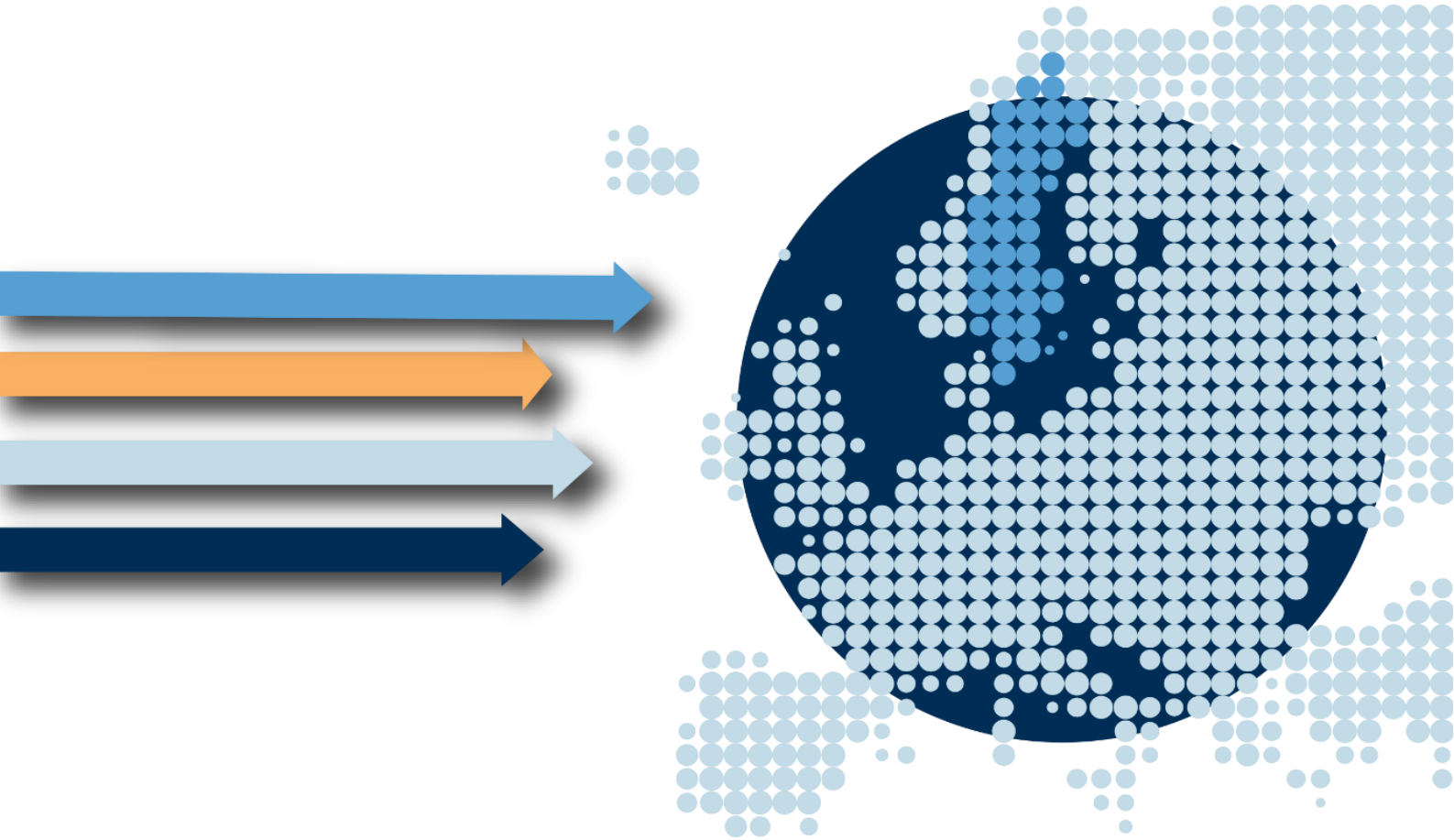
A new model for the evaluation, introduction and reimbursement of new therapies against rare diagnoses



Ulf Persson

IHE Report
2023:5b

A NEW MODEL FOR THE EVALUATION, INTRODUCTION AND REIMBURSEMENT OF NEW THERAPIES AGAINST RARE DIAGNOSES

Ulf Persson

IHE - The Swedish Institute for Health Economics, Lund, Sweden

Please cite this report as:
Persson U. A new model for the evaluation, introduction and reimbursement of new therapies against rare diagnoses. IHE Report 2023:5b. IHE: Lund, Sweden.

The study was conducted with financial support from the Commission for Innovative Orphan Drugs and which did not has had any role in the design, implementation or approval of the report. The author is responsible for the design, analysis and conclusions of the study.

IHE REPORT 2023:5b
e-ISSN: 1651-8187
ISSN: 1651-7628

The report can be downloaded from IHE's website.

Preface

Today, there is concern that the industry will not be stimulated to develop innovative orphan drugs and, above all, that the uptake of orphan drugs will not be optimal. The government's assignment to TLV confirms that there is an increased awareness that the valuation of orphan drugs is no longer optimal and that it may not be enough to just look at QALYs and cost savings.

What is the value of having access to treatment if you become ill? What is the value of hope? This discussion has been initiated by ISPOR (International Society for Pharmaeconomics and Outcomes Research) and is called the Value Flower. There is also an international discussion advocating that the valuation of health-related benefits for different degrees of difficulty be revised so that it is compatible with economic theory.

This discussion is called GRACE "Generalized Risk-Adjusted Cost-Effectiveness". The implications of such revisions in the evaluation of health-related quality of life benefit and survival are that those conditions that are considered severe and very difficult are valued.

This report summarizes the international discussion on these new and revised value attributes to investigate how they can be estimated, how much value they generate and discuss the policy implications and importance for future health economic analyses.

The study was conducted with financial support from the Commission for Innovative Orphan Drugs. The Commission for Innovative Orphan Drugs is an initiative consisting of nine research-intensive pharmaceutical companies with the aim of highlighting proposals that can help improve the Swedish care model for people with rare diseases. The Commission consists of the following pharmaceutical companies: Alexion, Alnylam, Amicus, BioMarin, Chiesi, Janssen, Roche, Sanofi Genzyme and Vertex.

The Commission for Innovative Orphan Medicinal Products has had no role in the design, implementation or approval of the report. The author is responsible for the design, analysis and conclusions of the study.

Lund, September 2023

Peter Lindgren
Managing Director, IHE

Summary

The pharmaceutical market is undergoing major changes and is moving towards more orphan drugs, gene and cell therapies, ATMP (Advanced Therapy Medicinal Products) and precision medicine. This leads to new challenges for established methods of valuation and financing of medicines. Internationally, there is an increased awareness that for the evaluation it is no longer enough to just look at QALYs and cost savings.

ISPOR (International Society for Pharmaeconomics and Outcomes Research) has highlighted two central concepts "The Value Flower" and GRACE ("Generalized Risk-Adjusted Cost-Effectiveness"). Both aim for the valuation to be compatible with individuals' preferences.

In Sweden, during 2023, TLV must report on two government assignments:

(1) TLV must analyze and propose how patients' access to medicines for the treatment of rare diseases can be strengthened (September 29, 2023).

(2) TLV must develop methods for health economic evaluations of precision medicine and payment models for ATMP (September 15, 2023)

The purpose of this report is to discuss new methods and ways to modify the current calculation and valuation bases for orphan drugs in Sweden to better reflect the willingness of policyholders, taxpayers and potential patients to pay for new innovative orphan drugs.

