Rare essentials?

Drugs for rare diseases on the Essential Medicines List

A discussion paper prepared for the WHO Expert Committee on the Selection and Use of Essential Medicines

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Chapter I

INTRODUCTION

Societies all over the world have always faced the challenge of bringing efficacious, safe and affordable medicines to patients who are in need for such treatments. This challenge has countless scientific, medical, economic, and political angles. There is probably no segment in the health care sector where public and private interests meet in such a intense, and sometimes counterproductive, fashion as seen in the pharmaceutical field. Public concern about a deficient pharmaceutical market and a public-health policy failure to serve patient's treatment needs have been strong drivers for action. As a response, the international community has developed in the late 70s and early 80s of the twentieth century two important systems of prioritising resources and allocating incentives in order to fill the gap between public and individual patient needs and what the international pharmaceutical market place could deliver.

First of all, the World Health Organization (WHO) has paved the way for bringing really necessary drugs to patients in the less-affluent countries through the system of Essential Drug Lists (EDL), the first published in 1977 and with a well-deserved celebrated 25th anniversary in 2002 1. The concept of the EDL has helped since then over 150 countries all over the world to establish the principle that essential medicines save lives and improve health, but only when they are available, affordable, of good quality, and properly used 2. Secondly, a variety of incentive systems has been developed in different, mostly affluent, countries to stimulate research, production and marketing of drugs for patients with a rare disease, so-called orphan drugs (ODs). Because of their small market potential such drugs are not attractive for the pharmaceutical industry to develop and to market 3.

Although, both policy systems of prioritising resources and allocating incentives for pharmaco-therapy (EDL and OD) have many differences (e.g. background, goals, conceptual frame, etc), it is becoming obvious that there may be 'common grounds' between the two, i.e. there may be rare diseases in need for essential drugs. This means that the question is on the table what happens when both approaches (i.e. EDL and OD) 'encounter'. This is not a theoretical question as the current Essential Medicines List (EML) contains a number of drugs for rare diseases (some have been deleted in recent years; some have been identified for possible future deletion from the EML). In the advent of more ODs becoming available (ODs constitute for instance nowadays about 25% of all new applications in the EU), we may anticipate future questions as to whether these drugs should be included on the EML.

In this paper, we will discuss and review the present and future position of medicines for rare diseases on the EML. Topics to be included in the analysis are scope, background, and logic of the two systems of filling the gap between patient needs and what the pharmaceutical market delivers. Moreover, we aim to provide a framework of reasoning for analysing and solving future public health questions when both systems 'encounter'.

Chapter 2

ESSENTIAL MEDICINES: big numbers with impact

The Essential Medicines List (EML) was the result of a resolution at the 1975 World Health Assembly of WHO. Two years later the first Essential Drug List was established and published, containing essential medicines that were 'of utmost importance, basic, indispensable and necessary for the health needs of the population'. Since its origin the EML has been dynamic by nature and by 2002, the definitions of the EML had changed. Since then essential medicines are 'those that satisfy the priority health care needs of the population. They are selected with due regard to public health relevance, evidence on efficacy and safety, and comparative cost-effectiveness.' In 2002, it was also decided that essential medicines should be selected on evidence-based arguments, rather than experience-based.

The EML consists of two 'sections', a most essential core list, and a complementary list. Although it was decided at the 2003 meeting of the WHO Expert Committee on the Selection and Use of Essential Medicines that the two lists should not be published individually, separate definitions do exist. The core list is, according to the current definition, 'a register of minimum medicines needs for a basic health care system, listing the most efficacious, safe and cost-effective medicines for priority conditions. Priority conditions are selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment'. The complementary list presents 'essential medicines for priority diseases, for which specialized diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training are needed. In cases of doubt, medicines may also be listed as complementary on the basis of consistently higher costs or less attractive cost-effectiveness in a variety of settings.' The key difference between the core and complementary list is whether or not drugs require specialized facilities or services. The requirements of public health relevance, efficacy, safety and cost-effectiveness are present in both definitions.

Thus, the criteria for selection have evolved over the last decades and currently essential medicines are largely selected based on public health relevance, available data on efficacy, safety, comparative cost-effectiveness, stability, pharmacokinetic properties and need for special diagnostic or treatment facilities. The absolute costs of treatment and the patent status are not considered to be exclusion criteria.

The latter is also illustrated by the absence of a discussion about patent status when the Committee decided to add antiretroviral therapy to the List in 2002 for the treatment of the 'priority disease' HIV/AIDS.

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7 Ibid. p. 26-30.
Within the context of the EML the term ‘neglected diseases’ refers to geographically based diseases: common in some places, but uncommon globally. Diseases like Trypanosomiasis, Buruli ulcer or Chagas disease are typical examples of this group. Medicines for these diseases may be included in the EML based on the criteria described above since they meet the priority needs of a specific population. These diseases constitute a large public health treat in some places in the world in contrast to ‘rare diseases’, diseases with a low prevalence everywhere (i.e. without a large geographic variation).

Role of the EML
Three important functions for the EML can be discerned: an operational, an educational and a symbolic purpose. As an operational tool, the EML is an important guide for health policy makers to identify the most important drugs that must receive priority attention in terms of production, prescribing, availability and access. Furthermore, the list is an educational tool for health professionals and policy makers, helping them to improve formulary building, prescribing and usage processes. Finally, the list has important symbolic value. Being classified as ‘essential medicine’ provides worldwide recognition, preferred position in pharmaceutical management and may provide incentives to stimulate adjacent policies (e.g. production, investments in infrastructure related to the disease, establishment of quality systems, etc.).

