

1. Introduction to the Market Access

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1.1 Origin of the Market Access Term

Market Access for Goods

The Market Access (MA) term was first introduced by the World Trade Organization (WTO) to define the competing relation between the domestic and the imported products of a country.

The WTO defines MA as a set of conditions, tariff and non-tariff measures, agreed by WTO members for the entry of specific goods into their markets, that is to say, the government policies regarding trade-barriers in general, and specifically the issues of import substitution (to promote local production) and free competition.

Healthcare Market Specifics

In spite of many similarities between healthcare products and other goods in a free market economy, the healthcare market challenges the traditional economic paradigm. There are four features that clearly differentiate the healthcare market from other markets.

1. **The price is not determined by supply and demand.** In a traditional market economy context, the price is determined by supply and demand. In the healthcare market, however, the prices are determined by payers through negotiation or are simply notified by the manufacturer. Further, in the traditional market, a single entity assumes the functions of the buyer, the payer, and the consumer. In the healthcare market, however, the buyer is the physician who prescribes the treatment, the payer is the health insurance provider, and the consumer is the patient. The three parties do not necessarily have convergent views on the value of healthcare goods.
2. **Payers are committed to purchasing health for the society.** The healthcare payers' intent is to provide health for the patient. When payers fund medicine they wish to fund health production. However, they can only buy a proxy of health through the purchase of medicine and healthcare services. The actual outcome in terms of health improvement remains uncertain.
3. **Health is specific to each individual.** Unlike food or technology, health cannot be shared or traded between individuals. The outcome of a treatment procedure also depends on individual characteristics of the patient. The patients' characteristics may be not fully known *a priori* because of the lack of appropriate tools. This repertoire of

medical tools is evolving and changes our understanding of the disease and our approach to therapies.

4. **Externality of health.** Medicines can have a positive impact on the health of people, other than the ones who consume it. This is particularly the case for vaccinations and antibiotics. The treatment and prevention of contagious diseases at the level of an individual can protect the global population from a potential epidemic. Therefore, i) restricting access to health care for a population's subgroup can have dramatic impact on that population health status, ii) poor health care in a population's subgroup will affect the health of the remaining part of the population that has good access to health care. This is one of the main reasons for the creation of national health care systems. Illustratively, it has been iteratively reported that, despite the highest *per capita* healthcare expenditure, the US does not have the best population health status, notably because of the wide disparity in access to health care.

1.2 Healthcare Market Access Definition

The concept of MA is complex to define, depending on whether we are dealing with a private, public or mixed health care system. MA is the process by which a healthcare goods company gets its product available on the market after having obtained a Marketing Authorization (MAu) from a regulatory agency and by which the product becomes available/affordable for all patients for whom it is indicated as per its MAu.

The following definition will be used in this chapter:

MA for pharmaceuticals defines the ability for a drug to achieve through a health insurance system a reimbursed price and a favorable recommendation for medical prescriptions.

It covers a group of activities intended to provide access to the appropriate medicine for the appropriate group of patients and at the appropriate price.

For the manufacturers, the ideal outcome of the MA process is to achieve the optimal price with maximum reimbursement for the approved target population with no limitation on prescription or funding procedures. However, in practice the company needs to strike a trade-off between:

- Price and reimbursement conditions;
- Target patient population selection;
- Prescription and funding procedures.

Therefore, MA can be also seen as activities that support the management of potential barriers, such as non-optimal price and reimbursement level, the restriction of the scope of prescription for a drug or complicated prescription or funding procedures.

The scope of these activities encompasses the management of pricing and reimbursement, Health Technology Assessment (HTA) and formularies. The formularies are the lists of medicines that may be prescribed at the expense of the institutionalized payer.

MAu from a regulatory agency, which could be the Food and Drug Administration (FDA) in the US or the European Medicines Agency (EMA) in the EU, is issued based on consideration of the product's safety, efficacy, and quality in the highly controlled conditions of Randomised Clinical Trials (RCT). In the case of UE, national agencies are responsible for the implementation of this authorization in their local settings. Once a medicine is approved for marketing, HTA bodies are responsible for assessing its real-life efficacy (i.e. effectiveness), cost-effectiveness, relative efficacy, related medical need, budget impact and other evidence that will be later used by payers for pricing and reimbursement (P&R) decisions, as well as formulary listing and prescription guidelines.

Institutionalized healthcare payers (such as the national health funds, health insurers, etc.) themselves are typically not qualified to evaluate those criteria, so they delegate these activities to independent groups of experts which elaborate the HTA evidence. HTA evaluations aim to inform payers' decisions and help them set the appropriate P&R conditions.

Finally, MA is not and should not be confused with the following activities: obtaining regulatory approval (license, MAu), medical marketing and sales (e.g. medical representatives getting access to doctors or pharmacists), distribution (access to pharmacy shelves), choosing the right channel to promote product (e.g. marketing, direct-to-customer advertising etc.).