In the EU, a diagnosis is considered unusual if it occurs in no more than 5/10,000 individuals, but in Sweden it is considered unusual if it occurs in fewer than 1/10,000. The EU regulation on "orphan drugs" was adopted by the European Commission on April 27, 2000 (Commission Regulation (EC) No 847/2000). Although rare diseases only occur in small populations, it is estimated that 10% of the US population is affected by rare diseases. This corresponds to approximately 30 million individuals in the United States. In total, it is estimated that there are 350 million people in the world who suffer from 700 rare diseases and 80% of these are estimated to be genetic.

At the end of 2022, there were a total of 140 orphan drugs on sale in Sweden, according to TLV (2023). This is twice as many as at the end of 2012. During this ten-year period, the sales value of orphan drugs increased more than four times to reach around SEK 5.5 billion in 2022. Pharmaceutical costs in Sweden total 53.7 billion in 2021 according to LIF (2023). The specialty drugs then account for approximately 10% of the total drug costs.

Despite the large number of new orphan drugs in recent years, there are largely no estimates of the costs of developing new orphan drugs. However, some studies suggest that R&D costs for new innovative orphan drugs may be only half as large as for non-orphan drugs. Although the costs of developing an orphan drug are lower than an average conventional drug, it is still a significant amount. The costs of developing a new innovative drug have been estimated at approximately 2.6 billion US dollars, which corresponds to approximately 26 billion SEK. To compare with something, the construction of the Öresund Bridge cost SEK 20 billion in 2000. Perhaps the cost of a new orphan drug is in the same order of magnitude as the cost of building a slightly smaller Öresund Bridge.

Perhaps the explanation for the moderate interest in the size of the R&D costs can be found in the fact that, after all, the prices are not to be explained in the costs. Cost pricing or cost-plus pricing can, firstly, lead to wrong incentives in that high research and development costs would justify a higher price. Investments in medicines that do not progress to the final phase must be covered, It would lead to a perverse situation if companies with many such errors could justify a higher price. Cost pricing does not stimulate the development of new innovations that benefit patients. It does not reward value. That's why we have value-based pricing.

Value-based pricing means that we have to understand the value of the new therapy and today it is above all reduced costs and increased QALYs that are expected to capture the value. Shortcomings in the QALY measure as a reflection of patient benefit have been discussed for a long time. Already at the formation of TLV (the predecessor of LFN) in 2002, flaws in the QALY measure as a reflection of the value of health loss were noticed. This is not a new discussion, but it has increased and now may be the time to revise and improve valuation methods.

Several aspects are missing in the QALY measure. Firstly, there is a lack of risk assessment. It is assumed that individuals are risk neutral and do not care about the value of treatment until they are in need of it. Second, severity is missing, it is assumed that individuals have the same preference for an improvement from, say, 0.2 to 0.3 as from 0.8 to 0.9 on a scale between 0 and 1 for health. Thirdly, the value of cure or hope is missing, it is assumed that individuals do not give any value to being able to cure a disease. Fourthly, there is a lack of process-related benefit, such as the benefit of less demanding treatment. The criticism is about the valuation not including or based on individuals' preferences.

My suggestions for how valuation methods can be improved can be divided into three groups:

1. The assessment of health benefit for different severity levels should be revised for all evaluated therapies to be consistent with economic theory and to be based on individual preferences. This is closely related to the valuation of diminishing marginal utility of health-related extended survival.

Both of these consequences are included in what is discussed in international literature under GRACE ("Generalized Risk-Adjusted Cost-Effectiveness"). The implications of this revision of the assessment of the health-related quality of life benefit and survival are that the conditions considered severe and very severe are valued up. At the same time, treatment of such conditions that individuals regard as mild will be devalued.

2. The valuation of new therapies, especially orphan drugs, should be revised by including additional value attributes beyond cost savings and life expectancy and quality of life gained. Here it is about health-related quality of life having more benefits than those covered by the five dimensions in EQ-5D. The international discussion about the "Value Flower" and which attributes should be assigned value without double counting must also include Sweden and our Swedish HTA organizations.
3. The HTA evaluation of orphan drugs should take place in several stages with the aim of not delaying the process of evaluation. It is the same ideas that have made it through in the regulatory process, where the assessment of safety and effectiveness also takes place in several steps. One possible route is to apply forms of orderly introduction with conditional payment. Payment is made when various milestones have been achieved, i.e. some form of outcome-based compensation.

The report presents a brief overview of alternative financing models that may be interesting for orphan drugs. The overview is based on existing literature and experience in the field, but there are opportunities to also go "outside the box" and retrieve examples from other discussions where innovative payment models are discussed. One such example is antibiotics. So far, the consequences for total drug costs of introducing GRACE, of expanding the value attributes and of modifying the valuation so that it takes place in several steps are unknown. Work is underway to try to gain a better understanding of the consequences. Perhaps it makes more sense to discuss funding models more fully when the cost implications become better known.

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1. Background

The development of the pharmaceutical market is moving towards more orphan drugs, including more gene and cell therapies, precision medicine and the group of drug treatments that go by the name ATMP (Advanced Therapy Medicinal Products). It means new challenges for our established methods for valuation and financing of medicines, (Tunis et al 2021, Dabbous et al 2022). For many years, Sweden has relied on what is usually called value-based pricing (VBP) for medicines (Persson & Olofsson 2021). In short, this means that the drugs are valued based on the benefit that the treatment brings. Alternative pricing strategies such as cost pricing, - cost plus pricing - where the drugs are valued based on how much it cost to develop the drugs, give the wrong signals. Since even failed development projects have to be financed with revenue from successful projects, this would mean a perverse situation where companies responsible for many failures could be well paid for their few successful products. Cost-plus-pricing gives completely the wrong incentive and Sweden has long ago chosen VBP as the most suitable method for evaluating new medicines.

VBP has meant that new innovative medicines in Sweden and also in many other countries have been evaluated based on the health improvement and cost savings that the new therapies provide. The health improvement is of two kinds, improved survival and improved quality of life. Health economists have developed the measure called quality adjusted life years - Quality Adjusted Life Years (QALY) - which is a weighted measure of longevity and quality of life. Furthermore, the resource consumption valued with market prices for the new treatment has been compared with the current best treatment and if cost savings then occur, it has been considered as an additional value attribute in addition to the QALY gain.

The value attributes health gains and cost savings have long been the dominant "value drivers" for pharmaceuticals in large parts of the world. The industry that developed the drugs has gone to great lengths to set up clinical trials that have sought to demonstrate the health benefits and cost savings. The payers, the insurance companies and, as in Sweden, the state and the healthcare authorities, have had the help of the HTA organizations (Health Technology Assessment) organizations such as the TLV (Dental and Medical Benefits Agency) to help them assess the value of the new drugs. This has worked relatively satisfactorily for many years, but the question now is whether it is not time for a review of the methods for evaluating new medicines. Many believe that the methods must be further developed and improved to adapt to the changing pharmaceutical market, Lakdawalla et al (2021) and Lenahan & O´Rourke (2023).