While selection occurs at a global level, implementation of the WHO EML concept occurs at country level. Countries are invited and stimulated to formulate national policies with the EML as a ‘routing vehicle’. This would result in a separate national list, which can vary from the WHO list due to local circumstances such as demography, epidemiology, public health relevance, financial resources, capacity of the health system and other factors. Whether a medicine is included in a national list can be considered as an indicator for the level of adoption and dissemination of the EML. Although there is an ongoing debate about the impact of these lists on national policy and drug utilization, the balance sheet of the role of the EML, particularly in the less-affluent countries, looks very positive.

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12 Levy M, Reidenberg M. What has been the impact of the concept of essential drugs? Clin Pharm Ther 2003; 73:275-278.
Chapter 3

MEDICINES FOR RARE DISEASES: small numbers with impact

The term rare disease constitutes a (semi)quantitative component. What kind of criteria can we apply to classify a disease as being rare? This is not an easy question to answer, as we have to deal with a complex and heterogeneous mosaic of various conditions, which are mostly not easily categorised. For many of these diseases no appropriate epidemiological date, medical interventions or care exist. At this moment several criteria are applied worldwide to identify and classify rare diseases. Most often these criteria are laid down in so called ‘orphan drug legislation’ to provide incentives for the development and marketing of medicinal products for diseases that may otherwise be hampered by the non-viability of the market. The non-viability of the market has been also increased by scientific deficiencies, greater regulatory demands on new drugs in terms of safety and effectiveness, and a lack of public awareness on the issue. It is a well-known fact that political pressure for putting a disease on the policy agenda is also affected by the number of concerned patients. The responsiveness to this recognized market failure, among other factors, led to the first OD legislation in the United States in 1983. Other countries (e.g. Japan, Australia) followed in the nineties and in 2000, the European Union established its own OD legislation. Table 1 provides an overview of relevant features of both the US and the EU OD systems.

Table 1  Features of the US and EU Orphan Drug incentive system

<table>
<thead>
<tr>
<th></th>
<th>US</th>
<th>EU</th>
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<tbody>
<tr>
<td>Prevalence criterion for rare disease</td>
<td>Less than 200,000 patients in USA (&lt;7.5:10,000)</td>
<td>Life-threatening or chronically debilitating disorder that affects less than 5:10,000 in EU</td>
</tr>
<tr>
<td>Requirements for designation</td>
<td>Rare disease or R&amp;D costs cannot be recovered in 7 years</td>
<td>Rare disease, or product unlikely to be developed without incentives or new product will be of significant benefit</td>
</tr>
<tr>
<td>Products eligible for orphan designation</td>
<td>Drugs and biologicals (including vaccines and in vivo diagnostics)</td>
<td>Drugs and biologicals (including vaccines and in vivo diagnostics)</td>
</tr>
<tr>
<td>Market exclusivity</td>
<td>7 years; prevents same product being approved for the same indication unless clinical superiority is shown</td>
<td>10 years; can be reduced to 6 if orphan criteria no longer met</td>
</tr>
<tr>
<td>Other benefits</td>
<td>Regulatory fee waivers, 50% tax credit on clinical research after designation; grants for clinical research (pharma and academia eligible); protocol assistance; faster review if indication warrants; research grants for medical devices and medical food</td>
<td>Regulatory fees can be reduced or waived, access to centralized procedure, protocol assistance. Individual Member States have to implement measures to stimulate the development of orphan medicinal products</td>
</tr>
</tbody>
</table>

It is important to notice that OD regulations are becoming in place in many parts of the world. Methods often used in these regulations in order to stimulate research into and availability of ODs include extended regulatory guidance and advice, waivers of regulatory fees and market exclusivity. Particularly the latter issue has been a recurring driver for public concern as it may adversely result in monopolistic behaviour of the industry, high prices, etc \textsuperscript{14}. Moreover, some drugs may deserve to be designated as OD at the start of development, but turned out to be commercial successes later on in their lifecycle, e.g. zidovudine (AZT, Retrovir), epoetin alfa (Eprex) or imatinib mesylate (Gleevec). In 2003, with the 20th anniversary of the Orphan Drug Act in the US, its impact on drug development and public health was evaluated \textsuperscript{15}. Since its introduction in the early eighties, about 1,100 drugs have received an Orphan Drug Designation. Of these, 231 products were marketed, having provided an estimated 11 million patients with new medical treatments for their disease. The EU system for stimulating OD development started about twenty years later, but is developing rapidly with at the moment more then 150 designations and about 10\% of these authorized for marketing \textsuperscript{16}.

Drug development and providing access to ODs have been extensively discussed in recent years in the context of bringing new drugs to patients not having effective and safe treatment so far. A key issue in this debate is: what does ‘appropriate incentives’ mean? Under normal market conditions orphan products would not be developed, as the cost of bringing them to the market would probably not be compensated by the expected sales. Given the small number of patients who would benefit from an OD, there is little motivation for industry to invest in a pharmaceutical agent with poor market potential. However, scientific issues, e.g. small numbers of subjects for clinical trials, lack of mechanistic knowledge about the disease, absence of valid biomarkers, and inappropriate diagnostics also limit OD development. Moreover, ongoing uncertainty about pricing and reimbursement (particularly the case in Europe) may also make investors reluctant and hamper orphan patient’s access to important medical products \textsuperscript{17}. Still, the issue of rare diseases and orphan drugs is beginning to demand a greater place in health rationing and decision-making as healthcare continues to cover far more varied and diverse programs for the treatment of rare diseases \textsuperscript{18}. Despite the lack of quantitative data for the burden of disease, it is generally known that people with a rare disease may suffer significantly \textsuperscript{19}. Particularly, rare diseases caused by genetic changes at a single genetic location are responsible for substantial mortality. For some monogenetic rare diseases not only the burden for the patients themselves but also the burden for the society in a specific area is significant, like in the case of thalassemia or sickle cell anaemia \textsuperscript{20}.