1.3 Market Access Key Concepts

If we consider the WTO definition, obtaining MA should be the ability to access the whole market in a given country, sell the product and achieve revenue from the market without obstacles. In the case of pharmaceuticals, these obstacles are: obtaining MAu, P&R levels, logistics (storage and supply conditions), the drug surveillance (follow up on potential and actual product adverse effects), etc. In practice, however, the pharmaceutical industry has become proficient in addressing all those hurdles except P&R. Thus, MA for the industry has become equivalent to the addressing the hurdle of achieving optimal P&R levels.

Measuring Value

MA is related to the concept of 'value for money' from a payer's point of view. As a result, the primary objective of MA studies is to define and measure the value of health services and products.

In economics, the value is a concept that refers to two different theories. The first one is an objective theory, or the intrinsic theory of value, where the value of an object, good or service, corresponds to the cost of the production that is the cost of raw material and human work needed.

The second one is a subjective theory and is more consistent with the idea of value as perceived in the healthcare market. According to this theory, the value of a good is neither determined by any inherent property of the good, nor by the amount of labor re-

quired to produce the good, but is determined by the importance of acting individual place on a good for the achievement of their desired outcome. The price offered is therefore not a measure of the subjective value; it is just a means of communication between the buyer (healthcare payer) and the seller (the manufacturer).

As far as healthcare and MA are concerned, this last definition is the most relevant and should be used. In MA, the value of a drug or a health service depends on the institutionalized payers' subjective perception of a particular medical need in the society and how the product addresses that need.

This assessment of value made by payers is subjective, yet based on scientific evidence, such as clinical trials, epidemiology, cost-effectiveness or other HTA studies. Most institutionalized payers formally require drug manufacturers and healthcare providers to submit evidence that corroborates the value of their product in terms of clinical outcomes and/or the cost of achieving such outcomes. Achieving a positive coverage decision at an optimal price depends on the ability of the pharmaceutical industry to submit pertinent evidence. If they succeed, this translates into successful MA for the concerned product. This calls for a thorough understanding of this evidence-based concept of value on the part of this industry.

The kind of evidence required by the payers for the assessment of a product differs from one country to another and covers a wide array of indicators, such as proof of clinical and economic value and more specific considerations of ethics, equity and/or politics. The set of evidence generated and presented by the manufacturer for the payer is called the value proposition. The development of such proposition is the ultimate aim of MA activities from an industrial perspective.

However, from a payer's perspective, the objective is to relate the drug's value to its price considering all available evidence. This is one of the most debated issues at the moment among healthcare actors and is often called value-based pricing.

Market Access and the Structure of Healthcare Markets

Pharmaceutical markets can have a varying degree of fragmentation, from countries with a single national insurer to countries with multiple private insurers or a mix of both. In the latter two cases, securing MA is the ability to systematically gain access at optimal conditions in each and every geographic area with each and every insurer. Depending on the type of healthcare market organization (e.g. centralized vs. decentralized or fully fragmented) the MA strategy may focus on different aspects as described below.

Publicly-funded health care systems

Within publicly funded national health insurance in Europe, Australia and Canada, the government defines the overall public health goals and the corresponding budget. Then, the rules of access to the public healthcare market by the industry are laid out by a central agency or agencies. These rules involve the kinds of evidence which are required for the value assessment of health products and the criteria for making the funding decision. In principle, the public healthcare payers represent the society's interest and try to integrate the societal perspective when making the funding decisions.

Mixed or private health care systems

The US is an example of a country where health insurance is fragmented and largely private. There is no unified framework which regulates the conditions of obtaining MA in the US and the public, as well as each of the private insurers, follow their own pathway. In this setting, for-profit private healthcare payers engage in independent negotiations with the industry. This can be seen a negotiation between two business entities that are looking to maximize their profits. However, in the US, the public payers (the Centers for Medicare & Medicaid Services – CMS, e.g., Medicare, Medicaid, and the Children’s Health Insurance Program – CHIP) represent an increasing proportion of the healthcare budget that is almost nearing the commercial insurance sector. The CMS pathway resembles that of many European countries, Australia or Canada, except that formal health-economic analysis or HTA is not compulsory in the US, excluding very rare cases. Further, unlike in some European countries, the high cost of a product should not be a cause for a negative reimbursement advice by the CMS.

Centralized and regional market access

A trend towards decentralization is emerging in the public healthcare settings, as policy-making is increasingly devolved from the central, national bodies to local health authorities. As healthcare payers are compelled to restrain their pharmaceutical budgets, in a context of the economic recession, local policy makers are faced with funding decisions. However, these responsibilities are not always matched with competencies at the regional level. In many countries, the regional authorities accountable for medicine spending are seldom prepared to negotiate the costs of the drugs or to assess their value.