The previous Swedish government took several steps in that direction. Among other things, TLV and the NT Council (the Regions' collaboration for new therapies) were tasked by the politicians to jointly

test outcome-based payment models with companies. The payment models would, among other things, be designed so that the size of the payment to the companies depends on how large the health gain and cost savings will be in actual clinical use. The purpose of innovative payment models is several. One purpose is to manage budget barriers that may arise, for example, when a new treatment is given as a one-off treatment or for a very short time. One-off treatment then means that payment would take place at one point in time, but the introduction is delayed if budget funds are not available for that point in time while the treatment is considered cost-effective. Innovative payment models could mean delayed payment and thus bridge the budget barrier. Another purpose of innovative payment models is to reduce the uncertainty of effect, since the effect of one-off treatments is spread over a much longer period of time than the payment. An innovative payment model can then lead to rapid introduction while making the payment conditional on a certain expected outcome actually occurring at a later time. A third purpose of innovative payment models is to deal with the fact that value often varies with the patient population being treated. There are well-known examples with cancer treatments where adjuvant treatment is more valuable than palliative treatment and where the value of the treatment varies with the "line" at which the treatment is started, Persson and Norlin (2018). If the price could be varied according to indication, so that it better reflects the value, then the introduction and spread of a new effective drug for all approved indications would happen much faster. Indication pricing is such pricing (Lindgren et al. 2022).

The NT Council and TLV have also introduced a new approach in their valuation of medicines where degree of severity combined with rarity gives acceptance for a higher price than would otherwise have been the case, TLV (2021) and Liljemark et al (2021).

According to TLV's practice, the limit for what a QALY may cost is approximately SEK 1 million. In 2016, TLV made a decision that the willingness to pay for rare diseases with a very high degree of severity can amount to SEK 2 million. New reports from TLV also open up the possibility that the valuation methods could be further developed, for example by weighing new therapies that reduce the burden on relatives as an additional value attribute.

During 2023, TLV must report on two government assignments. (1) The first means that TLV must analyze and propose how patients' access to medicines for the treatment of rare diseases can be strengthened. TLV's mission involves analyzing different courses of action that develop access to medicines for the treatment of rare diseases. The authority must also investigate and identify any areas where there is a need for legal amendments. The starting point must be based on analysis of patients' access to medicines for the treatment of rare diseases. The assignment must be reported to the government no later than September 29, 2023.

The second mission (2) means that TLV will develop methods for health economic evaluations of precision medicine and payment models for ATMP. TLV will continue work on developing methods for health economic evaluations of precision medicine and payment models for advanced therapy medicines (ATMP). The authority shall proceed from the proposals it submitted in the two previous assignments Health economic assessments of precision medicine and payment models for ATMP (S2020/04362 and S2021/04971). The assignment must be reported to the government no later than September 15, 2023.

At the same time, work is underway at the EU level to revise the current EU regulation on orphan medicinal products (Orphan Medicinal Products Regulation) in a stricter direction and where, for example, the NT Council through Swedish Associations of Local Authorities and Regions (SKR) wants to see the Swedish more restrictive approach also at the EU level: EU pharmaceutical legislation (europa.eu)
https://skr.se/skr/tjanster/rapporterochskrifter/publikationer/kunskapsunderlagpolicybrief.67378.html

The new assignments to TLV confirm that there is now an increased awareness that it is no longer enough to just look at QALYs and cost savings. Internationally, this is confirmed by the scientific publications and seminars that highlight the importance of better knowledge of individuals' preferences. For example, it is about how the individual's perspective and freedom of choice come into play when treatments are evaluated. What is the value of having access to treatment if you get sick? What is the value of hope? This discussion has been initiated by ISPOR (International Society for Pharmaeconomics and Outcomes Research) and is called the Value Flower, (Persson & Olofsson 2022). The idea is that ISPOR's Value Flower will help find the answer to many new questions. This international discussion is relatively absent in Sweden and there is an interest in bringing more knowledge about the international discussion to Sweden.

In summary, there are several factors today that lead to the industry not being stimulated to develop innovative orphan drugs and the uptake of orphan drugs not being optimal. There are problems with the valuation of orphan drugs, which are due to the uncertainty surrounding the clinical effect. There are also problems with the value attributes usually used for medicines not capturing the value of orphan medicines in a fair way, (Postma et al 2022).

In addition to valuation problems, there are pricing and financing problems that can contribute to delaying the uptake of orphan drugs. These problems are related to budget barriers, uncertainty about effects and rigid pricing models, (Lindgren et al 2022).

2. Purpose

The purpose of this report is to discuss new methods and ways to modify the current calculation and valuation bases for orphan drugs in Sweden to better reflect the willingness of policyholders, taxpayers and potential patients to pay for new innovative orphan drugs.

3. Disposition

The specialty drugs have been given special treatment by the regulatory authorities in order to guarantee market exclusivity and rapid approval. The purpose of the special treatment is to stimulate the development of new therapies for the treatment of the patient populations affected by rare diseases. In the introduction, I will explain why there is a special regulatory framework for orphan drugs. The costs of developing a new drug are significant and newly published studies of development costs will be briefly touched upon. Development costs must be covered to stimulate companies' future development of new products. This is followed by a brief description of the cost-effectiveness analyzes that are today generally accepted in many parts of the world and that aim to highlight the value of drugs and treatment. Next, I will try to explain why these methods of drug evaluation are flawed when applied to orphan drugs. Some of TLV's drug evaluations and the NT Council's published recommendations for orphan drugs are reported here . They intend to show examples of the general problems with the established valuation method. In one section, I try to reproduce the international discussion for the evaluation of orphan drugs. Based on the noted shortcomings in established valuation methods and the international discussion around orphan drugs, my own proposals for revisions of valuation methods follow.

4. Orphan drugs

Since 2000, there has been a special regulatory framework for orphan medicinal products in Europe, Regulation (EC) No. 141/2000 of the European Parliament and of the Council. The reasons for this are stated in the regulation:

"1. Some conditions are so rare that the cost of developing and bringing to market a drug intended to diagnose, prevent or treat the condition would not be covered by the expected sales of the product. The pharmaceutical industry is therefore unwilling to develop the drug under normal market conditions. These drugs are called orphan drugs.

2. Patients suffering from rare conditions should be entitled to the same quality of treatment as other patients. It is therefore necessary to promote the pharmaceutical industry's research, development and sales regarding appropriate medicines".

Classification criteria

"A drug must be classified as an orphan drug if its sponsor can demonstrate:

a) that the medicinal product is intended to diagnose, prevent or treat life-threatening or chronically disabling conditions and from which no more than five out of 10,000 people in the Community suffer at the time of application, or

that it is intended to diagnose, prevent or treat life-threatening, severely disabling or serious and chronic conditions within the Community and that, without incentive measures, it is unlikely that sales of the medicinal product within the Community would generate sufficient returns to justify the necessary investment;

and

b) that there is no satisfactory method approved in the Community to diagnose, prevent or treat the condition in question or, if such a method exists, that the medicinal product will be of great benefit to those suffering from that condition.

The experience in the USA and Japan shows that the strongest incentives to get the industry to invest in the development and sale of orphan drugs are if there is an opportunity to get exclusive rights on the market for a certain number of years, in order to be able to get back a part of the investment. In the interests of patients, the exclusive right granted to an orphan drug must not prevent a similar product that could be of great benefit to those suffering from the condition from being placed on the market.

Although rare diseases only occur in small populations, it is estimated that 10% of the US population is affected by rare diseases. This corresponds to approximately 30 million individuals in the United States. In total, it is estimated that there are 350 million people in the world who suffer from 700 rare diseases and 80% of these are estimated to be genetic. With so many individuals with rare diseases around the world, there is an important market for orphan drugs. The orphan drug market has been estimated at US$195 billion by the year 2022, (Gibney M, Pharmavoice February 21 2023). This market is growing rapidly and is expected to increase to US$435 billion by 2032.

5. The development of the orphan drug market in Sweden as well as benefit decisions and NT recommendation

At the end of 2022, there were a total of 140 orphan drugs on sale in Sweden, according to TLV (2023). This is twice as many as at the end of 2012. During this ten-year period, the sales value of orphan drugs increased more than four times to reach around SEK 5.5 billion in 2022. Pharmaceutical costs in Sweden total 53.7 billion in 2021 according to LIF (2023). In that case, the orphan drugs correspond to approximately 10% of the total drug costs.