\textsuperscript{14} Maeder T. The orphan drug backlash. Sci Am 2003; 288:80-87.
The burden of rare diseases

In terms of prioritising limited public health resources it is important to have access to reliable data on disease burden. So far, this has been a difficult task in the field of ODs. It is important to note that there are differences between the US and EU definitions of a rare disease. In the US Orphan Drug Act the definition used relates to an absolute number of cases (less than 200,000 patients in the US), while the European regulation uses a relative measure (< 5:10,000 inhabitants) and requires the disorder to be life-threatening and/or chronically debilitating. When these definitions are used, it is estimated that between 5000 and 8000 conditions would qualify as a rare disease. This brings the total number of patients suffering from all of these diseases in Europe and the United States alone to 55 million. Data about number of patients suffering from a rare disease in the rest of the world are scarce, but as noticed before the issue of rare diseases and ODs is becoming a virtually worldwide topic.

One of the primary reasons why sound epidemiological data on rare diseases is often lacking is the absence of proper classification, coding, and registration. Although an International Classification of Disease (ICD) code is available for some of the better-known rare diseases such as thalassaemia, cystic fibrosis or Haemophilia, many are not registered in medical registries and databases. Often these rare disorders are grouped under general headings such as ‘endocrine metabolic disorders’. As a consequence, it is difficult to identify and classify people with a rare disease on a (inter)national basis and in a reliable fashion. A second reason for the lack of reliable epidemiological data is the frequent absence of appropriate biochemical and genetic diagnostic data. Furthermore, many disorders are not present at birth but become apparent later at juvenile age or in adulthood. Thus, studies that include follow-up data from birth are needed to assess the true prevalence and disease course.

Generally speaking, currently applied indicators, such as the DALY, to quantify disease burden are not very useful in the case of individual rare diseases. The small numbers of (possible) affected people brings any DALY estimate of a rare disease at the bottom of a priority list of priority diseases. Partly this is also an issue of choosing the appropriate level of classifying a disease. Cardiovascular diseases will show up in the higher ranks of any DALY listing, but not a rare cardiovascular condition like pulmonary hypertension. The same is true for cancer and the rare condition chronic myeloid leukaemia (CML), or metabolic diseases and the orphan Gaucher disease.

Despite the problems of acquiring reliable data on rare diseases, there are rare diseases that have been fairly prominent for decades (e.g. Haemophilia, cystic fibrosis, Crohn’s disease). Nobody could make a case that these diseases are neglected or ignored in affluent countries.

Access to and affordability of medicines for rare diseases

So far, despite all the progress made during the last decades, for many of the rare diseases no effective and safe treatments are available. However, when there are treatments available, many other obstacles are encountered that may hamper effective access and use of these drugs. We will discuss some of these.

Evaluating and assessing clinical relevance and cost-effectiveness

The development and regulation of ODs is, in many cases, still in an experimental phase. As said before, the small number of patients, the ongoing debate about choosing appropriate trial methodology and outcome parameters, lack of knowledge

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about natural disease course, etc hamper firm positioning of the OD in clinical practice, also in terms of cost-effectiveness.

**Lack of knowledge and training**
It is estimated that currently about 1300 rare diseases are medically well defined \(^{22}\). For many other rare diseases available information is still inadequate. This feature is also reflected in the training of health professionals. Against this background health professionals often are deficient in appropriate training and awareness to diagnose and treat adequately patients with a rare disease.

**Deficient diagnostic systems**
For several rare genetic diseases the diagnosis can be made via genetic or other molecular tools. However, for the majority of these diseases still no diagnostic methods exist or the facilities for diagnosis are not available. In these cases the diagnosis may be only clinical, with consequent problems of validity, coding and reproducibility.

**High prices**
The prices of ODs per individual patient or treatment episode vary significantly. A cyanosis patient may be treated for about $10,000 per year, whereas treatment costs of patients with enzyme replacement therapies may reach levels of > $ 150,000 per treatment-year. On a population level the costs may be reasonable because of the small number of patients, but when more patients need treatment this may require an unaffordable share of available budgets. Affordability of ODs has become a major issue for payers and is a strong driver of tensions between the different stakeholders involved. Some pharmaceutical companies have responded to these tensions by developing programs to facilitate and increase access to ODs (e.g. treatment of Gaucher patients worldwide) \(^{23}\).

All these struggles surrounding ODs exemplify and mirror the global debate of deficiencies in bringing new drugs to patients who need them. The recently published WHO report 'Priority Medicines for Europe and the World – a public health approach to innovation' gives an elaborate and thoughtful account on this and has provided a priority listing of gaps in pharmacotherapy \(^{24}\). One of these gaps, if not one of the most relevant ones, is the crisis in the discovery and development of new antibiotics. This crisis has been linked to the OD issue in *Science* in the context of a more general question: will all drugs become orphans in the future, not because the rareness of the disease, but because other factors hinder sufficient investments in drug discovery and development \(^{25}\)?

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\(^{22}\) www.orpha.net


CHAPTER 4

DRUGS FOR RARE DISEASES ON THE ESSENTIAL MEDICINES LIST

In the previous two chapters we have provided introductory information on two systems of prioritising resources and allocating incentives in order to bring relevant medicines to patient care. As said before, the two systems are not alike although they share principles as justice and equity (although probably not the same weighing of these two principles). In Table 2 we compare some important features of the two.

