt to describe the impact of regulatory policy on the use of biopharmaceuticals and associated costs in the Russian Federation.

4. Results

Four tables present the main results of our findings. Thirteen preparations of monoclonal antibodies and eleven recombinant DNA preparations have been registered for use in the Russian Federation (RF), the first being epoetin alfa (Eprex) in 1990 (see Table 1). All thirteen of the registered monoclonal antibody preparations were foreign originator brands. Among recombinant DNA preparations there were four originator molecules with registered bio-generics. These were interferon alfa-2b with six registered generics, filgrastim with seven registered generics, epoetin alfa with three registered generics and epoetin beta with six registered generics (Table 1).

Five of six generics for interferon alfa-2b, five of seven generics for filgrastim, two of three generics for epoetin alfa and five of six generics for epoetin beta were developed and produced in the RF.

Comparison of primary registration dates for biological products in the RF with the years of approval by the FDA revealed differences ranging from one to ten years with a median of three years (see Table 1). Peginterferon alfa-2a (Pegasys) and peginterferon alfa-2b (PegIntron) were the only two products registered in the RF in the year of FDA approval. Interferon beta-1a, epoetin alfa, daclizumab and bevacizumab were registered in the RF one year after FDA approval. Basiliximab was registered in the RF eight years after the FDA approval, interferons alfa-2a and alfa-2b were registered respectively seven and ten years after the FDA approval. We could not discover any pattern in the RF registration/FDA approval time.

The number of registered uses ranged from one to sixteen, the sixteen being for Interferon alfa-2b. Thirteen uses were registered for interferon alfa-2a, five uses for filgrastim, epoetin alfa and epoetin beta. All of the other included in this analysis of biopharmaceuticals had less than five registered uses with the majority of them having one registered use with a median of two uses (see Tables 1 and 2).

Our analysis of policy recommendations on the use of the studied biopharmaceuticals revealed that nine of 24 were listed for the Supplementary Medicines Supply Programme in 2005. The number nearly doubled by the year 2006 with fifteen of 24 biopharmaceuticals included on this list in the three consecutive years of 2006–2008 (see Table 3).

The national Essential Medicines list of the year 2007 listed seventeen of 24 biopharmaceuticals including all eleven of the studied recombinant DNA products and six monoclonal antibody preparations. Again, all eleven recombinant DNA products were included in the Federal Standard Treatment Guidelines (STG) for the out-patient service. One of the monoclonal antibody products, infliximab, was recommended by the STG for out-patient use.

Finally, the Standard Treatment Guidelines for specialized service listed seven of the 24 studied biopharmaceuticals: bevacizumab and trastuzumab among monoclonal antibodies and granulocyte stimulating agents, both epoetins and eptacog alfa among recombinant DNA preparations (see Table 3).

Treatment costs' comparisons showed that cost considerations apparently were not the ones that determined the policy decisions of listing and recommending the use of biopharmaceuticals. Table 4 presents cost calculations and Federal spending on the biopharmaceuticals in 2006. The total spending amounted up to nearly 10 billion rubles, i.e. €275 millions (9,719,084,206.00 rubles, equals to 267,320,489.608 euros with exchange rate of €1 = 36.3574 rubles and 1 ruble = €0.0275047).

Currently nearly all monoclonal antibodies are procured by the government at the high monopoly prices of originator brands. There is no information on the outcomes of the use of these biologicals. We did not find any publicly available indication of adverse effects monitoring with either brand or generic biologicals.