In December 2022, there were 145 medicinal products with a marketing authorization classified as orphan medicinal products in the EU, TLV (2023). Of these, 53 (35%) had been evaluated by TLV after the benefit application. A further 41 (28%) were evaluated by TLV on behalf of the NT Council. In addition to these, 12 (8%) have sales without having been evaluated by TLV.

According to the TLV, the number of medicines that are classified as orphan medicines by the EU, have a marketing authorization but are not sold in Sweden, i.e. are not available on the Swedish market, amounts to 39 (27%)

Table 1. Positive benefit decision and recommended use of medicines for the period 1 January 2015 - 1 December 2022.

Decision by TLV / recommendation by the NT council	Not an orphan drug	Orphan drugs in total	Ultra orphan, orphan drugs for populations with 20 patients or less
Approved by TLV	About 80%	37/61 =61%	3/10 =30%
Recommended use of the NT Council	Not specified	22/42 =52%	7/13 =54%

Source: TLV (2023)

Table 1 shows that the probability that TLV gives positive approval to price and subsidy decreases with the population to which the application relates. For the NT Council's recommendation, we do not see any difference in the probability of recommended use between the population size for orphan drugs, according to TLV (2023).

Benefit decisions for orphan drugs with significant patient benefit (provides more than one QALY gained per patient) and are intended for conditions with a high or very high degree of severity have been specially studied by TLV. TLV has granted approval for 10 out of 15 (67%) of such orphan drugs. Among the 5 applications that were not approved, 4 had an estimated cost per QALY gained over SEK 2 million, of which 2 had an ICER (Incremental Cost-Effectiveness Ratio) of over SEK 5 million.

TLV has also specially studied the importance of price negotiations in connection with benefit applications. TLV finds that for benefit applications where three-part negotiations have been carried out more often leads to a positive decision. For the 14 orphan drugs where three-part negotiations were carried out, the application was approved for two thirds. The regions refused three-part negotiations for 10 orphan drugs and the application was written off or rejected. For five of these, TVL assessed the degree of severity as high and for three as high patient benefit (greater than one QALY per patient).

6. What determines the costs of developing a new drug?

There are a number of calculations of what it costs to develop new innovative medicines. Two relatively recent compilations of cost estimates are Schlander et al (2021) and Rennane et al (2021). The estimates are often based on the methods developed by, among others, DiMasi et al (2016). DiMasi estimated drug research and development costs by randomly selecting about a hundred new drugs from a survey of 10 drug companies. The costs of abandoned preparations were linked to new preparations that succeeded in obtaining marketing authorisation. The estimated expenditure for an approved drug was thus calculated at 1,395 million US dollars in 2013 prices. Capital costs to market approval at a real interest rate of 10.5% give a total cost to approval of US$2,558 million in 2013 prices.

To give an idea of the size of the costs, we can first convert the approx. 2.6 billion US dollars into Swedish kroner. With today's exchange rate, it will be approximately SEK 26 billion. To compare with something, the construction of the Öresund Bridge cost SEK 20 billion in 2000.

The method means that they estimate direct expenses for pre-clinical research as well as direct expenses for research in different phases, phase I, phase II, phase III and phase IV. They also estimate the probability of success in each phase and time in the various phases. Finally, they estimate the capital costs to tie up the capital for the development costs until approval.

Schlander et al (2021) conducted a systematic literature search and found 22 articles with 45 cost estimates. All estimates were recalculated to the 2019 price level and they then found a wide range of cost estimates. Estimates ranged from US$161 million to US$4.54 billion per drug. They also found an increasing trend of development costs over time.

Rennane et al (2021) also found a large variation in estimates from US$113 million to just over US$6 billion per drug in 2018 prices. When they only included estimates of new innovative drug substances, the range shrank to US$318 million to US$2.8 billion per substance.

Schlander et al write that R&D costs probably differ significantly for different therapy areas, but that this is not particularly well documented. Costs can be expected to be lower for developing new innovative cancer drugs because several cancer drugs have been shown to have a high probability of success in the various phases. This is also reflected in the large number of cancer drugs under development.

Despite the large number of new orphan drugs in recent years, there are largely no estimates of the costs of developing new orphan drugs. However, some studies suggest that R&D costs for new

innovative orphan drugs may be only half as large as for non-orphan drugs. This would then be explained by the fact that clinical studies with orphan drugs often include fewer patients, are to a lesser extent randomized and double-blind, and often have end-points that measure disease response rather than overall survival. In addition, the regulatory process is often different in that it shortens the time to market approval. On the other hand, the conditions with a simpler regulatory process have led to more uncertain clinical evidence until conditional approval, which in turn has led to demands for follow-up and post-launch R&D costs.

There are also more reasons to expect higher R&D costs for orphan drugs than for conventional drugs. For example, it can mean higher costs to recruit patients as these are rare and difficult to find and coordinate in one and the same study

7. Individuals' valuation

What do individual preferences look like? After all, it is the population that pays, via taxes or via insurance, and it is the population that authorities and healthcare providers are responsible to.

A systematic literature search for published studies of individuals' preferences for valuations of value attributes that construct orphan drug valuations was conducted and recently published by Dabbous et al (2023). They found 38 published studies including 33 for individual preferences and five reviews. They found in 19 of 27 studies that assessed severity, that individuals prioritized giving the same health gain to individuals with severe illnesses, over those with milder illnesses. Individuals (General population) also tended to prefer treatments for diseases where no alternatives existed or where existing alternatives had limited efficacy. Individuals were more likely to give greater value to orphan drugs than to drugs intended for the treatment of more common diseases. This was not due to rarity per se, but mainly due to the severity of the diseases and lack of treatment options. Healthcare is associated with a lot of risk. This means that individuals' relationship and attitude to risk is important for their evaluation of health care.

A constant value for a QALY also assumes that the preferences are independent of the degree of severity, i.e. that a given health gain (e.g. 1 QALY) has the same value for someone who is severely ill as for someone who is mildly ill. This is not consistent with economic theory and diminishing marginal utility. These limitations have been highlighted for many years and there is both theoretical, Hammit J (2013), and empirical, Nielsen JM (2021), evidence that a constant value for a QALY is incompatible with individuals' preferences.

Lakdawalla and Phelps (2021) have raised these issues in health economics and developed a model to be able to adjust QALYs so that they are consistent with individuals' preferences. This model is called GRACE ("Generalized Risk-Adjusted Cost-Effectiveness") and has begun to gain some diffusion in health economics, although, as far as I know, applications are still lacking. GRACE is based on neoclassical expected utility analysis where we have diminishing marginal utility not only for consumption but also for health-related quality of life.

GRACE illustrates why a unit of health has different utility or value for individuals depending on severity. It also shows why a gain in quality of life for people with a serious health condition is worth more than an equal health improvement for an individual in better health. It is also based on risk-averse individuals (individuals who do not like risk or uncertainty) willing to pay to reduce uncertainty. It is the same reason why we want to pay for insurance.

In traditional Cost-Effectiveness Analysis (CEA), the willingness to pay (WTP) for health is equal to the marginal utility of health divided by the marginal utility of consumption. The willingness to pay per QALY can be called the threshold value T = C/ Ui where C is annual non-health consumption and Ui is the ratio by which utility changes with income.