Table 2   EML and ODs compared

<table>
<thead>
<tr>
<th></th>
<th>Essential Medicines</th>
<th>Orphan Drugs</th>
</tr>
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<tbody>
<tr>
<td>Concrete policies in place since</td>
<td>1977 worldwide</td>
<td>1983 in US, 2000 in EU</td>
</tr>
<tr>
<td>Primary focus</td>
<td>Public health: bringing effective medicines to as many patients as possible</td>
<td>Individual patient: even a single patient warrants everything what is possible</td>
</tr>
<tr>
<td>Initiated and developed by</td>
<td>WHO, and member states</td>
<td>Governments of US, Japan, Australia and EU; Patient groups</td>
</tr>
<tr>
<td>Criteria</td>
<td>Drug driven (i.e.. drug to be listed at EML is efficacious, safe, cost-effective, based on evidence based data, etc.)</td>
<td>Disease driven (i.e. disease to be classified as OD has low prevalence &lt;5-7.5: 10,000, is life threatening, etc.)</td>
</tr>
<tr>
<td>Policies directed at</td>
<td>Bringing already available medicines to patients</td>
<td>Bringing new medicines to so far untreated patients</td>
</tr>
<tr>
<td>Target populations</td>
<td>Initially in less-affluent countries, now all countries</td>
<td>In affluent countries, developed world</td>
</tr>
<tr>
<td>Economics</td>
<td>Cost-effectiveness, sustainable and affordable access</td>
<td>Relatively (very) high prices per individual patient, cost-maximization per population</td>
</tr>
</tbody>
</table>

Essentially the two systems differ on how is dealt with the criteria:

1. Prevalence of the disease
2. Burden of disease
3. Cost-effectiveness of available treatment

In recent years there have been no additions to the EML of drugs for rare diseases. The last addition of a drug for a rare disease to the complementary list was in 1988. Desmopressin, was added to the core list in 1992, but deleted recently because of its rare indication.

There has been ample discussion about the prevalence of diseases in the context of deleting products from the List. We will turn to this discussion now.
In the 2002 definition of an Essential Medicine the ‘prevalence’ of a disease was not explicitly mentioned, neither in the definitions of what criteria core medicines should meet, nor as a criterion for listing as a complementary medicine. Moreover, in the 2002 Expert Committee meeting defining Essential Medicines the words ‘disease prevalence’ were replaced by ‘public health relevance’ in order to include preventive treatments as well. In their definitions the core and complementary lists speak only of the public health burden of disease.

In their ninth report, the WHO EML Expert Committee emphasises that the model list should be seen as ‘a common core of basic drugs that are the most cost-effective for meeting the health care needs of the majority of the population’, while acknowledging that ‘in certain situations, there is a need to make available additional drugs essential for rare diseases.’ Some drugs for rare diseases are included in the Complementary List, tagged with a code (C) that the drug is for ‘rare disorders or in exceptional circumstances’. In the twelfth edition of the EML, a total of eighteen pharmaceuticals were labelled as such. Of these only four were associated with a rare disease, one has already been deleted (fluadrocortisone) and two are currently under review (Factor VIII concentrate, Factor IX complex).

An interesting case is the deletion of fludrocortisone in 2003, in which extra qualifications are given for the deletion of a drug for a rare disease. Although the WHO EML Expert Committee recognized the value of fludrocortisone in the treatment of adrenal insufficiency (considered a rare condition), the committee still decided to delete fludrocortisone from the list based on the following criteria:

1. The drug is included in only a few national essential drugs lists
2. It is not listed in the International Drug Price Indicator Guide
3. It is not being supplied by either UNICEF or the International Dispensary Association

The Committee also said in the same chapter ‘that selected medicines, such as fludrocortisone, were deleted from the Model List because, on reflection, the Committee considered the diseases for which they are needed are too rare for these items to meet the selection criterion satisfy the priority health care needs of the population’. Moreover ‘The Committee fully recognized the essential and even life-saving nature of certain medicines for patients with rare but treatable diseases. While the treatment of such diseases, on reflection, falls outside its remit, the Committee nevertheless urged that effective treatments for serious uncommon diseases be made available whenever possible. At the national level, special arrangements for specific individuals may need to be made in this regard.’

Case I: Haemophilia

Background and prevalence

Haemophilia is a group of inherited bleeding disorders. (1) The X-linked recessive types are known best: Haemophilia A (prevalence 1:10,000) and Haemophilia B (also known as Christmas disease; prevalence: 0.25 in 10,000 life born males). Haemophilias occur in mild, moderate, and severe forms (corresponding to various plasma coagulation factor levels). In Haemophilia A the patient has a coagulation factor VIII deficiency, in hemophilia B factor IX deficiency is the main problem. Both deficiencies lead to a disturbed blood clotting process, making the untreated disease debilitating and often resulting in death due to fatal haemorrhage. Internal bleedings into joints, muscles and soft tissue cause most problems, whereas external bleedings are less threatening. In the past, the treatment with factor VIII and IX was often risky because these were extracted from donor blood. In the 1970s and 1980s this has led to extensive contamination with hepatitis B, C and HIV.

Treatment

Factor VIII complex is an effective treatment in Haemophilia A, Factor IX concentrate for Haemophilia B. In the developed world, human factor VIII has been available since the early 1960s, when an easy and reliable method was developed to isolate the product (2). Nowadays, recombinant factor products are also available, eliminating the risk of viral contamination, but against increased costs. A serious complication of treatment with factor VIII or IX is the formation of antibodies, resulting in a loss of treatment effectiveness and increasing costs. It is estimated that between 5 – 25% of patients with classic Haemophilia A develop antibodies (3). In mild to moderate patients desmopressin can also be effective, with the added benefit that blood derived products can be avoided. However, often these patients also receive on-demand factor VIII.

