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# Rare Diseases and Essential Medicines
## A Global Perspective

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**Abstract**

This article addresses the question 'to what extent medicines for rare diseases can be considered as essential'. Essential medicines are those that satisfy the priority healthcare needs of the population; they should be available at all times to all who need them. Rare diseases can be orphan diseases, which are universally rare, or neglected diseases, which are rare in industrialised countries but common in certain low- and middle-income countries. In both cases there is no profitable market for drug development.

In low- and middle-income countries, medicines for neglected diseases can be classified as essential if the disease is common and the treatment is cost effective. If the treatment is costly, efforts should be made to reduce the price and ration its use. Medicines for orphan diseases do not address the priority healthcare needs of the population and should therefore not be listed as essential. Yet they could be supplied through special centres, provided the treatment is no less cost effective than treatments for common diseases which are not universally available. Orphan drugs that are less cost effective can only be supplied through the private sector or special programmes. In richer countries the same approach could be applied, but with a higher cut-off level of relative cost effectiveness.

For the World Health Organization (WHO) Model List of Essential Medicines, a disease should be 'non-rare' somewhere in the world for a safe and effective treatment to be included. For true orphan diseases, which do not constitute a global public health priority, there is no justification for the WHO to list the treatment as essential.

'Essential medicines' are those that satisfy the priority healthcare needs of the population; they should be available at all times to all who need them. This is the core of the concept of essential medicines as it has been promoted by the World Health Organization (WHO) since the first Model List of Essential Medicines was published in 1977.[1] But how does this apply to rare diseases? Is fludrocortisone for Addison's disease an essential medicine? And factors VIII and IX for the treatment of patients with haemophilia? This article addresses the question 'to what extent medicines for rare diseases can be considered as essential'.

### 1. Orphan Diseases

Rare diseases can be orphan or neglected diseases. The definition differs slightly between Europe and the US. In Europe a disease is classified as an 'orphan' disease when the prevalence is less than 5 per 10 000 population, while in the US it is less than approximately 6 per 10 000.[2]

Currently there are about 5000–8000 orphan diseases, of which approximately 80% are of genetic origin. About 1300 of these are life-threatening or severely debilitating. Some are well known, such as cystic fibrosis and haemophilia. Within the European Union about 30 million people (6–8% of the population) have an orphan disease. For about 60% of orphan diseases some form of symptomatic treatment is possible. However, many are never recognised and treated. Orphan diseases are basically too rare to create a profitable market for medicine development and, as a consequence, those medicines that are available are usually very expensive. Orphan diseases need orphan drugs; many industrialised countries have special mechanisms in place to promote the development of orphan drugs.

Orphan diseases are universally rare; however, some tend to affect specific regions or ethnic groups, such as thalassaemia and glucose-6-phosphate dehydrogenase (G6PD) deficiency. Tuberculosis, malaria and HIV/AIDS are rare in Europe but very

common elsewhere. Some of these diseases are migrating, for example, tuberculosis, sickle cell anaemia and, possibly, severe acute respiratory syndrome (SARS); they may have been rare in the industrialised world but are becoming more frequent now.

## 2. Neglected Diseases

From a global point of view there are more rare diseases than those we commonly call orphan diseases; these are often called 'neglected' diseases. Neglected diseases are rare in developed countries but common in certain regions or most of the developing world. For these diseases there is also no profitable market for medicine development, but the reason is different: there are many patients, but most are too poor to pay. Yet, new treatments are badly needed. Examples of neglected diseases for which there are no, or very few, effective treatments include malaria, tuberculosis, paediatric HIV/AIDS, sleeping sickness, Leishmaniasis, Chagas disease and Buruli ulcer.

## 3. The Concept of Essential Medicines

Essential medicines are those that satisfy the priority healthcare needs of the population. They are selected on the basis of current and future disease prevalence, evidence on efficacy and safety, and comparative cost effectiveness within the therapeutic class. Essential medicines are intended to be available at all times, in adequate amounts, in the appropriate dosage forms, with assured quality, and at a price which the individual and community can afford. The concept of essential medicines is intended to be flexible and adaptable; however, the decision on which medicines are regarded as essential remains a national responsibility.[3]

The selection of essential drugs is a two-step process.

1. **Regulatory:** market approval of a pharmaceutical product is usually granted on the basis of efficacy, safety and quality, and, rarely, on the basis of a comparison with other products already on the market (or of cost). The regulatory decision defines the availability of a drug in the market.
2. **Supply or reimbursements:** most public drug procurement and insurance schemes have mechanisms to limit procurement or reimbursements of drug costs. To make these decisions an evaluation process is necessary, based on a comparison between various drug products and considerations of value for money.

This second step leads to a list of essential drugs. The WHO List of Essential Medicines[1] serves as a model for this second step, and is intended to support the development of national or institutional lists of essential medicines.

A national list of essential drugs is best developed for different levels of care, on the basis of clinical guidelines for common diseases and conditions that can and should be diagnosed and treated at that level. Consideration of both expert opinions and evidence of effectiveness and cost effectiveness should lead to the development of clinical guidelines. Both these guidelines and the essential drugs lists for the different levels of care must be updated regularly, preferably every 2 years.

The clinical guidelines then lead to a national list of essential medicines, which should be the basis for supply, reimbursement, training and all other interventions to promote access. More than 150 countries have a national list of essential medicines; two-thirds of these lists have been updated within the last 5 years. Some developed countries, such as Australia, have national reimbursement lists which can be considered as national essential medicines lists. The concept of essential medicines is truly global.[4]

## 4. Can There Be Essential Medicines for Rare Diseases?

This is a question that both national reimbursement authorities and the WHO have been struggling with for some time. Recently, the WHO received the following question from a government official from one large Member State: "I work in the Essential Medicine Department of the Medicine Evaluation Center. During the process of revising the National Essential Medicine List (NEML) this year, we have a technical question to ask you. There is one medicine which is named an orphan drug, it's effective but it's also at a price most of our people can't afford. We want to know whether such a drug can be included in the NEML. We are looking forward to your reply."

