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GENERAL

BRIDGING EAST WITH WEST OF EUROPE – A COMPARISON OF ORPHAN DRUGS POLICIES IN POLAND, RUSSIA AND THE NETHERLANDS

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Abstract: The goal of this article is to provide an in-depth review of rare disease policies and the reimbursement of ODs in 3 European countries, two EU members (Poland, the Netherlands) and a non-EU one (Russia). A review of publicly available information on rare disorder policies and HTA processes was performed. Experts were consulted in case of unclear or scarce information. Russia has a five times higher frequency threshold for its rare disease definition than Poland and the Netherlands (both using the EU definition). The Netherlands has vastly increased its disease registries by instituting 300 expert centers via its National Plan, in Poland there are only 6 registries while in Russia one central registry exists. All 3 countries have an HTA process in place, however, the Russian one is relatively undeveloped. Access to ODs in the Netherlands is the broadest with 80 out of 83 EMA approved ODs reimbursed in 2015; Poland reimbursed 49, whereas Russia reimbursed 4 on the federal level and 43 in Moscow region. In all countries, new rare disease policies are under development. The availability of healthcare system solutions and the reimbursement of ODs differs greatly between all 3 countries. Even though both states are EU member with common regulations and access to EMA approved drugs, marked differences exist between Poland and the Netherlands in the range of policies, access to treatments and screening programs.

Keywords: orphan drugs, rare diseases, reimbursement, policy, disease registries, national plan for rare diseases, newborn screening

Rare disorders and orphan drugs are increasingly a topic of interest for the pharmaceutical industry as well as regulators and payers. The main reasons for the high interest are identified gaps in the access to medical treatment (or complete lack thereof) that rare disease patients often experience, difficulties in getting regulatory approval for new drugs as well as high prices associated with orphan drugs. HTA processes for orphan drugs are often subject to the same approach as drugs for common diseases, which creates exceptional situations due to small and heterogeneous patient groups, a lack of strong outcome data and high prices. This often leads to either failure to achieve reimbursement or granting of reimbursement without adequate evidence on cost-effectiveness. The HTA issues come on top of the existing difficulties to get new orphan drugs developed and licensed: less than 3% of the estimated 5000 to 8000 rare diseases have an actual medicinal treatment approved by EMA (1, 2). The number of new orphan drug approvals was ~ 14 per year in 2015-17 (3).

While regulatory processes are harmonized and well-defined in the EU's rare disease policies, HTA processes still differ significantly between countries and reimbursement decision-making are not always transparent. There are several publica-

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tions describing OD policies in single countries in Central and Eastern Europe and a few covering a larger number of countries in this geographical area, mostly focusing on reimbursement, pricing and HTA processes (4-7). However, there is still limited information in English on orphan drugs, rare diseases policies, and reimbursement in the Russian Federation. The authors aimed to fill this void and in addition compare Russia with the second largest market in Eastern Europe and its neighbor – Poland. In an effort to capture a broad spectrum of regional characteristics within a limited number of countries the authors wanted to include a western European country for comparison. The Netherlands was chosen because its healthcare system is considered to be one of the highest rated systems in Europe (8).

The goal of this article is to provide an in-depth review of the differences and/or similarities in rare disease policies and orphan drug legislation between these three European countries, as well as the impact on patient access their policies have. Using this approach a comparison between healthcare systems between old and new EU countries (and west vs. east) as well as outside the EU (Russia) can be made along with their effectiveness in addressing the issues surrounding rare diseases. A secondary goal is the identification of potential best practices that could be shared elsewhere.

MATERIALS AND METHODS

For this publication, the authors created a list of topics that were deemed of relevance for rare diseases and patient access to orphan drugs: rare disease definition and epidemiology, diagnostics and newborn screening, national plans, patient registries and reimbursement of orphan drugs (HTA process). The selected topics were in the scope of most of the focus areas that the EU has targeted (e.g. by the EU Council Recommendation of 2009 (9)). The area of patient organizations, however relevant to patients, was thought to be too variable and hard to measure objectively, qualitatively and quantitatively, and was therefore not selected for this publication. Finally, a review of publicly available resources on RDs and relevant HTA processes was performed, including legislative documentation, guidelines, governmental publications, and relevant literature in order to map the current situation for the chosen subjects in these countries. In some instances of unclarity, experts from the Polish and Russian ministries of health were interviewed to provide insights into the practical implementation of these policies. Due to the larger availability of public documentation, no expert interviews were necessary for mapping the situation in the Netherlands.

RESULTS

Poland

Rare disease definition and epidemiology

Poland uses the EU definition of rare disorders, which considers a disease as rare if it affects less than 1 in 2000 people (< 5 in 10000 people) ultra-rare being <1 in 50000 people (10). It has been estimated that about 2.3 mln to 3.0 mln patients with rare disorders live in Poland (on a total population of 38.5 mln) (11).

Diagnostics and newborn screening

A complete genetic diagnostic test is offered by 44 medical centers contracted by the National Health Fund (a sole state payer, reimbursed) as well as by private clinics (not reimbursed) (2). Tests are available for identification of 217 genes related to 323 diseases (2).