Cost

The costs of treatment for Haemophilia are high. A Dutch evaluation has shown that in the year 2000 the costs of the recombinant clotting factors alone amounted to € 46,994 per patient on average (range 30,000-125,000 depending on disease severity; this refers to the recombinant factor VIII) (4). In the literature a number of cost-effectiveness/cost of treatment analyses can be found. Most focus on the difference between on-demand and prophylactic therapy. A British study in 2002 estimated the total lifetime cost at 966,078 GBP (1999/2000 values) and 406,539 GBP for primary prophylaxis of Haemophilia A and B respectively and 272,000 GBP for on demand treatment in both Haemophilia A and B (5).


Uptake of drugs for rare diseases in National Medicines lists

To study whether the uptake of drugs used for rare or special indications in National Essential Medicines Lists differed from other drugs on the WHO EML, we analysed the uptake in National Lists of medicines for rare diseases on the 11th Model List (1999). Thirteen non-randomly selected National Lists were provided by WHO for this analysis. The following medicines for rare diseases were included in the analysis:

Factor VIII concentrate

Available since 1966 and included in the EML since 1979; the main indication is for the treatment of Haemophilia A and Von Willebrand disease (see text Cases I and II). The prevalence of Haemophilia is estimated to be 1 in 10,000. The drug is not supplied by the International Dispensary Association and not listed in International Drug Price Indicator Guide.
Factor IX complex

Available since 1966; on EML since 1979; Factor IX complex consists of the vitamin K-dependent clotting factors, namely factor II, VII, IX and X. It is used in the treatment of Haemophilia, primarily Haemophilia B (see text Case I). The prevalence estimate for Haemophilia is 1 in 10,000 live male births. The drug is not supplied by the International Dispensary Association and is not listed in International Drug Price Indicator Guide.

Testosterone

Available since 1951; on EML since 1988; testosterone is an androgenic anabolic steroid. The main indication is testosterone replacement therapy in hypogonadal males. The exact prevalence is unknown, but a rough estimate of prevalence of testosterone use in The Netherlands (2003) shows that about 4.6 in 10,000 inhabitants use a testosterone preparation 29. The drug is not supplied by the International Dispensary Association and is not listed in International Drug Price Indicator Guide.

Desmopressine

Available since 1973; on EML since 1992, deleted in 2003; desmopressin, a derivative of the anti-diuretic hormone is a specific agonist for the V2-receptor. The main indications are Von Willebrand’s disease (prevalence ranges from 0.3-0.4 per 10,000 to 1,30 per 10,000), mild Haemophilia (prevalence 1 in 10,000 live male births) and central diabetes insipidus (prevalence 0.4 in 10,000) (see Case I, II and III). The drug is not supplied by the International Dispensary Association, but is listed in International Drug Price Indicator Guide.

Fludrocortisone

Available since 1954; on EML since 1979, deleted in 2003; fludrocortisone is a powerful corticosteroid of the mineralocorticoid group. Its main indication is in the treatment of Addison’s disease (adrenocortical insufficiency) as an addition to glucocorticoid therapy. Addison’s disease is considered a rare disease (prevalence in the United States: 0.1 in 10,000). The drug is not supplied by the International Dispensary Association and is not listed in International Drug Price Indicator Guide.

Case II: Von Willebrand disease

Background and prevalence

Von Willebrand disease (VWD) is considered to be one of the most prevalent inherited bleeding disorders. In patients with VWD there is a dysfunction of the Von Willebrand Factor (VWF) in the blood. Under normal conditions, the main role of VWF is in haemostasis, where it is a carrier protein for factor VIII. The factor is essential in the adhesion of platelets to vascular sub endothelial structures and platelet aggregation after vascular injury. Three ‘types’ of the disease can be discerned, either resulting in a reduction in the levels of Von Willebrand Factor (Type 1 & 3) or a malformation of VWF (type 2). In the most common variant, the autosomal dominant Type 1 (in 70% of cases), a quantitative deficiency in VWF is observed. Since VWD is a very heterogeneous disease and the level of symptoms may vary, estimating prevalence is difficult. In the literature the prevalence ranges from 0.3-0.4 per 10,000 to 1.3% of the population (1). Part of this variation may also be explained through ethnic differences. With respect to the developing world a large variety of prevalence figures is reported. However, whether this is a true difference in prevalence or due to complex diagnosis, is not known (2).

Treatment

The treatment in VWD depends on the severity of the disorder in an individual. In people with a more severe form of the disease, the goal of treatment is to raise the plasma levels of factor VIII and/or VWF, thereby decreasing the bleeding. The two main pathways to achieve this are by inducing the production of VWF or supplementing factor VIII/VWF through blood concentrates. In mild VWD Desmopressin, a derivative of the anti-diuretic hormone (ADH), is the treatment of choice. It is. Desmopressin induces the secretion of VWF. The main benefits are that desmopressin is cheaper than blood products (i.e. factor VIII concentrates), widely available and being safe with regards to the risk of contamination with blood-borne viruses (e.g. hepatitis B, C, HIV) (3). In more serious cases, in major surgery or in types of the disease where VWF is malformed, supplying factor VIII/VWF blood products is necessary. Factor VIII concentrate with Von Willebrand Factor is made from pooled human plasma. Recombinant factor VIII is not used for the treatment Von Willebrand disease due to the lack of VWF in this purified preparation.

Cost

Currently, little is known, about the cost of treatment for Von Willebrand disease. Due to the rarity of the disease, little or no cost-effectiveness studies have been published. As seen in other rare diseases, the treatment is relatively expensive. Cost of treatment will depend on disease severity (number of bleeds) and required treatment (desmopressin or Factor VIII/VWF). A recent British study estimated the cost for severe Von Willebrand to be about equal to Haemophilia A, about 272,008 GBP (1999/2000 values) for on-demand treatment with factor VIII, and about 966,078 GBP for primary prophylaxis (4).