Table 1
Registration details of biopharmaceuticals of two classes in the Russian Federation

INN	Type	Brand	Available generics (number: names)	Year of first registration of originator	FDA approval year/difference	Number of registered uses in RF
1. Abciximab	mAb	ReoPro	–	1998	1994/4	4
2. Adalimumab	mAb	Humira	–	2006	2002/4	3
3. Alemtuzumab	mAb	Campath	–	2004	2001/3	1
4. Basiliximab	mAb	Simulect	–	2006	1998/8	1
5. Bevacizumab	mAb	Avastine	–	2005	2004/1	1
6. Daclizumab	mAb	Zenapax	–	1998	1997/1	1
7. Infliximab	mAb	Remicaid	–	2001	1998/3	2
8. Omalizumab	mAb	Xolair	–	2007	2003/4	1
9. Ranibizumab	mAb	Lucentis	–	2008	2006/2	1
10. Rituximab	mAb	Mabthera	–	1999	1997/2	2
11. Trastuzumab	mAb	Herceptin	–	2000	1998/2	1
12. Cetuximab	mAb	Erbitux	–	2007	2004/3	3
13. Efalizumab	mAb	Raptiva	–	2006	2003/3	1
14. Interferon alfa-2a	rDNA	Roferon-A	–	1993	1986/7	13
15. Peginterferon alfa-2a	rDNA	Pegasys	–	2002	2002/0	2
16. Interferon alfa-2b	rDNA	Intron A	6: Alfarona-R, Interferon alfa-2 human recombinant-R, Lifeferon-R, Realdiron, Reaferon-EC-R, Eberon-alfa-R	1996	1986/10	16
17. Peginterferon alfa-2b	rDNA	PegIntron	–	2001	2001/0	1
18. Interferon beta-1a	rDNA	Rebif	Avonex	1997	1996 (Avonex)/1	1
19. Interferon beta-1b	rDNA	Betaferon	–	1995	1993/2	1
20. Filgrastim	rDNA	Neupogen	7: Granulocyte colony stimulating factor human recombinant-R, Grasalva, Leucostim-R, Leucita, Mielastra-R, Neupomax-R, Filgrastim-R	1994	1991/3	5
21. Lenograstim	rDNA	Granocyte	–	1996	NA	3
22. Epoetin alfa	rDNA	Eprex,	3: Epocryn-R, Epocomb, Repoetin-SP-R	1990	1989/1 Epogen/Procrit	5
23. Epoetin beta	rDNA	Recormon	6: Erithrostim-R, Erithropoetin human recombinant-R, Erithropoetin-R, Epoetin, Vero-epoetin-R, Epostim-R	1991	–	5
24. Eptacog alfa (activated)	rDNA	NovoSeven, Eptacog alfa activated	–	2001	–	2

Notes: -R denotes generic versions manufactured in the Russian Federation.

Table 2

Registered uses of biopharmaceuticals of two classes in the Russian Federation

INN	Registered uses
Abciximab	Prophylaxis of myocardial ischemia in high-risk patients undergoing transcutaneuos coronary intervention (in combination with heparin and aspirin). Post angioplasty or atherectomy – for prophylaxis of acute ischemic complications in patients with high risk of re-occlusion (intra coronary thrombus, lesions longer than 20 mm). Coronary thrombosis, including Q-wave acute myocardial infarction within 12 hours after onset; post-infarction angina. Unstable angina (in patients non responding to traditional therapy) when planning for coronary angioplasty in the next 24 hours.
Adalimumab	Exacerbation of moderate or severe rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis.
Alemtuzumab	Chronic lymphatic leukaemia.
Basiliximab	Prophylaxis of acute transplant rejection (in combination with cyclosporine and glucocorticoids).
Bevacizumab	Metastatic colorectal cancer: as first-line therapy in combination with fluoropyrimidine derivatives.
Daclizumab	Prophylaxis of acute renal transplant rejection (in combination with cyclosporine and glucocorticoids).
Infliximab	Rheumatoid arthritis (in cases of failing conventional therapy, including therapy with methotrexate). Crohn's disease (severe, with fistulas; in cases of failing conventional therapy with glucocorticoids and immunodepressants).
Omalizumab	Persisting atopic bronchial asthma, moderate and severe, inadequately controlled by inhaled corticosteroids.
Ranibizumab	Not specified.
Rituximab	B-cell non-Hodgkin's lymphoma (relapsing or resistant to chemotherapy). Rheumatoid arthritis (active) in adults in combination with methotrexate in cases of intolerability or insufficient response to treatment including one or more inhibitors o tumour necrosis factor.
Trastuzumab	Metastatic breast cancer with hyper expression of HER2 (monotherapy after one or more chemotherapies; in combination with paclitaxel in cases of no previous therapy).
Cetuximab	Not specified.
Efalizumab	Psoriasis moderate and severe.
Interferon alfa-2a	Neoplasms of lymphatic and blood systems: leukaemia, multiple myeloma, cutaneous T-cell lymphoma, chronic myeloleukemia, thrombocytosis in myeloproliferative diseases, non-Hodgkin's lymphoma. Solid tumours: sarcoma Kaposi (in AIDS patients), advanced liver carcinoma, metastatic melanoma, melanoma (after surgical resection, thickness over 1.5 mm, without lymph nodes involvement and metastatic lesions). Viral diseases: chronic active hepatitis B (in adults, with replication markers); chronic active hepatitis C (in adults with antibodies to hepatitis C virus or viral RNA in serum and elevation of ALT activity); pointed condyloma.
Peginterferon alfa-2a	Chronic hepatitis C without cirrhosis or with compensated cirrhosis in adults (monotherapy or in combination with ribavirin as first-line therapy). Chronic hepatitis B, replication phase with inflammatory signs, without cirrhosis or with compensated cirrhosis.