According to Phelps and Lakdawalla, a reasonable estimate of Ui in the US is between 0.3 and 0.5, making T about 2 to 3 times annual non-health consumption. The GDP (gross national product) in Sweden in 2022 in current prices is according to the National Accounts, (SCB statistics authority, 2023) SEK 5,926,336 million. The consumption of healthcare in Sweden was about 11% of GDP and with a population of 10 million, non-health-related annual consumption per capita in Sweden is SEK 52,744. In a study of willingness to pay for traffic safety in Sweden, the income elasticity was estimated at 0.237 and in an earlier study at 0.341, Persson et al (2001). A simple estimate of a general threshold value for CEA in Sweden could then be T = SEK527,444 / 0.237 and 0.341 respectively, i.e. SEK 1.55 million - SEK 2.23 million.

In addition to this general threshold value, the GRACE model means that individuals' relative valuation on the margin of health-related quality of life and longevity is valued according to the theory of diminishing marginal utility. The model is based on an adjustment of the value of a QALY using a severity multiplier based on the relative health loss and the relative risk aversion.

To apply GRACE, two central parameters are required: (1) the marginal substitution ratio between life years and quality of life and (2) the relative risk preference for quality of life, Phelps and Lakdawalla (2023) .

Standard CEA values all QALYs equally. A gain in quality of life from 0.2 to 0.3 gets the same value as a gain in quality of life from 0.8 to 0.9. Similarly, a gain in life expectancy of an additional year of life gets the same value regardless of whether the gain in life expectancy is long or cards.

GRACE, on the other hand, can mean a downward adjustment of the value of the annual life expectancy improvement depending on whether it is many years that life expectancy increases, or an upward adjustment of the value if it increases by a few years. GRACE adjusts the value of the quality of life gained to reflect a higher value for severe conditions. The size and direction of these adjustments are based on individuals' preferences for marginal rates of substitution and relative risk preferences.

As an example, Lackdawalla and Phelps state that current established cost-effectiveness analyzes likely overestimate treatments for relatively mild diseases such as peptic ulcers, benign prostatic hypertrophy and urinary incontinence. At the same time, current methodology underestimates the treatment of severe diseases such as Alzheimer's disease, metastatic cancer and acute pulmonary

embolism. It may be that we overestimate by a factor of 2 for mild diseases and underestimate for severe diseases by a factor of 5 or more.

In summary, we can say that GRACE adjustment means that the health gain is valued based on individual preferences for:

1. Level of severity
2. Duration - life expectancy

The GRACE severity adjustment leads to health gains in the treatment of severe conditions being valued higher and the corresponding treatment of mild conditions being valued lower.

GRACE duration adjustment means that treatment where the health gain extends over many years is adjusted for diminishing marginal benefit

8. HTA organizations severity adjustment

A few HTA organizations apply severity adjustment already today Great Britain (UK), Netherlands (NL), Norway (N) and Sweden (S). This severity adjustment refers to how high a cost per QALY gained can be accepted and is not based on individual preferences. The HTA organizations' adjustment confirms that it is not considered that a QALY is always worth the same amount, but the adjustment made by the HTA organizations is "arbitrary" in the sense that it is not based on knowledge of individual preferences. If we assume that a QALY gained in the case of a non-severe disease is valued by TLV at SEK 702,000, while a QALY gained in the case of a severe disease is valued at SEK 988,000, this means a multiplier of 1.4 for the value of severity. Phelps and Lackdawalla indicate how the HTA organizations in Norway and the Netherlands believe that the threshold values (cost per QALY) can be adjusted significantly more. These adjustments vary for different degrees of difficulty, which for some degrees of difficulty are higher than the average multiplier, 1.4, as calculated by Svensson et al (2016) based on TLV's decision-making during the years 2005-2011.

The ICER (Institute for Clinical and Economic Review) in the USA recommends a threshold that varies between $50,000 to $200,000 per QALY gained, Lakdawalla and Phelps (2021). NICE (National Institute for Health and Care Excellence) in England uses an official threshold of £20,000 to £30,000 per QALY, but also provides an alternative estimated supply value as low as £13,000 per QALY.

Phelps and Cinatl (2021) liken this supply value to the fixed budget analysis that may be relevant in short-term profit maximization of firms with fixed capital investments. It is something completely different from optimization where capital is freely available. The analysis in this report focuses entirely on the more general concept where the opportunity cost is displaced consumption, not displaced production.

However, NICE regularly makes exceptions to these thresholds when evaluating treatments for rare diseases where they can accept costs per QALY gained of up to £300,000 and for end-of-life care of up to £50,000. In the UK, a special cancer fund was also established in 2011 where many cancer treatments did not have to meet the requirement to cost less than the then stated threshold of £30,000 per QALY gained.

TLV and the NT Council apply a modified threshold for acceptable incremental cost per QALY saved (ICER). This means that the authority TLV and the healthcare authorities via the NT Council make an assessment of society's willingness to pay for health. According to the NT Council's document "Policy for the NT Council's assessment of society's willingness to pay", the willingness to pay can vary from

case to case depending on the ethical platform's first two principles: (1) The human value principle (principles of justice and equality in the treatment of patients) and (2) the need/solidarity principle (patients with the greatest needs should go before those with lesser needs).

For the third principle, the cost-effectiveness principle, the NT Council assesses willingness to pay using the four criteria of severity, rarity, effect size and reliability. "Assessment of **the severity of the condition** is affected by, for example, the risk of dying prematurely, the impact on quality of life, functional impairment and, in the case of preventive treatments, the risk of suffering from the disease in the future. The disease's rarity can also be attributed to the principle of need and solidarity. If the disease is rare, there is a great risk that the treatment will not be developed unless society is prepared to accept a higher willingness to pay".

This means that the NT Council's willingness to pay increases for the treatment of rare conditions, especially when the degree of severity of the condition is high. There is an upper limit to the willingness to pay even for extremely rare diseases. However, where the upper limit goes is not specified.

For TLV, there is a review of the subsidy for the drugs Cezyme and Vpriv, which are used in the treatment of the rare Gauchers disease. TLV concluded that they can accept twice the cost for the effect and benefit that Cerezyme and Vpriv provide compared to treatments against more common but equally severe diseases, TLV 20 December 2016.

A review of TLV's subsidy decisions for medicines between 2005 and 2011 shows that the cost per QALY varies between SEK 700,000 and SEK 1,220,000. At a cost per QALY of SEK 702,000 for non-severe diseases, there is a 50% chance of receiving a subsidy. For severe diseases, the corresponding amount is SEK 988,000, Svensson et al 2015. This could be interpreted as the degree of severity justifying an approx. 40% higher price.

9. Shortcomings in the QALY measure

Shortcomings in the QALY measure as a reflection of patient benefit have been discussed for a very long time. Already at the formation of TLV (the predecessor of LFN) in 2002, flaws in the QALY measure as a reflection of the value of health loss were noticed. In the guidelines for how health economic valuation should take place, it was pointed out that the QALY measure has its limitations and can lead to errors, which is why other methods must sometimes be used to demonstrate the patient benefit. An example cited was taken from an article by Bala & Zarkin (2000). There, it is shown how the calculation of the value of anesthesia for root filling of a tooth is calculated using the traditional use of a health index such as EQ-5D. Health-related quality of life during the time the dentist is drilling into the root of the tooth can be assumed to be comparable with the quality of life of the dead patient, but since the procedure takes no more than perhaps 30 minutes, the loss in terms of QALYs is not that great. If you recalculate the QALY loss to willingness to pay, you get a value for the anesthesia that is no more than a few hundred SEK. However, it is obvious to everyone that individuals' willingness to pay for an anesthetic in connection with a root canal would amount to significantly more, perhaps several thousands of SEK. QALY as a method therefore gives too low a value in this and several other cases. TLV/LFN was therefore, right from the start, open to, for example, willingness to pay as an alternative method to demonstrate the value of treatments where QALYs do not work well.