"Reference laboratories" do not exist in Poland. If diagnostic tests are not available in Poland, the NHF might reimburse such tests abroad, based on a referral from an appropriate national or regional consultant (appointed medical doctor). (2) Newborn screening was extended in 2015, from 23 to 28 RDs (see Table 1), financed by the Ministry of Health (MoH), approved by the Polish Agency for HTA and Tariff System (AOTMiT) and coordinated by the Institute of Mother and Child (Instytut Matki i Dziecka) with a budget of approx. 5.5 mln EUR (10). Eight regional centers in Gdańsk, Katowice, Cracow, Warsaw, Wrocław, Poznań, Łódź and Szczecin perform newborn screening in Poland (2).

National plan for RDs

At present rare disorders are not officially part of the Polish National Health Program. There is a Plan for RDs for 2017-19, developed recently under the auspices of the Polish MoH (11). It describes improvements in healthcare and social care for patients with RDs and their families, the creation of a monitoring system covering epidemiology, diagnostics, and therapy of these diseases, reference/expert centers specializing in diagnosis and treatment of RD and it elaborates on education, science and information policies regarding RDs in Poland. The previous national plan for RDs was developed by the National Forum for Rare Disorders in collaboration with the Team for Rare Disorders (2, 12, 13), which described in detail screening, genetic tests, medical help, integrated systems of social support

Table 1. Newborn screening of RDs in The Netherlands, Poland and Russia.

	The Netherlands (21)	Poland (28)	Russia (5)
Argininemia		X	
Argininosuccinic aciduria (ASA)		X	
Alfa -Thalassemia/HbH disease	X		
Beta-Thalassemia	X		
Beta-ketothiolase deficiency	P	X	
Biotinidase deficiency (BIO)	X	X	
Carnitine-acylcarnitine translocase deficiency (CACT)	P	X	
Carnitine transporter deficiency (OCTN2)	X	X	
Carnitine palmitoyltransferase deficiency type I & II (CPT-1, CPT-2)	P	X	
Congenital adrenal hyperplasia (CAH) or Adrenogenital syndrome (AGS)	X	X	X
Congenital hypothyroidism (CH)	X	X	X
Cystic fibrosis (CF)	X	X	X
Citrullinemia type I & II		X	
Developmental hip dysplasia			
Galactosemia (GAL)	X		X
Galactokinase deficiency (GALK)	P		
Guanidinoacetate methyltransferase deficiency (GAMT)	P		
Glutaric acidemia type 1 (GA-1)	X	X	
Glutaric acidemia type 2		X	
HMG-CoA-lyase deficiency (HMG)	X	X	
Homocystinuria (HCU)		X	
Isovaleric acidemia	X	X	
Long Chain 3-hydroxyacyl-CoA Dehydrogenase Deficiency (LCHADD)	X	X	
Maple syrup urine disease (MSUD)	X	X	
Medium Chain Acyl-CoA Dehydrogenase Deficiency (MCADD)	X	X	
3-Methylcrotonyl-CoA carboxylase deficiency (3-MCC) (3-methylcrotonylglycinuria)	X	X	
Methylmalonic acidemia (MMA)	P	X	
Mitochondrial trifunctional protein deficiency		X	
Mucopolysaccharidosis type 1 (MPS I)			
Multiple CoA carboxylase deficiency (MCD)	X	X	
Phenylketonuria/hyperphenylalaninemia (PKU)	X	X	X
Propionic acidemia (PA)	P	X	
Severe combined immune deficiency (SCID)	P		
Sickle Cell Anemia	X		
Sickle Cell Disorder (bearer)	X		
Tyrosinemia type 1 (TYR-1)	X	X	
Tyrosinemia type 2 (TYR-2)		X	
Very Long-Chain Acyl-CoA Dehydrogenase Deficiency (VLCADD)	X	X	
X-linked adrenoleukodystrophy (X-ALD)	P		

for patients and their families, education on RDs, availability of information and a central registry of rare disorders (2, 12). Nevertheless, this national plan has never been implemented.

Patient registries and designated centers of expertise

There are 6 disease-specific registries in Poland (for hereditary disorders, neuromuscular disorders, cystic fibrosis, cancers, severe and chronic neutropenia, primary immunodeficiency) (2) but there is no central registry for rare disorders that gathers data on all rare disorders collectively. Poland has 65 designated centers of expertise for rare diseases, 14 of which are participating in 16 of the 24 disease-specific European Reference Networks (ERNs) that were launched in March 2017. Poland does not have any centers with a coordinating role in any of the ERNs (14, 15).

The reimbursement of orphan drugs/HTA process

As a tailored approach to HTA for ODs does not currently exist in Poland, standard HTA rules for 'standard' medicinal products apply, which take into account: health priorities, results of sequelae of disease, public health significance, social preferences, organizational, legal aspects and ethical aspects.

The cost-effectiveness threshold is based on an ICER (Incremental cost-effectiveness ratio) that needs to be lower or equal to 3 × GDP per capita to consider a medical technology cost-effective (3 x 41.985 PLN = 125.955 PLN ~ 29.989 EUR in 2016, EUR rate from 16.03.2018 1 EUR = 4.2 PLN) (16).