Table 2
(Continued.)

INN	Registered uses
Interferon alfa-2b	Viral infections: papillomatosis of larynx, pointed condiloma, plantar wart, acute viral hepatitis B, chronic active hepatitis B, chronic hepatits C, herpes zoster, HIV-infection, dengue fever. Neoplasms: leukaemia, chronic myeloid leukaemia, non-Hodgkin's lymphoma, solid tumors (metastatic renal carcinoma, carcinod tumors, sarcoma Kaposi in AIDS patients, basal cell carcinoma and melanoma).
Peginterferon alfa-2b	Histologically confirmed chronic hepatitis C (as monotherapy in cases of ribavirin intolerance or contraindications to it).
Interferon beta-1a	Multiple sclerosis.
Interferon beta-1b	Multiple sclerosis: relapsing, secondary progression.
Filgrastim	Granulocytopenia (including patients with non-myeloid neoplasms on cytostatic therapy); preparation for bone marrow transplantation; persistent granulocytopenia in AIDS patients (<1000/mkl and less); mobilisation of peripheral stem cells (including after myelosuppressive therapy); granulocytopenia (hereditary, periodic or idiopathic: <500/mkl) and severe relapsing infections in the last 12 months.
Enograstim	Reduction of granulocytopenia period and its complications (in patients with non-myeloproliferating neoplasms), undergoing chemotherapy and bone marrow transplantation. After standard myelodepressive therapy. Mobilisation of peripheral precursor cells.
Epoetin alfa	Anemia (prophylaxis and treatment): in chronic renal failure in adults and children, undergoing haemodialysis or peritoneal dialysis and in pre-dialysis patients; in HIV-infected patients treated with zidovudine (when endogenous erithopoetin concentration is 500 IU/ml or less); non-myeloid tumours (including on cytotoxic therapy). Prior to major surgery with anticipated massive blood loss (2–4 units or 900–1800 ml) without anaemia, with mild or moderate anaemia (Hb 100–130 g/l) with the aim to reduce the need of allogenic haemotransfusions and to boost erythropoesis. Prior to major surgery in patients with haematocrit (packed cell volume – PCV of 33–39%).
Epoetin beta	Prophylaxis and treatment of various anaemia: anaemia in chronic renal failure (including haemodialysis patients); anaemia in patients with solid tumours, on platinum preparations (cisplatin 75 mg/sq.m per cycle, carboplatin 350 mg/sq.m); anaemia in adult patients with multiple myeloma and non-Hodgkin's lymphomas (low malignancy) and chronic lympho-leukaemia undergoing chemotherapy with relative insufficiency of endogenous erythropoietin. Increased volume of blood for the subsequent auto-transfusion. Prophylaxis of anaemia in premature newborns: body mass 0.750–1.5 kg before the 34 week of gestation.
Eptacog alfa (activated)	Bleedings (including prophylaxis in major surgery) in patients with hereditary or acquired haemophilia with inhibitors to blood clotting factors (VIII or IX). Hereditary deficiency of clotting factors VII, II, V, X; thrombocytopenia and trombocytopathy (Glancmann thrombo-astenia, Bernard–Sulie syndrome, 'grey platelets' syndrome).