Another area, apart from orphan drugs, where TLV has drawn attention to problems with traditional QALY measurement is consumables. To assist the companies, TLV issued a handbook to indicate possible ways to produce health economic information on patient benefit that TLV could use in its benefit decisions, see TLV handbook for consumables (2011). An example from international literature that QALY is too narrow can be taken from the recent international discussion about how medical innovations should be valued. Several aspects are missing in the QALY measure according to Lackdavalla (2022):

a) **No process-related benefit** – the benefit of less demanding treatment
b) **No severity-related value** – assumes that individuals have the same preference for an improvement from, say, 0.2 to 0.3 as from 0.8 to 0.9 on a scale of 0 to 1 for health.
c) **No risk preference** – assumes that individuals are risk neutral and do not care about the value of treatment until they are in need of it
d) **No value of cure** – assumes that individuals place no value on being able to cure a disease

The criticism is about the valuation not including or based on individuals' preferences. Of course, both market prices for valuation of resource consumption and QALY for health-related quality of life gains are preference-based insofar as they are based on established methods (Time trade off, Standard Gamble, etc.). The problem with drug evaluation is that in several cases it does not start from the

patients' perspective, (Olofsson et al 2021). The patients' perspective refers to both past, present and future potential patients. We thereby miss the insurance perspective in the valuation. The insurance value is the value of having a treatment available should it be needed. For risk-averse people, this value is higher than for those who are risk-neutral. The value is greater for individuals who initially have poorer health. Values generated by reduced risk and security - the insurance value - are not included today.

The criticism is also based on the fact that today we miss the value of freedom of choice that applies at the individual level. The drug evaluation takes place by considering medians, mean values and expected outcome at group level. This may deviate from the value at the individual level. At the individual level, value depends on an expectation of potential cure and the value of hope. The value of hope means that the expected value from a social perspective differs from the value when one chooses for oneself, i.e. a personal perspective. A value is assigned to the chance that one can belong to the patient group that responds best to the treatment. The value of hope can explain why individuals looking for the "last straw" are prepared to pay out of their own funds to access a treatment that "society" has collectively judged as not cost-effective. In other words, the value of hope can explain why the individuals' wishes, based on individual preferences, deviate from the treating doctor's assessment.

Healthcare is a business that is conducted under uncertainty and orphan drugs increase uncertainty, among other things, because it will not be possible to demonstrate clinical effect with large randomized clinical trials if development costs are to be kept at a level that stimulates investors. A relevant and important question is therefore how can we reduce uncertainty?

Here I select and report some of TLV's drug evaluations and the NT Council's published recommendations for orphan drugs. These evaluations and recommendations contain, among other things, information on incremental cost per QALY ratios for various orphan drugs. The documents that are available on the website for nationally ordered introduction of new therapies and on TLV's website must be used for analysis of limitations and opportunities with the currently established methods for valuation and recommendation for price and subsidy decisions.

Here are reported some of the TLV applications for orphan drugs where it was not possible to find an accepted price or agreement, such as when applying for drugs for the treatment of MPS or for the treatment of beta-thalassemia. The information that is publicly available is used. The selected examples should show examples of the general problems with the established valuation method. Problems that arise when the new pharmaceutical market meets the demands of new times from patients and that are manifested in the desire for freedom of choice and freedom to choose.

Example 1. Zolgensma for the treatment of spinal muscular atrophy (SMA)

- Zolgensma received a conditional EMA approval in May 2020.
- The NT Council requested a valuation of Zolgensma from TLV in May 2019 which was delivered in February 2021.
- The NT Council recommended Zolgensma for SMA type 1 in February 2022.
- Cost per QALY when compared with Spinraza was estimated at SEK 3.2 million (approximately €320,000) for 10 years of effect and at SEK 0.9 million (approximately €90,000) for a lifetime without assumption of diminishing effect.
- Confidential discount without outcome-based payment model.
- For confidential reasons, it is not possible to share follow-up data from the National Board of Health and Welfare's register with the companies as the regions had expected.

Example 2. Zynteglo for the treatment of transfusion-dependent beta-thalassemia in the Nordic countries

- Zynteglo was approved for treatment in Europe in 2019, as the first gene therapy for the blood disease transfusion-dependent beta-thalassemia.
- Clinical and financial assessment of FINOSE, HTA organizations in Finland, Norway and Sweden.
- Negotiations between all 5 Nordic countries, Finland, Norway, Sweden, Denmark and Iceland.
- No agreement reached!

Doug Danison, Bluebird bio's Europachef, medgav att det nuvarande ersättningssystemet innebär utmaningar för enstaka genterapibehandlingar.

Bluebird bio meddelade i juli 2021 att de kommer att dra tillbaka en genterapi för sällsynta sjukdomar som nyligen godkänts i Europa när företaget avvecklar verksamheten där.

Example 3. Libmeldy for the treatment of Metachromatic Leukodystrophy (MLD)

- Approved in Europe in 2020.
- Assessment by FINOSE, three HTA organizations in Finland, Norway and Sweden.
- Negotiation with all 5 Nordic countries, Finland, Norway, Sweden, Denmark and Iceland.
- Cost/QALY was estimated at SEK 3.4 -6.9 million (Cost of one treatment SEK 33 million (about $3 million)).
- The NT Council in Sweden recommended use in January 2023.

10. The international discussion around valuation & pricing of orphan drugs

In recent years, the international discussion around orphan drugs has included what it costs to develop new innovative orphan drugs. Several overviews with the aim of highlighting the development costs have been published in recent years, including Schlander et al (2021) and Rennane et al (2021). Despite this, estimates of the costs of developing new orphan drugs are largely missing.

Perhaps the explanation for the moderate interest in the size of the R&D costs can be found in the fact that, after all, the prices are not to be explained in the costs. Cost pricing or cost-plus pricing, according to Annemans (2019), can firstly lead to wrong incentives in that high research and development costs would justify a higher price. An effective research and development process should not be designed to be costly, but rather to use as few resources as possible to reach the goal.

Second, drug research and development processes are characterized by the fact that many projects never reach their final goal of being used clinically to treat patients. This may be due to the failure of the expected effect or unwanted side effects. However, costs of these failed projects must be financed and these costs must be borne by the few successful projects where the drug reaches the market. Pricing on the basis of costs could then lead to the bizarre situation that a research organization/company with many failed projects could justify higher prices for its few drugs that reach the market than they could if they had an overall higher proportion of successful projects and were more successful in their research and development activities.

Third, cost pricing lacks incentives for innovation. Without consideration of patient benefit, costs are rewarded, which is completely against our desire to reward the value of better treatment.

If you want to understand the development of the prices of orphan drugs, it is probably more fruitful to focus your interest on the value of the new therapies. The VBP aims to base pricing and subsidy decisions for drugs on their estimated value. The value must reflect the benefit of the drug treatment. In practice, the discussion of value is often limited to the estimated increased health gain, often measured in Quality-Adjusted Life-Years (QALYs), compared to the standard treatment, and the reduced treatment cost. The health gain consists of both increased longevity and increased health-related quality of life. The saved costs can be limited to reduced expenses for a healthcare organization or considered with a broad societal perspective and then include costs and benefits outside healthcare as well, such as patients' reduced expenses for medicines, aids, doctor's visits, care contacts, care and productivity losses. By letting the price, the compensation to the producers, reflect the value of a medicine, incentives are created for innovations.