(2) Srivastava A. Von Willebrand disease in the developing world 2005; 42:36-41.

We assessed the uptake of medicines by calculating for each drug the percentage of National Lists on which the drug was mentioned. We also calculated the time between the first inclusion of the drug on the Essential Medicines List and the reference year (2000). Figure 1 shows the results of the analysis. In general the medicines for rare diseases have been on the EML for a relatively long time when compared to all medicines on the complementary or core list. The uptake on national lists of medicines for rare diseases varies widely, ranging from 23.1 % for desmopressin to 69.2 % for testosterone. Medicines on the core list have a higher uptake on National Lists than medicines on the complementary list, indicating that the prioritisation used by the WHO also has an impact on the selections made in various countries. Also the possible symbolic value of a medicine on the core list may play an important role here.
To summarise, the percentage uptake of medicines on National Lists is a useful metric to evaluate perceived relevance of medicines in individual countries. For rare diseases the uptake varies very much, indicating that the perceived importance of medicines for rare diseases is also subject to significant national variation. Uptake of drugs for rare disease is in the same range as uptake of all other drugs, 51.8% for drugs on the core list, respectively 34.5% for drugs on the complementary list. Although few cases have been evaluated, being a medicine for a rare disease does not seem to be associated with low uptake on national lists.
Case III: Diabetes Insipidus

Background and prevalence
Diabetes Insipidus (DI) is a disease in which there is an abnormal outflow of urine (polyuria) and an increased fluid uptake (polydipsia). There are four different types of DI, of which the 'central' form is the most prevalent, but still rare. An estimated prevalence of DI is 0.4 in 10,000 (1).

The hormone vasopressin plays a central role in DI. In healthy humans, the water balance is regulated by three mechanisms: thirst, kidney function and vasopressin secretion. The release of vasopressin (from the pituitary) is regulated by changes in plasma osmolality. Increased release of vasopressin causes an increase of osmolality of urine in the kidneys. This results in less urine secretion and decreasing osmolality of the blood. In patients with DI, there is dysfunction of vasopressin. In the central form of DI, there is a deficiency of the secretion of vasopressin; in nephrogenic DI there is renal resistance to vasopressin (2).

Treatment
Here we focus on the central form of diabetes insipidus, which is the most prevalent form and also offers good opportunities for pharmacological treatment. In central DI, there is a deficiency in vasopressin, which results in a deficient regulation of plasma osmolality. Since there are no treatments available which can cure DI, therapy focuses on supplementing the function of vasopressin.

Synthetic vasopressin analogues are the treatment of choice in central DI. The most important member of this group is desmopressin. Its effect in diuresis is stronger and longer acting in comparison with vasopressin, resulting in a strong and relatively long-lasting effect. It can be administrated in different ways, but it has been shown that the oral way of administration is less effective than the nasal way of administration (2), (3), (4). Although the efficacy of desmopressin in central DI has been proven in several studies (3), (4), it is important to note that only small numbers of patients were included. This is also a reason for the lack of effectiveness studies: the rarity of the disorder makes it difficult to find enough study subjects for a long-term follow-up.

Cost
As far as we know, no studies are published about the costs of therapy with desmopressin. Nowadays, DI cannot be cured yet, which implicates that patients with DI have to use desmopressin for the rest of their life. Based on Dutch insurance data we estimate the costs a daily intake of 20-40µg of about 700 Euro per treatment-year.

Chapter 5

GENERAL DISCUSSION AND RECOMMENDATIONS

We started this paper with the notion that there are 'common grounds' between the EML and the OD field. The primary focus in the rare disease arena is the individual patient, irrespective of the demands of society at large. This contrasts with the more 'utilitarian' public health approach of the EML. From its inception in 1977 the EML has focused on essential health needs of the population at large. In the first model list essential medicines were those 'of utmost importance, basic indispensable and necessary for the health and needs of the population'. In recent years this has been called the 'priority health care needs of the population'. Moreover, the two systems differ, as said before, on the drug/disease orientation.

In Figure 2 these two dimensions are captured in a graphical display. The figure shows the different domains inhabited by the discussions about rare diseases and Essential Medicines. The domain of the Essential Medicines discussion is increasingly dominated by public health concerns (i.e. priority diseases) and proven effectiveness of medicines through the methods of 'evidence based medicine'. The most recent revisions of the definitions and the discussion in the Committee show an increased move towards the upper-right of this quadrant.

Figure 2 Two dimensions of bringing important drug to patients
In recent years no additions have been made to the EML for the treatment of rare diseases; on the contrary, medicines used for these conditions have been deleted or are currently under review. This declining role for rare diseases in EML context is further illustrated by the Haemophilia case. One of the main lines of argument of the World Federation of Haemophilia (WFH) against deletion was arguing why Haemophilia is not a rare disease. Going beyond the ‘numbers issue’, we want to underline that Haemophilia remains a public health issue on a global scale.

**Case IV: Primary immunodeficiency diseases**

**Background and prevalence**

Primary immunodeficiency diseases (PID) are a heterogeneous group of inherited disorders in which the body’s immune system is not working properly. PIDs are characterised by an increased susceptibility to infections and autoimmune diseases (1), (2). As with other (groups of) rare diseases, estimating the prevalence of the group of PID is difficult because of clustering of different conditions under the heading of PID. A study in Australia showed that the prevalence ranges between 0.12 to 0.46 per 10,000 (3). A Norwegian study estimated the prevalence of PID at 0.68 per 10,000 (1). In both studies large regional variability was observed. Some PIDs are very rare, while others are more prevalent (4). WHO currently recognizes various PIDs, including X-linked agammaglobulinemia (Bruton’s Disease), Common Variable Immune Deficiency (Hypogammaglobulinemia), Selective IgA Deficiency, Severe Combined Immune Deficiency (coined as ‘boy-in-the-bubble’ disease).