After regulatory approval by the EMA, applicants need to send their reimbursement application to the MoH (containing clinical effectiveness, cost-effectiveness, and budget impact analyses), which transfers it to AOTMiT for evaluation. AOTMiT gathers and assesses information on health, social, economic and ethical aspects of the medicinal technology. The Transparency Council (part of AOTMiT) gives its recommendation on pricing and reimbursement and the final recommendation is issued by the President of AOTMiT. The final approval is given by the Healthcare Minister (see Figure 1). Official timelines for reimbursement assessment and price setting allow for 180 days, but in practice, this can take longer (17).

In the first quarter of 2018, 49 medicinal products for rare disorders were reimbursed in Poland (11, 18, 19, 20) (for detailed information on the reimbursed medical products in Poland please refer to Table 4). Most of the ODs are reimbursed within 'Drug Programs' (DPs) introduced by the MoH in 2012 for expensive medical technologies replacing previous 'therapeutical programs'(18, 19, 20). DPs are mainly designed to control consumption of the most expensive drugs (11).

Patients are qualified and monitored to gain reimbursed access to ODs. A list of contracted clinics where patients can be qualified, included and treated within the DP is defined by the NHF. Two

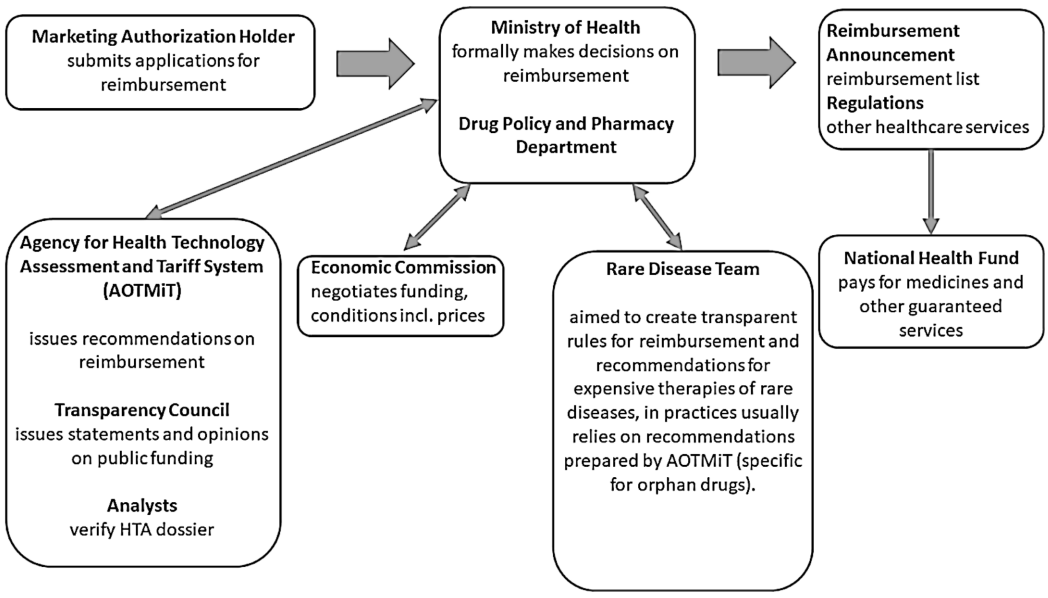

Figure 1. The reimbursement system of ODs in Poland

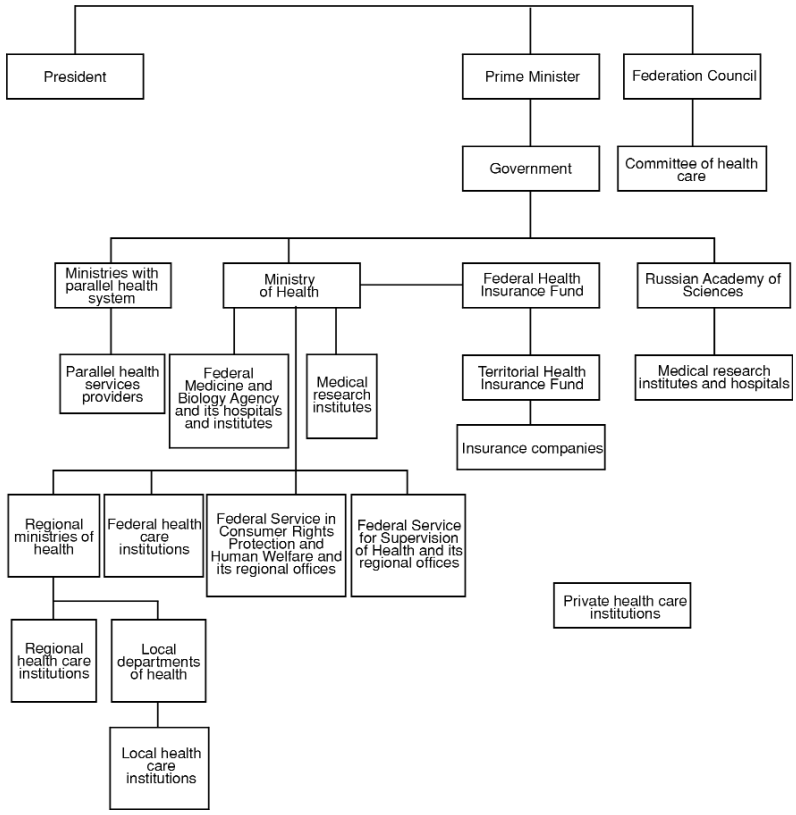

Figure 2. The structure of Russian Healthcare System (21)

main types of treatments exist within the DPs: oncological and non-oncological. In April 2016, 61 treatments were reimbursed within DPs: 21 oncological and 40 non-oncological (18).