The international development and the discussion among many countries' HTA authorities confirm that they see the difficulties with orphan drugs that the old accepted method of evaluating the therapies may not work so well anymore, Graf von der Schulenburg & Pauer (2017), Magalhaes (2021), Postma et al (2022). It occurs, for example, that in many countries people try to adjust the threshold values upwards, add additional value drivers such as degree of difficulty, rarity, near-death valuation and others, often based on arbitrary inventions.

The international discussion in the last five years is very much about including multiple value attributes and how these are based on individual preferences, Neuman et al (2022). These value attributes are usually summarized in the Value Flower. This includes the value of hope, the value of security, the insurance value of reducing health risks and financial risks, the value of knowledge spillover, the value of the treatment process itself, etc.

11. Suggestions on how the valuation methods can be improved

My suggestions for how valuation methods can be improved can be divided into three groups:

First, the valuation of health benefits for different severity levels should be revised to be consistent with economic theory and to be based on individual preferences. This is closely related to the valuation of diminishing marginal utility of health-related extended survival. Both of these consequences are included in what was previously discussed under GRACE ("Generalized Risk-Adjusted Cost-Effectiveness"). The implications of this revision of the assessment of the health-related quality of life benefit and survival are that the conditions considered severe and very severe are valued up. At the same time, treatment of such conditions that individuals regard as mild will be devalued. Expected survival and the related health-related quality of life benefit will be valued on the basis of diminishing marginal utility, ie all life years gained will not have the same value. What the sum of these revisions will be cannot be said until empirical estimates have been made. It is not obvious that this leads to increased willingness to pay for drugs or other innovative medical therapies.

This proposed modification according to GRACE I believe should include not only orphan drugs but also all drugs and the evaluation of other medical interventions. In order to obtain a basis for making these modifications, measurements must be made of individuals' preferences for risk and marginal benefit. It is not a very large and particularly expensive project, but it can be compared to the work that, for example, the Swedish Transport Administration participates in to continuously revise its risk assessment and update the values for reduced risk of death and serious and minor injuries in road traffic. It is reasonable that this work is organized in collaboration between a research council. It could be the Riksbankens jubileumsfond (the Swedish Foundation for Humanities and Social Sciences) and the Swedish Association of Local Authorities and Regions (SKR)or Sweden’s Innovation Agency (Vinnova), and some pharmaceutical companies or why not organized as a collaboration between LIF (the research-based pharmaceutical industry) and Vinnova.

Second, the valuation of new therapies, particularly orphan drugs, should be revised to include additional value attributes beyond cost savings and life expectancy and quality of life gained. Here it is about health-related quality of life having more benefits than those covered by the five dimensions in EQ-5D. The international discussion about the " Value Flower" and which attributes should be assigned value without double counting must also include Sweden and our Swedish HTA organizations. The international discussion is ongoing and will probably be eternal. There is therefore no reason to wait for answers from other parts of the world without immediately starting the process

of approving and requesting new innovative studies that should be produced in connection with the application for price and subsidy of orphan drugs.

Most likely, we can expect that the values would improve if the HTA authorities start requesting so-called vignette studies, which can highlight health-related benefits that are not satisfactorily captured by the EQ-5D measure. Studies that highlight the value for those who are not currently being treated but who would feel satisfied if a treatment was available if and when it was needed, the so-called insurance value, is another example. The international and to some extent also Swedish discussion about paying for the development of new antibiotics is closely related to this. Sweden has recently introduced a compensation that is not related to the use but related to the availability of new antibiotics. This is an example of us already understanding that the value lies in the option, the option value, and that this is something that the policyholders/taxpayers want funds to be reserved for.

Thirdly, the HTA evaluation of orphan drugs should take place in several stages with the aim of not delaying the evaluation process. It is the same ideas that have made it through in the regulatory process, where the assessment of safety and effectiveness also takes place in several steps. One possible route is to apply forms of orderly introduction with conditional payment. The payment results when various milestones are achieved, i.e. some form of outcome-based compensation. It is reasonable that the companies applying for a price and subsidy for the orphan drug also develop proposals for what such a payment model should look like. Two of the drugs used as examples in this report, Zolgensma for the treatment of SMA and Zynteglo for the treatment of beta-thalassemia, have proposed such payment models. However, these payment models never came into use.

The shortcomings of the current evaluation system for orphan drugs in Sweden can be commented on based on the international discussion. All of the components addressed in the Value Flower are probably not equally relevant to solving the problems with the valuation of orphan drugs. There are risks in implementing changes based on all the additional value attributes that are included in the Value Flower. Above all, there is a risk of double counting. There are also arguments based on the fact that the established methods have served us well after all. Proposing modifications can create new problems and questions that increase both the costs of data collection and can lead to increased uncertainty.

An example that I consider relevant for orphan drugs is to include the public's (general population's) willingness to pay so that there is a treatment available for those at risk of suffering from a disease. This is the insured value. This value has, for example, been calculated in a study, Shafrin et al (2021) for a drug for lung cancer. Shafrin et al's study shows that the insurable value of having a treatment available is much greater ($145.7 billion per year) than the value that can be estimated using

established methods that only estimate the risk-neutral expected value—conventional value—calculated to be $16 .5 billion USD per year.

The value of a therapy depends, in addition to the results of randomized clinical trials, on factors such as patient characteristics, which treatment is compared with and on how the healthcare is organized. The latter conditions may mean that the value varies in different countries or jurisdictions and they may be handled, for example, with the pricing instrument and subsidy restrictions.

12. Financing

A brief overview of alternative financing models that may be interesting for orphan drugs is presented here. The overview is based on existing literature and experience in the field, but I will also go "outside the box" and collect examples from other discussions where innovative payment models are discussed. One such example is antibiotics.

Traditionally, people usually talk about a number of alternative forms of financing. (1) One such example is "earmarked" funds such as building up an orphan drug fund. It can be compared to the building of a cancer fund that exists, for example, in England or the development of the so-called solidarity fund. (2) Another form of financing is temporary regional and state budget additions like what we saw in connection with the introduction of hepatitis C drugs. (3) A third form is public and/or private research funding. In this case, it is not the consumption that is financed but the production, and it probably requires international cooperation because the development costs can amount to such large amounts that it is probably not possible to get that far with Swedish research funds.

These three forms of financing are based on earmarking funds for a special type of input factors in healthcare, in this case drugs intended for the treatment of small or seriously ill patients, or patient populations that can be distinguished using screening, tests or other diagnostic methods. This means building special silos or culverts for earmarked money that may not be used for other purposes.

(4) A fourth type of financing is the build-up of private or public insurance. This is also financing tied to consumption. Funding via insurance means that a certain rights legislation comes into play and that those who have taken out the insurance in advance can be relatively certain of getting access to a treatment that has been paid for in advance.

In addition to these forms of financing, there are also various types of arrangements with the aim of speeding up the introduction to new innovative technology or where commercial conditions for sales are lacking. Here we can mention (5) introductory financing that is used in the Västra Götaland region and this type of arrangement can also include the compassionate use program (CUP), the hospital exemption and license prescription. Introduction funding is a local process where new and resource-demanding drug treatments can be allocated extra budget funds after the decision of experts who make a medical and scientific evaluation, Wallerstedt (2016). Compassionate use (use for humanitarian reasons) is a treatment option that makes it possible to use an unapproved drug. Under strict conditions, products under development can be made available to groups of patients who have a disease without satisfactory approved treatments and who cannot participate in clinical trials. The company finances and is responsible for providing the drug to a pre-defined patient group according to the program until

the product is available for sale in Sweden. The hospital exception can occur for gene therapy, somatic cell therapy or tissue engineering products according to rules that are common to the entire EU. When the product is intended to be used for treatment in Sweden, by individual patients under the exclusive responsibility of the prescribing physician, a special manufacturing permit can be granted, known as the hospital exemption.