**Treatment**

The wide variety of primary immunodeficiency disorders results in a proportional variety in the treatments. Due to the defects in the immune system, infections occur frequently in patients with PID. These are treated with antibiotics. In PID disorders therapies may include bone marrow transplantation and enzyme replacement therapy. Immunoglobulin replacement therapy is also applied in the treatment of various PIDs. Immunoglobulins (or antibodies) in identifying antigens and activating the immune system. The use of immunoglobulins reduces the risk of infections. Immunoglobulins as medicine can be produced in two ways: acquired from human blood donors (human immunoglobulins), and immunoglobulins produced with biotechnology. The biotech immunoglobulins are very expensive, but the risk of contamination with viruses (e.g. hepatitis B, C, HIV) is low in comparison with the risk in products from human donors (5).

**Cost**

It is difficult to give an estimate of the costs per years of therapy with immunoglobulins. The costs of treatment largely depend on the differences of indication, the differences in use of immunoglobulins and the differences between individuals. A Swedish group has studied the yearly costs of immunoglobulin replacement therapy. The study showed a large difference between the different routes of administration: subcutaneous therapy is about four times cheaper than intravenous therapy ($3,100 versus $13,200) (6).

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Generally speaking, rare diseases pose an important public health problem to policy makers in bringing efficacious, safe and affordable medicines to patients suffering from such a disease in terms of equal rights to good medical treatment as everyone else. This principle can be found in for instance in the preamble of the EC Orphan Drug Regulation 141/2000 where it is stated that patients with rare diseases: ‘deserve the same quality, safety and efficacy in medicinal products as other patients’. The activities in this domain set out to stimulate research for new medicines, driven by the disease and the needs of the individual patient. The same philosophy can be found in other systems to stimulate rare disease research all over the world. Furthermore, as our analysis on national lists in Chapter 4 shows, there are no systematic differences between the uptake of medicines for rare diseases and other drugs on the EML.

Priority setting on medicines for rare diseases from a public health point of view requires a thoughtful weighing between [1] the prevalence of the disease, [2] the effectiveness (and safety) of available drugs and [3] related costs. When the prevalence is not too low, available products are effective and the costs are moderate, there is probably not a big problem. However, when the disease is very rare, the costs are relatively high and a full picture of the effectiveness/safety balance is not yet settled yet, selecting such a drug for inclusion on the EML is difficult to justify.

Although the driver of such a weighing process should be available scientific evidence, it is important to notice that in the case of medicines for rare diseases it is not always possible to meet state of the art standards of evidence based medicine, particularly when a OD product is newly developed and limited data are available on effectiveness, safety, tolerance, etc. Moreover, the method is not free of subjective influences. Against this background we propose in the next section a set of criteria for selecting drugs for rare diseases for inclusion on the EML.

**Recommended selection criteria for selecting drugs for rare diseases**

For inclusion on the EML we propose the following, primarily ‘drug driven’, criteria:

1. **Prevalence:** medicine used to treat a rare disease EU/US criteria < 5-7.5 cases per 10,000 persons and life-threatening or chronically debilitating
2. **No alternatives on EML:** there are no medicines on the list that are an effective alternative treatments
3. **Diagnosis:** the diagnosis of this disease is technically possible in most countries
4. **Expertise infrastructure:** the special knowledge/training infrastructure to diagnose and to treat the disease are available in most countries
5. **Effectiveness:** the treatment is effective
6. **Safety:** the treatment has a positive safety profile
7. **Availability:** a sustained supply of the product is feasible

Assessment of these criteria could lead to the establishment a second complementary list, i.e. a special list for ODs. When a medicine does not fulfil the first criterion it should be evaluated according to the standing criteria for inclusion on the EML. When the prevalence of the disease is low enough to qualify as a rare disease, the following criteria (2-7) should be evaluated and weighed. If two or more of the 2-7 criteria can’t be met, the drug would operationally not be suitable to be included on the EML.

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Using the criteria introduced above, we evaluated Factor VIII concentrate as an example. The product is evaluated using each of the seven criteria.

1) In the US about 18,000 people have Haemophilia. Bringing the prevalence to about 1 per 10,000 inhabitants. Prevalence in emerging countries may be different, but is within the ‘rare diseases’ range of table 1.
2) Although often laboratory infrastructure is lacking, good progress in diagnosis has been made; this is still a problem in many emerging nations.
3) Programs have been in place for some years to increase knowledge about the diagnosis and treatment of Haemophilia.
4) Inclusion of blood products on the EML has been an important factor to facilitate and stimulate local infrastructure/training on blood transfusion, etc.
5) Supplementation of Factor VIII concentrate directly intervenes in the pathological pathway of the disease. The treatment is generally regarded to be highly effective in Haemophilia A.
6) When a safe supply of blood products can be guaranteed Factor VIII is a relatively safe product taken into account seriousness of the indication.
7) Programs like ‘Operation Access’ have improved the supply of this product in many countries.