Table 3

Costs and policy indicators (lists in force) of biopharmaceuticals of two classes in the Russian Federation

INN	Price per unit, rubles (euros)	Cost of treatment calculated as unit price multiplied by length of treatment, rubles (euros)	Supplementary medicines supply list				EML	STG (outpatient service)	STG (specialized service)
			2005	2006	2007	2008			
1. Abciximab	–	–	–	–	–	–	–	–	–
2. Adalimumab	68,000–77,000 (1864–2112)	1.8–4.2 mln per year (49,366–115,188)	–	–	–	–	–	–	–
3. Alemtuzumab	68,000 (1864)	2.5 mln per year (68,561)	–	–	–	–	–	–	–
4. Basiliximab	72,000 (1974)	144,000 (3949)	–	–	–	–	+	–	–
5. Bevacizumab	23,000 (4 ml) (628) 87,000 (16 ml) (2376)	600,000 per year (16,455)	–	+	+	+	+	–	+
6. Daclizumab	55,500 (1522)	111,000 (3044)	–	–	–	–	+	–	–
7. Infliximab	40,000 (1096)	200,000–240,000 (5485–6582)	–	+	+	+	+	+	–
8. Omalizumab	16,000–17,000 (439–466)	180,000–720,000 (4937–19,744)	–	–	–	–	–	–	–
9. Ranibizumab	65,000 (1783)	–	–	–	–	–	–	–	–
10. Rituximab	34,000 (10 ml) (929) 85,000 (50 ml) (2322)	1.7–1.8 mln per year (46,618–49,366)	+	+	+	+	+	–	–
11. Trastuzumab	33,500 (150 mg) (915) 98,000 (440 mg) (2689)	9 mln per year (246 800)	–	+	+	+	+	–	+
12. Cetuximab	17,000 (466)	2–2.6 mln per year (54,859–71,317)	–	–	–	–	–	–	–
13. Efalizumab	–	12 units	–	–	–	–	–	–	–

Table 3
(Continued.)

INN	Price per unit, rubles (euros)	Cost of treatment calculated as unit price multiplied by length of treatment, rubles (euros)	Supplementary medicines supply list				EML	STG (out-patient service)	STG (specialized service)
			2005	2006	2007	2008			
14. Interferon alfa-2a	1500–6000 (41–165)	1,000,000 (27,430)	+	+	+	+	+	+	−
15. Peginterferon alfa-2a	12,000 (329)	576,000 (15,799)	+	+	+	+	+	+	−
16. Interferon alfa-2b	5500–8500 (151–233)	255,000 (6996)	+	+	+	+	+	+	−
17. Peginterferon alfa-2b	10,600 (291)	286,200 (7852)	−	+	+	+	+	+	−
18. Interferon beta-1a	12,000 (329)	648,000 (17,778)	−	+	+	+	+	+	−
19. Interferon beta-1b	49,200 (1349)	590,400 (16,198)	−	+	+	+	+	+	−
20. Filgrastim	10,500 (288)	30,000–380,000 (823–10,424)	+	+	+	+	+	+	+
21. Lenograstim	31,700 (869)	max. 177,000 (4855)	+	+	+	+	+	+	+
22. Epoetin alfa	5500–11,000 (151–302)	660,000–1,320,000 (18,105–36,210)	+	+	+	+	+	+	+
23. Epoetin beta	38,000–76,000 (1042–2084)	50,000–100,000 (1372–2744)	+	+	+	+	+	+	+
24. Eptacog alfa (activated)	153,000 (4196) (4.8 mg No. 2)	NA	+	+	+	+	+	+	+

Notes: EML – essential medicines list; STG – standard treatment guidelines; NA – not available.