There is no dedicated budget for rare disorders (2) but the NHF spends about 85 mln EUR on them. When patients turn 18 years old, reimbursement of their treatment is continued in pediatric centers. The continuation of the treatment is possible only following NHF consent, although this is not a long-term solution and mostly used in cases of hospitalization. In some cases (when patients became 18 years old), payers stop paying for preventative medicines (2).

The most commonly used pricing tool in Poland is price negotiation. Risk sharing agreements, mainly outcomes-based are increasingly used, however.

Russia

General considerations

Due to the structure of the Russian healthcare system, treatments (incl. some ODs and screening programs) are reimbursed from regional budgets and access to them differs depending on the region. Two main administrative levels exist, federal and regional, each subdivided into smaller bodies of representation, such as federal cities (e.g. Moscow), republics and oblasts (provinces). This structure has a large impact on budgeting and the availability of healthcare.

This publication focused mostly on the Moscow region as it is Russian biggest agglomeration and it is expected to be the region with the best coverage in the field of healthcare in Russia (including rare disease diagnostics and treatment, as well as access to orphan drugs).

Rare disease definition and epidemiology

RDs in Russia are defined as having a prevalence of less than 10 per 100.000 (22), i.e. 5 times less frequent than in the EU. Medicinal products intended to treat rare disease are considered ODs in Russia.

Diagnostics and newborn screening

Since 2007 neonatal screening for five hereditary diseases has been performed throughout Russia within the national priority project “Health” (Table 1).

The screening is at its most effective (> 95% screened) in the Urals, the Far Eastern and Siberian federal districts (23). Some regions screen for a wider range of diseases such as Moscow, where the Moscow Health Department has been reimbursing the screening programme for 35 hereditary diseases since June 2016 (24).

National plan for RDs

A national plan initiative to tackle problems of RDs, similar to the EU initiatives, does not exist in Russia.

Patient registries and designated centers of expertise

In contrast to the disease-specific patient registries that are used in the EU, Russia has one centralized Federal Register in order to collect data for all life-threatening and chronic progressive rare diseases (22). No reliable comprehensive source of information on centers of expertise on rare disorders was found.

Reimbursement of orphan drugs/HTA process

In Russia, there is no reimbursement system similar to the ones in most European countries. There are many lists, programs, levels, but the system is fragmented and not transparent, which makes it unwieldy to operate (Table 2).

The reimbursement of ODs is in the scope of both federal and regional programs. If a rare disease patient falls into a "citizen category" for whom drugs are reimbursed, e.g. veterans and their families, victims of the Chernobyl and Mayak disasters, patients with certain disabilities, and heroes of the Soviet Union (25), ODs are financed from the federal budget.

Additionally, ODs for 4 rare diseases (hemophilia, cystic fibrosis, pituitary dwarfism, Gaucher disease) are reimbursed on the federal level within the 7 Nosologies (diseases) Program. The 24 Orphan Nosologies List (ONL) exists on the federal level but treatments are financed by the regions which individually determine which drugs will be reimbursed. Other rare diseases which are not on the 24 ONL can be reimbursed if regional budget capacity allows for it. A court decision is often needed to decide in case of a dispute between patient and payer.

In the Moscow region, the City Health Department guarantees reimbursement of drugs and food for special medical purposes for their residents for diseases listed in Table 3 (26, 27).

The reimbursement of drugs on the federal level is based on two drug/disease lists:

- The Vital and Essential Drug List (VEDL) (28)
- The 7 nosologies program.

Reimbursed ODs in Poland and Russia have been compared in Table 4.

The HTA process for the inclusion of drugs onto these lists starts with a manufacturer preparing and submitting a dossier to the MoH. After a compliance check, an evaluation is done by a relevant MoH expert who focuses on a legally binding scoring scale, described below. After the evaluation, the dossier is passed on to members of a specially appointed Commission for a review and a recommendation, after which the MoH makes the final

Table 2. Overview of lists and programs within which orphan drugs are reimbursed in Russian Federation.

RUSSIAN REIMBURSEMENT SYSTEMS	
List, program	Financing
FEDERAL LEVEL	
Vital and Essential Drug List	List of drugs, created on the federal level, with price limits
Federal benefits	List of drugs, created on the federal level, available for some categories of citizens (specified below)*, financed from a federal budget
7 nosologies program	Financing of drugs included in the 7 nosologies program on the federal level, 4 of which are rare disorders
24 orphan diseases program - diseases list	List of diseases created on the federal level, but drugs financed by regions
REGIONAL LEVEL	
24 orphan diseases program - drugs list	Drugs included in this list: - are determined by each region - should be registered in Russian Federation
Regional programs	Drugs for diseases not included in 24 diseases can be also financed by regional budget within special regional programs

binding decision on inclusion of the drug. The scoring scale evaluation assigns specific weights to specific criteria, such as the type of supporting evidence (a systematic review, meta-analysis, randomized clinical trial), strength of the evidence, drug effectiveness (i.e. percentage of target outcome achieved) and safety during trials (frequency and severity of AEs). The total score will be a deciding factor in the

Table 3. List of diseases for which medicinal products and food for special medical purposes are reimbursed within the 24 Orphan nosologies list the City Health Department in the Moscow region.