In general, although there are still problems in terms of diagnosis and access, important progress is being made. Because many programmes are currently in place to improve awareness and access, in our opinion Factor VIII would fulfil all the criteria set above. Based on these considerations we would propose to add/keep Factor VIII for Haemophilia on the EML. Using the same criteria we also evaluated fludrocortisone, deleted from the list in 2003:

1) Fludrocortisone is used for the treatment of Addison’s disease, or primary adrenal insufficiency and for adrenogenital syndrome. The prevalence of Addison’s disease is about 0,1 in 10,000 and 0,6 in 10,000 for adrenogenital syndrome. This prevalence qualifies for a rare disease.
2) Although fludrocortisone is an effective mineralocorticoid treatment for both diseases, other glucorticoids that are already on the EML, such as hydrocortisone can also be used to treat the disorder.

In this way fludrocortisone does not meet criterion two, and could therefore be considered to be a candidate for rejection from the EML, which happened in 2003.

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By using the criteria in this way they can act as a ‘sieve’ to screen whether candidate drugs are eligible for inclusion. In Table 3 this process is displayed.

### Table 3  Factor VIII and fludrocortisone vs. selection criteria

<table>
<thead>
<tr>
<th>Factor VIII</th>
<th>Fludrocortisone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td></td>
</tr>
<tr>
<td>No alternatives on list</td>
<td>Yes</td>
</tr>
<tr>
<td>Diagnosis possible</td>
<td>Yes</td>
</tr>
<tr>
<td>Expertise infrastructure</td>
<td>No</td>
</tr>
<tr>
<td>Effectiveness</td>
<td>No</td>
</tr>
<tr>
<td>Safety</td>
<td>No</td>
</tr>
<tr>
<td>Sustained supply feasible</td>
<td>Yes</td>
</tr>
<tr>
<td>Include on list?</td>
<td>YES</td>
</tr>
</tbody>
</table>

### Discussion and recommendations

A pivotal question to be raised is what the impact of increasing evidence-based public health orientation of the EML, as described in previous chapters, is on the three main roles we identified for the EML i.e. operational, educational and symbolic (Figure 3). For the 'educational' role we expect little change. However, the 'operational' role of the EML (i.e. identifying the most important drugs for priority diseases that must be permanently available) will become much more significant. This could imply that the 'symbolic' role would shrink resulting in a loss of innovative opportunities for WHO in playing productive role in the OD arena.

For sure, according to the current EML concept that there is little to no room for inclusion of drugs for rare diseases. They are (by definition) not of interest for the majority of the population, and often little evidence is available at the time of regulatory approval about effectiveness and safety under real world conditions. The question of whether to include these medicines will virtually always be a 'symbolic' one. We want to argue against this shift towards an imbalance of the 'symbolic' functions of the EML.

### Figure 3  Increasing public health orientation of the WHO EML

symbolic

operational

educational

Increasing public health orientation
Thus, we recommend that WHO should welcome drugs for rare diseases in its policy hemisphere as more ODs will become available in the next decades and more member states worldwide will have to face tough questions as to how to address the need for treatment by patients with a rare disease. One possible avenue to approach this is to weigh up the ‘symbolic’ function of drugs for rare diseases. The seven selection criteria we introduced above could be of aid in this process. A good example of such a symbolic role is the treatment of the Haemophilia. It could be argued that one of the consequences of being listed on the EML has also been an increase in national investments in local safe blood transfusion infrastructure, education and training, etc. Items that have been of continuous concern of both the WHO and the World Federation of Haemophilia (WFH) ever since the inception of their collaboration in 1969. In a recent letter to the Expert Committee opposing the deletion of coagulation factor concentrates one of the arguments stated is that the Haemophilia programs that bring expertise from various sectors together can ‘spill over’ and act as an example for the treatment of other genetic diseases. When the drugs for rare diseases are deleted from the EML, their symbolic importance may be lost and WHO will have no more ‘natural link’ to the OD arena. This would imply a loss for all parties involved. This requires thoughtful weighing of interests and policy priorities.

A solution would be to rephrase the definition of the complementary list to include rare diseases. This would require a change of selection criteria and procedures. It is questionable whether this is the desirable route to take when the amount of progress in defining criteria for access to the EML are taken into account. For certain, the current EML with its updated definitions is not the best vessel to further the cause of patient’s access to medicines for rare diseases. However, the establishment of an easily retrievable international, and widely respected, expert opinion on the effective therapies for rare diseases that provides guidance for national programs that strive to improve access for patients, would be a large asset for both policy makers and patients, just as the EML has been for the past 25 years.

Until now, ODs have not been at the priority agenda of WHO for understandable reasons (‘first things first’) but that could change, and preferably should change in the advent of more ODs coming to the market, increasing attention for ‘rare’ diseases in countries like India, Egypt and others and the increasing spin-off of OD innovations with implications for drug treatment in general (e.g. imatinib mesylate as an example).

Rare diseases are going to increase in importance as diagnostics improve and new treatments are being developed. Member states of WHO will be seeking advice from WHO as to how to deal with this new reality. WHO needs to address this challenge. The establishment of a new special WHO Expert Committee on Medicines for Rare Diseases with a special focus to be a bridge between public health needs and the requirements of individual patients with a rare disease, could be a possible scenario. This committee could also catch-up with the increasing importance of genomic and

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proteomic diagnostics to classify patients in responders and non-responders. This trend will change the quantification of disease occurrences dramatically, with significant consequences for addressing the question: how rare is rare?

Conclusion
Rare diseases are going to increase in importance as diagnostics improve and new treatments are being developed. Member states of WHO will be seeking advice from WHO as to how to deal with this new reality. WHO needs to address this challenge either through the existing essential Medicines Expert Committee or through the establishment of a new Expert Committee.

We have proposed criteria which could be used by the present Expert Committee on the Selection and Use of Essential Medicines to guide which medicines for rare diseases could be retained or included in the existing or revised model list of Essential Medicines.