Table 4
Cost indicators and patient coverage with biopharmaceuticals of two classes under the Programme of supplementary medicines supply of the Federal priority project "Health" in 2006

INN	Type	Price per unit, rubles (euros)	Cost of treatment calculated as unit price multiplied by length of treatment, rubles (euros)	Supplementary medicines supply list 2006	Federal spending in rubles (euros)	Percentage of total and ABC category	Number of prescriptions served /percentage of total
1. Bevacizumab	mAb	23,000 (4 ml) (628) 87,000 (16 ml) (2376)	600,000 per year (16,455)	+	495,056,584.81 (13,582,320.99)	0.67/A	3430/0.00263
2. Infliximab	mAb	40,000 (1097)	200,000–240,000 (5485–6582)	+	483,571,564.82 (13,267,219.17)	0.65/A	3145/0.00241
3. Rituximab	mAb	34,000 (10 ml) (929) 85,000 (50 ml) (2322)	1.7–1.8 mln per year (46,618–49,366)	+	1,187,619,226.39 (32,583,397.62)	1.60/A	9626/0.00739
4. Trastuzumab	mAb	33,500 (150 mg) (915) 98,000 (440 mg) (2689)	9 mln per year (246,800)	+	940,932,180.04 (25,815,317.46)	1.27/A	4936/0.00379
5. Interferon alfa-2a	rDNA	1500–6000 (41–165)	1,000,000 (27,430)	+	377,786,816.52 (10,364,919.82)	0.51/A	36,711/0.02818
6. Peginterferon alfa-2a	rDNA	12,000 (329)	576,000 (15,799)	+ +	386,057,771.82 (10,591,840.89)	0.52/A	5476/0.00420
7. Peginterferon alfa-2b	rDNA	10,600 (291)	286,200 (7852)	+	275,725.86 (7,564.79)	0.08/C	8/0.00001
8. Interferon beta-1a	rDNA	12,000 (329)	648,000 (17,778)	+	109,575,223.48 (3,006,294.44)	0.0004/B	1778/0.00136
9. Interferon beta-1b	rDNA	49,200 (1349)	590,400 (16,198)	+	1,438,984,749.67 (39,479,835.98)	0.15/A	22,575/0.01733
10. Filgrastim	rDNA	10,500 (288)	30,000–380,000 (823–10,424)	+	258,977,571.08 (7,105,281.71)	1.94/A	4831/0.00371
11. Lenograstim	rDNA	31,700 (869)	max. 177,000 (4855)	+	251,177,326.06 (6,891,275.00)	0.34/A	6147/0.00472

Table 4
(Continued.)

INN	Type	Price per unit, rubles (euros)	Cost of treatment calculated as unit price multiplied by length of treatment, rubles (euros)	Supplementary medicines supply list 2006	Federal spending in rubles (euros)	Percentage of total and ABC category	Number of prescriptions served /percentage of total
12. Epoetin alfa	rDNA	38,000–76,000 (1042–2084)	50,000–100,000 (1372–2744)	+	1,854,858,838.61 (50,889,714.24)	2.49/A	37,418/0.02872
13. Epoetin beta	rDNA	38,000–76,000 (1042–2084)	50,000–100,000 (1372–2744)	+	1,027,484,372.68 (28,189,954.42)	1.38/A	44,165/0.03390
14. Eptacog alfa (activated)	rDNA	153,000 (4,196) (4.8 mg No. 2)	NA	+	906,726,253.99 (24,876,847.23)	1.22/A	1078/0.00083
Total					8,794,348,205.83 (241,280,823.02)	12.82	0.13918
15. Insulin biphasic	rDNA	1250 (32.3)	114,000–228,000 (3128–6256)	+	231,742,277.23 (6,358,057.02)	0.31/B	151,652/0.11640
16. Insulin-isophan	rDNA	1000 (27.4)	73,000–146,000 (2003–4006)	+ +	1,807,260,224.89 (49,583,803.63)	2.43/A	1527,851/1.17276
17. Insulin soluble	rDNA	1000 (27.4)	365,000–730,000 (10,014–20,028)	+	1,213,304,866.67 (33,288,106.17)	1.63/A	1086,794/0.83421