No	Disease	Reimbursed treatment
1	Hemolytic - uremic syndrome	Eculizumab
2	Paroxysmal nocturnal hemoglobinuria	Eculizumab
3	Unspecified aplastic anemia	Antithymocyte immunoglobulin Deferasirox Cyclosporine
4	Hereditary deficiency of factor II (fibrinogen), VII (labile), X (Stuart-Prauer)	Coagulation factor 7 Coagulation factor 8 Eptacog alfa (activated)
5	Idiopathic thrombocytopenic purpura (Evans syndrome)	Romiplostim Eltrombopag
6	Defect in the complement system	Danazol Aminocaproic acid Tranexamic acid Icatibant Human C1 esterase inhibitor
7	Premature puberty central origin	triptorelin
8	Disorders of aromatic amino-acid metabolism (classical phenylketonuria, other types of hyperphenylalaninemia)	Specialized clinical nutrition products
9	Tyrosinemia	Specialized clinical nutrition products
10	Maple syrup" disease	Specialized clinical nutrition products
11	Other types of amino acid metabolism disorders of branched-chain (isovaleric acidemia, methylmalonic acidemia, propionic acidemia)	Specialized clinical nutrition products
12	Violations of the fatty acid metabolism	Specialized clinical nutrition products
13	Homocystinuria	Specialized clinical nutrition products
14	Glutaric acidemia	Specialized clinical nutrition products
15	Galactosemia	Specialized clinical nutrition products
16	Other sphingolipidoses: Fabry disease (Fabry-Anderson), Niemann-Pick Disease	Miglustat Agalsidase alfa
17	Mucopolysaccharidosis Type I	Laronidase
18	Mucopolysaccharidosis Type II	Idursulfase
19	Mucopolysaccharidosis Type VI	Gasulfase
20	Acute intermittent (hepatic) porphyria	-
21	Violations of copper metabolism (Wilson's disease)	Penicillamine Zinc sulfate
22	Incomplete osteogenesis	
23	Pulmonary (arterial) hypertension (idiopathic) (primary)	Bosentan Iloprost Sildenafil
24	Juvenile arthritis with systemic onset	Leflunomide Adalimumab Tocilizumab Methotrexate Etanercept

Table 4. List of reimbursed orphan drugs in Poland and Russia.

No.	Active substance	Russia (43)	Poland (49)
1	Agalsidase beta	Yes	No
2	Idursulfase	Yes	Yes
3	Mecasermin	No	Yes
4	Iloprost	Yes	Yes
5	Bosentan	Yes	Yes
6	Betaine anhydrous	No	Yes
7	Miglustat	Yes	No
8	Sorafenib	Yes	Yes
9	Romiplostim	Yes	No
10	Temsirolimus	No	No
11	Nilotinib	Yes	Yes
12	Imatinib	Yes	Yes
13	Lenalidomide	Yes	Yes
14	Trabectedin	No	Yes
15	Dasatinib	No	Yes
16	Sildenafil	Yes	Yes
17	Nelarabine	Yes	Yes
18	Riociguat	No	Yes
19	Clofarabine	No	Yes
20	Icatibant	Yes	Yes
21	Plerixafor	No	Yes
22	Alglucosidase alfa	Yes	Yes
23	Galsulfase	Yes	Yes
24	Macitentan	No	No
25	Thiotepa	No	Yes
26	Tobramycin	No	Yes
27	Velaglucerase alfa	No	Yes
28	Eculizumabum	Yes	Yes
29	Laronidase	Yes	Yes
30	Deferasirox	Yes	Yes
31	Eltrombopag	Yes	Yes
32	Danazol	Yes	No
33	Human C1 esterase inhibitor	Yes	No
34	Coagulation factor VII (RU)/VIII (PL and RU)/IX(RU)	Yes	Yes
35	Brentuximab vedotin	Yes	Yes
36	Mannitol	Yes	No
37	Ibrutinib	Yes	Yes
38	Budesonide	Yes	No
39	Carfilzomib	Yes	No
40	Nintedanib	Yes	Yes
41	Pasireotide	Yes	No
42	Bedaquiline	Yes	No
43	Azacitidine	Yes	Yes

Table 4. Continued.