Licensing means that a pharmacy receives a sales permit and can sell a medicine that is not approved in Sweden. License granted by the Medical Products Agency. There are several different license types, and the license type is chosen according to the needs you have.

(6) CED (coverage with evidence development) means that the drugs or medical devices gain rapid access to the market and can be evaluated in clinical use. The financing is conditioned on the outcomes required for payment to be defined in advance. This may mean that compensation is paid for a certain period of time without the clinical outcome being known. The companies then run the risk that the product's price and subsidy will be withdrawn when and if the outcome is not as good as expected. Healthcare, for its part, runs the risk of having to pay for something that didn't work as well as originally thought.

Perhaps one can also include (7) prescribing outside the approved indication (off-label prescribing) as a method of financing orphan drugs.

Each financing model is fraught with advantages and disadvantages. It can also be discussed how well they fit into the Swedish healthcare system. Specialty drug funds have disadvantages because they involve building new silos or sinkholes that can lead to difficulties in effectively moving resources from one area to another if it proves cost-effective. On the other hand, orphan drug funds can be a way of guaranteeing funding for an input factor that would otherwise find it difficult to assert itself as the established valuation methods do not give the therapy justice. So far, we have been restrictive in building up separate silos in Sweden, even though, for example, Great Britain has chosen a different path with its cancer fund.

However, temporary earmarked budget supplements such as state and regional funds for hepatitis C treatment have been implemented in Sweden. However, they have tended to apply for fairly long periods of time. Private and possibly public insurance is applied to varying extents in many countries, even if it is not primarily intended to finance orphan drugs. In the US, there are commercial health plans that offer packages containing access to medicines should they be needed. Individuals sign contracts with a Health plan, which thereby receives income that is mainly paid by the insured's employer. The various health plans compete by trying to offer the most attractive packages possible. Insurance is an element of Swedish healthcare that has not always won the attention of political

representatives. It is, however, a possible outcome if public funding does not meet the population's expectations.

Public or private research funding is relevant and is discussed, among other things, as a way to create incentives for companies to be attracted to develop new antibiotics. It is then often called "pull" in contrast to measures that go under the concept of "push", i.e. trying to stimulate the companies by paying for the outcome (a new successful drug) and letting the process be handled by the market.

Introduction financing and CED involve certain risk-taking for the producer and payer respectively. It may also be associated with administrative costs for data collection and analysis. However, patients can be expected to get access to the drug treatment faster than if the traditional process takes place. In Sweden, there is both introductory financing and previously CED was common.

There are forecasts of how many and what type of orphan drugs are in the companies' pipeline and under development in collaboration with the healthcare system, such as for ATMP. What significance it can have for policyholders, taxpayers and individual patient groups is interesting to understand what different financing methods mean. There are investigations into whether the HTA authorities assess the companies' profitability in their decisions on subsidies for new medicines. There is also an ongoing discussion about whether companies' profitability should play a role in drug pricing decisions (Berdud et al 2020, Towse et al 2022).

An important aspect of financing and pricing is also looking at the drugs and their value over time. Value-based pricing for patent-protected products over the product's life cycle is not to be missed.

Patents stimulate the development of innovations. Patents are a way to cover development costs and patent expirations should reduce the price down to the marginal costs of the product. The patent price often remains high for about 12 years, after which the price drops down to the marginal cost. During the patent term, the surplus is expected to go to the company. In the period thereafter, i.e. from the patent expiry, the surplus is expected to accrue to the patients without the policyholders having to pay for it.

When we have gene therapies with the potential to cure or so-called SST (Single Short-Term Therapies), the patent has other consequences for the distribution of the surplus. Conventional CEA for VBP of new drugs largely ignores the implications of patent protection. HTA organizations do not normally assess the value of a drug over both the patent-protected period and the subsequent period when the price due to competition from generics or biosimilars has been pushed down towards the marginal cost. Garrison et al (2023), have constructed so-called adjusted cost-effectiveness analyzes

(A-CEA) to illustrate what the value is when you use the branded price, the patent-protected price, during the patent period and then switch to a generic price when the patent exit.

Garrison's analyzes have illustrated several deviations that create an unequal playing field between different types of innovative drugs. Conventional CEA leads to justification of prices other than adjusted A-CEA which also takes into account competition from later generics and biosimilar drugs. Free and flexible pricing of long-term treatments such as insulin for type 1 diabetes depends on how well competition works after the patent expires. One-time administration of, for example, gene therapies with the potential to cure has the potential to distribute a large part of the surplus over the life of the product to the producer. This unequal competing conditions may have significant implications for the incentives to develop new long-term treatment regimens or recurrent treatments for chronic diseases.

This could be an argument for not basing the analysis of the innovative drugs on conventional CEA but for carrying out adjusted A-CEA over the entire product life cycle. This may mean that more research is needed to further develop the methodology for VBP.

13. Discussion

In this writing, I have identified a number of conditions which lead to the fact that today's methods of valuing medicines hardly lead us to a satisfactory understanding of the value of orphan medicines.

Of course, there are difficulties with the clinical evidence. The clinical evidence is difficult to demonstrate when it comes to small patient populations and sometimes very small ones spread over very large geographical areas and several jurisdictions, countries. It then becomes costly, practical and ethically complicated to randomize and collect the requested data.

The difficulties with the clinical evidence have long been noted in other writings and I will not delve into it here. Just want to point out that a lot of solutions have been proposed to reduce the uncertainty in the clinical evidence. Examples of such can be found in documents from TLV (2020) and are about using innovative payment models, payment related to outcomes, delaying decisions on price and subsidy until satisfactory evidence is available, etc.

In this paper, I would rather highlight the shortcomings of the economic evidence, the evidence that should highlight the value of the clinical benefits.

The difficulties with the current accepted method of measuring the benefit of new innovative drug therapies can be traced to three areas in particular:

Insurance value is not included – the value of having a treatment available should it be needed and for the risk averse this value is higher than for the risk neutral. The value is greater for individuals who initially have poorer health.

The value of hope is not included – expected value from a social perspective differs from the value when one chooses for oneself, i.e. a personal perspective. A value is assigned to the chance that one can belong to the patient group that responds best to the treatment.

Process-related benefits are not included – The value of avoiding odors & leakage in case of ostomy bag, dietary restrictions & medical food in case of phenylketonuria (PKU), are examples of quality of life effects that are not included in the EQ-5D instrument.

These are not unknown flaws. TLV, for example, drew attention to shortcomings in the QALY measure already 20 years ago when it issued guidelines for how health economic valuation should be done. TLV (or LFN as it was then called) pointed out that in some cases the value could be better elucidated with surveys of individual preferences, e.g. willingness to pay or other trade-off studies, than with calculations based on standardized quality of life measures.

What has happened in recent years is that this has been noticed in the international literature and that a large number of studies have been published that have sought to remedy these shortcomings. On the one hand, many so-called vignette studies have been published that include the value of process-related benefit. The value of avoiding odor and leakage with ostomy bags is an example. Much of the discussion surrounding the value of antibiotics is precisely about this. We want a restrictive use of antibiotics to minimize the risk of resistance. At the same time, we want to stimulate the development of new antibiotics in case we need them. It is called option value, i.e. we want to pay for an option that should be available.

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