The ABC methodology applied for the expenditure information of the year 2006 revealed the following. For 8208.000 packages of bevacizumab (Avastin) the Supplementary Medicines Supply Programme ('DLO') spent 0.495 billion rubles (13.5 million euros). Costs of bevacizumab constituted 0.67% of all 'DLO' expenditures and bevacizumab was forty second on the list of the Federal expenditures for the Supplementary Medicines Supply Programme. Infliximab (Remicade) was purchased for an amount of 0.484 billions of rubles (13.3 million euros) (11,500 packages), which was 0.66% of the total 'DLO' expenditures and it was ranked 44th on the list of the highest federal spending. Rituximab (Mabthera) was purchased for an amount of 1.19 billion rubles (32.64 millions euros) (17,636 packages), 1.6% of total 'DLO' expenditure and it was ranked the 11th on the list of highest federal spending. Trastuzumab (Herceptin) with the purchase volume of 8824 packages (0.94 billion rubles (27.78 millions euros), 1.3% of total) was the 16th on the list of highest federal spending.

Our search for individual purchases of biologicals revealed that these occurred sporadically without any discernible pattern. For example, the State institution "The Principal Clinical Hospital" of the Ministry of Internal Affairs of the Russian Federation made an individual purchase of three packages of adalimumab (Humira) for 250,000 rubles (6860 euros) in early 2008 [10]. The Federal State Institution "Scientific Research Institute Rosmedtehnology" purchased 80 packages of baziliximab (Simulect) for the calculated sum of 5,762,061.6 rubles (158,026.03 euros) in 2007 which was in addition to the spendings on this medicine in the framework of the Supplementary Medicines Supply Program [9]. It also made an individual purchase of 240 packages of daklizumab (Zenapax) for a calculated amount of 13,318,817 rubles (365,257.21 euros) in 2007. The Department of Health of the city of Moscow purchased bevacizumab (Avastin) for an amount of 500,000 rubles (365,257.21 euros) [16]. The state institution "Kurgan Regional Oncology Clinic" purchased 46 packages of bevacizumab for 1 mln rubles [15]. The Central Clinical Hospital made an individual purchase of bevacizumab for 90,000 rubles (2,468.84 euros) in 2008 [13].

Additional to the 'DLO' Programme individual purchases of infliximab (Remicade) included the Ministry of Health of the Moscow Region for the amount of 490 mln rubles (13.4 million euros) [11]. The Federal State Institution "Central Scientific Research Institute for Dermato-Venerology Rosmedtehnology" purchased infliximab for the amount of 2.4 billions rubles (65.8 million euros) [17] and the Federal State Dermato-Venerology Institute of High-Technology Care made an individual purchase to the amount of 874 mln rubles (24 million euros) [7].

Trastuzumab (Herceptin) was purchased individually in 2008: 50 packages by the Federal Scientific Centre for Roentgen-Radiology [14]; 12 packages were obtained by Chita Oblast [8] and for an amount of 1.7 mln rubles (46,610 euros) of rastuzumab was purchased by the Ministry of Health of the Republic of Dagestan [12].