No.	Active substance	Russia (43)	Poland (49)
44	Everolimus	Yes	Yes
45	Mercaptopurine	Yes	Yes
46	Busulfan	Yes	No
47	Canakinumab	Yes	No
48	Ruxolitinib	Yes	Yes
49	Dexamethasone	Yes	No
50	Nitisinone	Yes	Yes
51	Ibuprofen	Yes	Yes
52	Levofloxacin	Yes	No
53	Hydroxycarbamide	Yes	No
54	Asparaginase	Yes	Yes
55	Sodium oxalate	Yes	No
56	Bosutinib	No	Yes
57	Pirfenidone	No	Yes
58	Obinutuzumab	No	Yes
59	Olaparib	No	Yes
60	Efmoroctocog alfa	No	Yes
61	Sunitinib	No	Yes
62	Temsirolimus	No	Yes
63	Stiripentol	No	Yes
64	Mitotane	No	Yes
65	Arsenic trioxide	No	Yes
66	Anagrelide hydrochloride	No	Yes
67	Thalidomide	No	Yes

final reimbursement. A comparative health economic analysis is also performed, which gives negative or positive scores to the treatment, using following criteria: the annual cost of treatment and cost-effectiveness/budget impact (which includes indirect costs) vs. the standard of care/comparator. All the scores are added up to generate a single number. A range of other treatment characteristics are also measured on a points scale: prevalence of the disorder in Russia (i.e. medical need), feasibility of the dosing schedule and inclusion into clinical guidelines, the presence of the drug on the lists with essential/important drugs and whether or not the drug is manufactured in Russia. The score needs to be above a certain threshold to get a positive recommendation for reimbursement (29).

The decision – making process for financing drugs on the regional level varies per region. In some regions, the Minister of Health decides, while in others the decision is made based on pharmacoeconomic studies and a consultation with disease experts (29).

The Netherlands

Rare disease definition and epidemiology

The Netherlands (like Poland) has implemented the EU definition of RDs, which amounts to 1.02 to 1.36M rare disease patients in the Netherlands (2016 total population size of 17.08M) (30, 31).

Diagnostics and newborn screening

Newborn screening is widely performed for 21 disorders (Table 1) (32). A further 10 diseases will be added to the screening programme over the next few years and additional screening of children aged 1-10 is being investigated (33).

Genetic testing can be done, either commercially (3rd party – not reimbursed, unless there is a medical indication) or within the healthcare system.

National plan for RDs

A National Plan for Rare Disorders was established, mainly focusing on identifying gaps in current rare disease healthcare and suggesting and promoting solutions (done by the ZonMW institute). In February 2017 ZonMW gave its final recommendation to the MoH, with a special focus on building networks of expertise. This led to the formation of 300 new reference centers, which will play a coordinating network role in providing medical and psychosocial healthcare and expertise down to regional healthcare providers and patients. Further recommendations included opening a national registry collecting patient data, building ICT infrastructure, healthcare and OD financing and the role of health insurers therein, funding long-term scientific research, standardization and creating guidelines, enhancing education for GPs and medical students to improve early diagnosis, expanding screening, creating a public website on genetic disorders, and promoting patient engagement. The MoH has been given clear objectives and solutions for the near and mid-term future, but obstacles in areas like finance, logistics, policy creation, research and development and the spreading of knowledge and expertise will need to be overcome, according to ZonMW (34).

Patient registries and designated centers of expertise

Until recently, only a small number of patient registries for rare disorders existed in the Netherlands, e.g. for neuromuscular, metabolic and oncology disorders, CF. The national plan has led to the establishment of 300 expert centers. Currently, there are 378 designated expert centers in the Netherlands of which 24 participate in European Reference Networks (ERN). Moreover, 5 ERNs will be coordinated by expert centers in the Netherlands (the highest representation together with France/ UK, who also have 5) (34). These are considered as first but important steps to collect and share rare disease knowledge and expertise. Regional healthcare centers and local institutions (welfare organizations, schools, housing corporations, and employers) will play an important role in the networks to bring healthcare closer to home. The relevant legislation is in place, but the budget needs to be allocated and networks need to be actively built (34).

Reimbursement of orphan drugs/HTA process

The Netherlands has an HTA process for medicines, but not for most other medical interventions. Prices are generally set by manufacturers. An independent but government-sponsored agency (ZiN) advises the MoH on which drugs should be included in the basic reimbursement package for all Dutch citizens. ZiN receives scientific advice from the Scientific Pharmaceutical Advisory Committee and key stakeholders if necessary, including manufacturers, patient associations, hospitals, medical specialists and the regulatory agency MEB. ZiN bases its conclusions on an integral assessment of 4 criteria: effectiveness, cost-effectiveness, medical need, and feasibility. The effectiveness criterion is given special weight and is legally binding. To be eligible for reimbursement, ZiN requires a medicine to be on par with the current "*state of science and practice*"(35), i.e. either comparable to or with added benefit over available standard of care medication (*relative effectiveness*). ZiN does not consider a marketing authorization from either EMA or MEB to automatically equal standard of care since regulatory approvals are often based on pure benefit-risk assessments and not on comparisons with common medical practice. If a drug has *less* therapeutic benefit than comparable medicines according to ZiN, it will not be recommended for reimbursement.

ZiN uses PICOT methodology to define and qualify literature reviews (Patient/Intervention/ Comparison/Outcome/Time) and two other factors (required clinically relevant outcome difference and 'fitting evidence profile'). The quality of scientific evidence is judged using GRADE methodology (Grading of Recommendations Assessment, Development and Evaluation), leading to 4 possible quality levels (35). ZiN does not perform its own health economic analyses, these are provided by the applicant. In case of doubt, experts will be consulted. Finally, ZiN makes a reimbursement recommendation to the minister.