In 2003, the WHO Expert Committee on the Selection and Use of Essential Medicines deleted fludrocortisone from the 13th Model List of Essential Medicines because it was only used in Addison's disease which is universally very rare (about 1 per 10 000 population, well below the rare diseases limit). But how realistic is the limit and how consistently is it used for the model list? For example, a large number of antidotes are still listed as essential, while some of these intoxications are very rare indeed. Factor VIII and factor IX for patients with haemophilia were marked for review and possible deletion at the next Expert Committee meeting in 2005 because "the public health relevance and/or safety have been questioned". The treatment is effective but costs $US40 000–$US150 000 per patient/year in industrialised countries. Can these be called essential medicines? The announcement of possible deletion led to a global protest,

with a large number of patient organisations officially requesting the WHO retain them on the list.

Can there ever be an essential medicine for a rare disease (orphan or neglected)? A closer look at the definition of essential medicines may help. Essential medicines are those that *satisfy the priority healthcare needs of the population*. Priority conditions are selected on the basis of *current and estimated future public health relevance*, and on the *potential for safe and cost-effective treatment*. A national list of essential medicines is intended to guide professional training and medicine supply in the public sector, and medicine reimbursement in public and private health insurance schemes. This means that the following questions should be asked: 'How effective is the treatment?' and 'What is the national prevalence of the disease?'. For example, in countries where thalassaemia and sleeping sickness are frequent, the diseases are a public health priority and their treatment may become essential if the drug therapies are relatively cost effective.

With regard to cost effectiveness, in developing countries vaccinations, free condoms for prostitutes and safe blood transfusion services cost less than $US5 per disability-adjusted life-year (DALY) saved.[5] With good differential pricing arrangements in place, antiretroviral treatment in developing countries may cost $US300–$US600 per DALY saved. The cheapest treatment with factor VIII and factor IX for haemophilia in developing countries will cost several thousand dollars per person per year. All of these demands for treatment are faced by countries with medicine budgets that are often less than $US10 per person/year; more than 30 countries have less than $US2 per person/year to spend on healthcare.

It is also important to note that not all cost-effective treatments are necessarily affordable. For example, many developing countries cannot afford the antiretroviral treatment of patients with HIV/AIDS (which is considered very cost effective in developed countries) in view of the large number of patients and the many other pressing healthcare needs. Governments can only spend their money once, and this confronts them with the question of "whom do they choose to ignore".

## 5. Essential Medicines for Neglected Diseases

Medicines for neglected diseases can sometimes be classified as essential. In low- and middle-income countries, if the disease is common and the treatment is cost effective (e.g. below $US300 per DALY saved), the necessary medicines can be classified as essential; examples are medicines for sleeping sickness and HIV/AIDS. If the treatment is relatively cost effective but also costly, the medicine should be listed as essential and efforts made to make the treatment affordable by reducing the price, rationing its use to priority patients and targeted fundraising initiatives; examples would be the new medicines for patients with malaria and paediatric HIV/AIDS.

## 6. Essential Medicines for Orphan Diseases

For orphan diseases, which are rare everywhere, the case is more complex. In general, in low- and middle-income countries the medicines should never be listed as essential because an orphan disease can never be a public health priority. However, if the treatment is relatively cost effective (e.g. below $US300 per DALY saved) the medicines can still be supplied through special centres. When the treatment is less cost effective than treatments for common diseases that are not yet available to all who need them, the medicine should not be supplied or reimbursed through the public sector. Examples are medicines for patients with haemophilia in the poor resource settings; in this case the more cost-effective treatment of other lethal diseases, such as HIV/AIDS, has preference. Factor VIII and factor IX can still be registered in that country and be supplied through private channels, but will only be available to patients who are able to pay.

In richer countries the same approach could be applied, but with a higher cut-off level of relative cost effectiveness (e.g. $US25 000 per DALY saved), below which public supply or reimbursement are provided. Above this threshold of cost effectiveness, special support funds or specific political decisions may be needed to meet the needs of individual patients – if the country can afford it.

## 7. The World Health Organization Model List of Essential Medicines

For the WHO Model List of Essential Medicines a disease should be 'non-rare' somewhere in the world for a safe and effective treatment to be listed. For example, for neglected diseases such as paediatric HIV/AIDS and sleeping sickness, the WHO should identify and list the most cost-effective treatment within the therapeutic class, together with evidence on safety and efficacy. These treatments would preferably cost less than $US300 per DALY, and if they cost more efforts should be made to reduce their price.

For true orphan diseases, which do not constitute a global public health priority, there is no justification for the WHO to list the treatment as essential. However, in those cases the WHO may still supply information on diagnosis and potential treatment which can guide national decisions on treatment and reimbursement.

## 8. Access to Essential Medicines as a Human Right?

An interesting aspect of this discussion is whether the human right to health can be restricted by a national list of essential medicines. The principle of incremental fulfilment of the right to health acknowledges that the right to healthcare cannot be realised immediately everywhere, and is restricted by national resources. Yet State parties to the various international human rights treaties are under an immediate obligation to continue to improve access to healthcare, and to ensure that available services are equitably accessible by all those who need them. This could support the case that if a State can afford it, expensive treatments for rare diseases should also be made available to those who need them. However, the right balance should always be found between the human right of the individual and the public health rights of the population as a whole.

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