5. Discussion

The huge expenditures on the studied biopharmaceuticals, potentially enough to pay good salaries for medical professionals, did not correlate with the number of patients receiving this form of medical care; this number of patients was small (see Table 3). We included recombinant insulins in Table 3 for comparison. The most problematic was the situation with recombinant interferons which are of questionable value for patients at best. Listing them on reimbursement lists and provided state guaranteed supply cannot be considered to be the most rational investment in healthcare. Furthermore, individual purchases of not listed biopharmaceuticals such as adalimumab (Humira, ATC code L04AB04) can also not be considered as best practice in patient care: firstly, because of the evidence that adalimumab is less effective

in the monotherapy of exacerbations of rheumatoid arthritis than in combination with methotrexate [6], secondly, due to serious safety concerns. Adalimumab is a "me too" product without any advantages over infliximab but being 10 to 20 times more expensive. A significantly higher incidence of malignancies and serious infections in patients treated with anti-TNF antibodies (infliximab and adlimumab) compared with placebo was shown in a meta-analysis of nine randomized controlled trials involving 5014 participants [1]. The pooled odds ratio for all trials which reported at least one malignancy in any group was 3.3 (95% CI: 1.2, 9.1). This effect was found to be dose-dependent. The number-needed-to-harm for malignancies was 154 (95% CI: 91, 500) in a treatment period of 6–12 months. For serious infections the number-needed-to-harm was 59 (95% CI: 39, 125) in a treatment period of 3–12 months while no dose dependency was shown.

Following this trend, five packages of omalizumab (Xolair) which is not on any of the policy lists, was purchased individually by the Russian Scientific Center on Roentgen Radiology for a calculated sum of 105,000 rubles (2,878.74 euros). Use of omalizumab for the treatment of asthma is not supported by evidence of its advantage over existing therapies as it has only been shown to be effective compared to placebo. There were no trials comparing it with inhaled corticosteroids or corticoids in combination with beta-agonists and also no studies of long-term effects [19]. Traditional inpatient topical treatment of plaque-type psoriasis in patients who failed ambulatory treatment was equally effective as efalizumab (Raptiva), but economically at least two times less costly [3].

The justification for the use of these medicines which put patients at risk of adverse effects more serious than the disease they are supposed to treat seems questionable and the policy to actively introduce them in patient care even more so.

6. Limitations of the study

We limited our overview to two classes of biological products, thus it does not present the situation with all biopharmaceutical products available currently on the Russian pharmaceutical market. Yet we hope that our findings reflect the major characteristics and trends in the field of biopharmaceuticals in the Russian Federation.

7. Conclusions

1. Biopharmaceuticals are registered with increasing speed in the Russian Federation.
2. Access and use of biopharmaceuticals are supported by existing pharmaceutical policies with state provision of the majority of them free of charge to designated categories of Russian citizens.
3. Policy disregards existing evidence regarding potential benefits and risks of newly marketed biopharmaceuticals.
4. There is no system of outcome monitoring of state delivered access to biopharmaceuticals, thus the effects of this policy and the costs implications are not known.
5. Generic substitution of a limited number of biopharmaceuticals was introduced without any documented adverse effects monitoring.
6. In 2006 federal spending on two classes of biopharmaceuticals under the Programme of Supplementary Medicines Supply of the Federal priority project "Health" reached almost 9 billion rubles (246.7 million euros).

7. Two classes of biopharmaceuticals require nearly 13% of federal spending and serve less than 0.15% of patients within designated categories.

Conflict of interest

We declare that we have no conflict of interest.

Competing interests

A.U.Z. and L.E.Z. work for the Formulary Committee of the Ministry of Health of the Republic of Tatarstan and actively participate in development of the national formulary list. R.R.N. works for GEOTAR Publishing House.

Authors' contributions

L.E.Z. conceived the overview, participated in its design, checked the searches, and drafted the initial and submitted version of the manuscript. All authors read and approved the final submitted manuscript. R.R.N. participated in data collection, performed searches.

A.U.Z. contributed to the analysis and helped to prepare the draft manuscript.

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