Since 2012, a *conditional reimbursement* has been possible to be granted in case of discussion/doubt over a therapeutic benefit, cost-effectiveness or predicted budget impact of a medical intervention (only available for outpatient drugs) (36). Conditional approvals would ensure patients got early access to innovative medicines while keeping budget control. A conditional reimbursement required additional scientific data to be provided within 4 years (or 7, in exceptional cases), for which a subsidy could be requested at ZonMW with a maximum of 400.000 €. However, the number of products that applied for conditional reimbursement up to 2017 turned out to be low. Therefore, the conditional reimbursement program has been replaced by a more general subsidy program, focused at SME's (37).

For outpatient medicines, ZiN bases its assessment on their therapeutic value (compared to stan-

dard of care) and budget impact. Most outpatient medicines will be listed in a group containing comparable or mutually replaceable medicines (Annex 1A) with a maximum reimbursement limit per pharmacotherapeutic group based on the average price of the individual medicines within this group (internal referencing). If a drug is has *added therapeutic value*, it can be placed on Annex 1B, which allows higher pricing (no upper reimbursement limit), but health economic evidence is required. The less common Annex 2 contains drugs which a subject to special restrictions (38). In addition to internal referencing, an external reference price mechanism exists that determines maximum prices every 2 years based on the average price in 4 neighboring countries: Belgium, Germany, the UK, and France. (39)

Drugs dispensed by medical specialists are placed in a separate group called "specialist drugs", which includes all orphan drugs. ZiN's guidelines (40) state that these medicines are assessed using a *risk-based approach*, taking into account several important factors that pose a 'risk' to the healthcare budget. If there is no or an overall low risk according to ZiN, the drug will be included in the basic reimbursement package for all Dutch citizens. A formal assessment will be made in case of risks, based on the following criteria that determine the level of 'risk' (on a yearly basis):

- (lack of) additional therapeutic benefit
- effective control over drug use by health insurances
- (lack of) convincing evidence for drug application
- level of self-management in the medical field via protocols, guidelines and registries
- budget impact
- 'dynamics' of the therapeutic area
- possible monopolistic positions of suppliers
- costs per patient year > 25000 € (not a hard limit, but it can influence the assessment)

For reimbursement of drugs with a claimed therapeutic benefit and a total budget impact > € 2.5 M, a formal assessment is performed based on effectiveness data and health economics data (i.e. cost-effectiveness, cost prognosis, budget impact), provided by the manufacturer. Medicines without a claim on therapeutic benefit but with a budget impact > € 2.5 M, will not be assessed because health insurances/hospitals are expected to procure other cheaper medicines of comparable therapeutic benefit.

A dedicated approach to HTA for ODs was introduced in 2006, however, most ODs are added to the basic package of reimbursed medicines. For reimbursement purposes, they are grouped with specialist medicines. ZiN believes that HTA for ODs should not be different, so standard HTA rules apply. However, ZiN has published a document that describes the context and requirements for reimbursement of ODs within the overall healthcare framework (41). Extramurally dispensed 'expensive medicines', which often includes ODs, have recently been transferred from the national reimbursement system towards individual hospital budgets, with the intention to create incentives for hospitals to negoti-

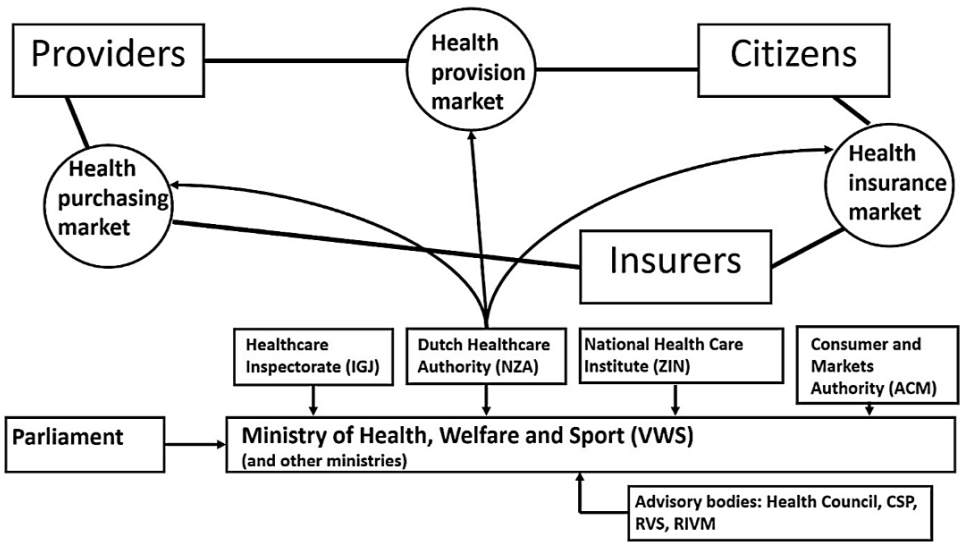

Figure 3. The structure of Dutch Healthcare system (42)

ate lower prices with manufacturers and stimulate cooperative procurement. Hospitals bear the full risk of exceeding budgets for specialist drugs agreed upon in contracts with health insurers.

Access to reimbursed ODs is very broad in the Netherlands: 80 out of 83 EMA approved ODs were reimbursed for all citizens in 2015 (40).

DISCUSSION

More aspects that go beyond the scope of this article could be taken into consideration to have a full picture of the rare disease policy landscape:

- the quality and extent of the social security system (e.g. welfare in case of long-term sickness, coverage, subsidies of housing adaptation, support at home, policies regarding employment options, etc.)
- the overall quality of the healthcare system in- and outside the orphan drug area, i.e. the quality and availability of high quality hospitals and surgical interventions, the existence of specialized care outside the hospital setting (e.g. palliative care), access to medical devices and supportive equipment, adequate education and experience of HCPs
- the availability and quality of special foods and medical nutrition, which are often the only option to manage rare metabolic diseases due to the lack of available medicinal treatment.

It is hard to measure in practice the effects and ultimate patient impact of certain policies, such as the quality and effectiveness of newborn screening, which can lead to inconclusive evidence (43). How the fact that Holland has 300 expert centers vs. 14 in Poland or 1 central registry in Russia translates into the overall quality of healthcare, scientific research or patient access to treatment remains to be seen.

Even though they can have a large impact on access, pricing policies were not discussed in detail in this article, due to the general lack of transparency and uniformity in this area. Even though many orphan drugs are reimbursed, the final price setting for expensive drugs is not often publicly available, such as in the Netherlands.

There are clear differences in healthcare expenditure and rare disease policies between Russia, Poland, and the Netherlands, each with their advantages and disadvantages from a patient perspective. Access to reimbursed ODs and other healthcare for RD patients varies widely between these 3 countries, and sometimes even within (Russia). Budgeting structures (i.e. federal vs. regional) play a large role in regional healthcare access for patients, especially in Russia, where local government institutions and budgets often determine the type and level of healthcare provided. This was not surprising, with Russia being > 400 times the geographical size of Holland, but it can have a large impact on patients with rare disorders nonetheless.

Poland and the Netherlands, whilst being both EU member states with common regulations and access to the same EMA approved drugs, show marked differences in the range of policies and access to ODs and screening programs. This is partly explained by different fiscal systems and healthcare spending levels (per capita) in these countries (44). All 3 countries have an HTA process in place although it is not as developed in Russia as in Holland and Poland. All countries take different approaches but a cost/benefit analyses always play an essential role. ODs often do not fit into the conventional HTA rules regarding evidence, costs and budget impact, so reimbursement decisions need to be based on exceptional circumstances, arguments of compassion and budget space. Even with elaborate scientific tools in place, ultimately, simple price rebates by the manufacturer can sway a reimbursement decision. The Netherlands has the most lenient approach towards making positive reimbursement decisions for ODs, with 80 out of 83 EMA approved drugs with orphan designation being reimbursed; Poland reimbursed 49, Russia reimbursed 4 on the federal level and the number of reimbursed ODs on the regional level was dependent on local budgetary space e.g. 43 in Moscow region.

For the approx. 98% of rare disease patients for whom no orphan drug is on the market, it is important that general healthcare and social systems are able to address their needs in a holistic approach. This includes proper diagnosis by adequately trained staff, the availability and reimbursement of symptomatic treatments, rehabilitation, and other medical and non-medical support that these patients might require. The EU initiative to create national plans for rare disorders was specifically designed to include these kinds of system solutions, although the implementation is still ongoing, also in Poland and Holland. National Plans can lead to vastly improved policies like in the Netherlands which created over 300 reference centers and where new legislation enables regional and local healthcare to support rare disorder patients and their families. Poland has 6 registries for rare disorders. Russia is the only one with a central registry for all rare disorders, which has the benefit of being a single source of information and which could improve earlier diagnosis, disease understanding and finding proper multi-disciplinary treatments.

Russia has several areas where it provides similar or better access to relevant healthcare than in

Poland or the Netherlands, e.g. neonatal screening in Moscow area targets 35 conditions, more than any other EU country including Poland (28) and Holland (21). Screening in other regions of Russia however, is often limited to only 5 disorders.

Although easly overlooked in the bigger picture, differences in the definition of frequency of rare diseases are likely to have a considerable impact on access to treatments and ODs. Russia, having a five times higher frequency threshold than Poland and the Netherlands, automatically restricts access to potentially beneficial policies to a lower number of rare disease patients. Access to healthcare varies also greatly within Russia, both between regions and individuals (citizen classes), therefore generalizing conclusions should be drawn carefully, if drawn at all (45).

CONCLUSION

Even though areas of improvement remain, these three countries show that RDs are increasingly being put on the political agenda, resulting in special policies and improved treatment and access. International scientific collaboration is taking place to promote successful development of ODs, e.g. by the implementation of European Reference Networks and the creation of new statistical methodology and clinical trial design for small population groups (as seen in the EU's FP7 framework) (46). In the field of regulatory and HTA processes, the EMA collaboration with EunetHTA (47) is a good example which could be extrapolated to rare disorders and ODs. These trends can only be encouraged.

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