This trend is blurring the traditional division between countries with decentralized healthcare systems, such as Spain, Italy, Sweden or Germany and countries with more

	France	Germany	UK
Objective	Secure access to all new products, but at the right price	Obtain savings on drug spending with no detriment to safety/ efficacy	Obtain rational allocation of resources
Process	Driver: Public health relevance of benefit compared to the next best alternative Method: Single/double-blind randomised clinical trial Effect size	Driver: Same effect – same price (e.g. jumbo groups) Method: Meta-analysis Efficiency frontier as a backup	Driver: Maximization of efficiency of the health care output Method: Cost-utility threshold is 30000 £/ QALY
Impact	Gate-keeper for market entry	Reimbursement level	Recommendation for prescriber Formulary listing

Table 1. Cultural differences between countries regarding the objective, the process and the impact of HTA evaluation in MA



Figure 1. The cultural differences among prescribers and payers in Europe

centralized ones, like France or England. E.g. in England, where strategic decisions affecting the National Health System remain in the authority of the national Department of Health, the power of execution is assigned to a large number of Primary Care Trusts (PCTs). This means that, apart from the national bodies, the pharmaceutical industry has to engage directly with PCTs, in order to access the regional markets in England.

1.4 Cultural Specificities of Market Access

Any MA strategy needs to be culturally-sensitive. For instance, European countries that employ formal HTA in the funding decision framework can still substantially differ in the objective, the process and the impact of the HTA in MA (Table 1).

Finally, in Europe, there is a geographical dichotomy between medicine prescribers and payers in the Northern and Southern European countries. The former countries are typically more centralized and reluctant to price negotiation than the latter ones (Figure 1).

1.5 Market Access from Payers' Perspective

The Payers of Healthcare

In healthcare markets, payers are generally entities that finance or reimburse the cost of health services. In the health care market, payers always act as gatekeepers for MA.

In most European countries, there is one main payer in each country, corresponding to the national public health insurance. Sometimes, there are additional payers at a regional level or a mix of national and fragmented private payers as in the US. Importantly, each payer can have different objectives, perspectives, and processes.

Payers should not be considered as a homogeneous audience, but rather as a complex and heterogeneous one. The arguments accepted by one payer may be counterproductive for another payer within the same country.

Payers' Tools to Control Drug Expenditure

Despite an increasing proportion of health care products that have cheaper, generic versions, the pharmaceutical market value continues to grow. To tackle this growth, payers have employed a variety of cost containment measures since the late '90. Nevertheless, they have failed to control the growth of the expenditure. In the Organization for Economic Co-operation and Development (OECD) countries, excluding the US, healthcare spending has almost doubled its share of Gross Domestic Product (GDP) over the last 10 years. The demographic changes (population aging) and the expected future healthcare innovations are expected to generate a disruptive pressure on healthcare budgets unless an appropriate action is taken. Pharmaceutical spending growth is a lot more significant than the healthcare spending growth and accounts for as high as 20% in many developed countries.

The most common regulation of drug expenditure is price control. This tool means that the institutionalized payer, rather than the manufacturer, decides on the appropriate price for a medicine. This decision is often preceded by a negotiation with the MAU holder. Only two developed countries still enjoy the free (uncontrolled) pricing process: the US and the UK. However, the two countries have put in place a number of regulatory processes that indirectly regulate prices. For instance, if a drug is thought to be overpriced by the national payer in the UK, the access to the market can be narrowed by means of the so-called negative list recommendations. Further, free pricing in the UK was supposed to be replaced by a controlled pricing process, following the recommendation of the UK's Office of Fair Trading (OFT). Although the initiative of value based pricing failed, the UK Department of Health is now routinely accepting very high discounts that remain confidential but are often above 50% of the list price of many costly medicines.

Other pharmaceutical cost-containment measures developed by payers include general price cuts, reference pricing or exceptional taxes on turnover and profit.

During the 90s, the pricing regulation in Europe was often based on the health authorities' subjective perception of what the right price was. In order to dissolve political pressure around patients' access to new medicines and incentives for the industry to innovate, the authorities needed to implement more clear and objective rules for establishing prices. This resulted in two key developments:

- The creation of national Health Technology Assessment (HTA) bodies across EU countries, Australia and Canada that assess evidence supporting the benefit of new medicines and other health technologies.
- The creation of reference pricing within the therapeutic class and across EU countries.

This trend is also seen in the US where The American Recovery and Reinvestment Act (ARRA) provided \$ 1.1 billion for comparative effectiveness research.

The Value Assessment by Payers

Given the limited financial resources, payers wish to contain drug expenditure and invest in products that can create best health outcomes for the insured. In this endeavor, they need to assess the uncertainty about the drug's potential health benefits, as well as the potential costs related to funding it. This process is referred to as the value assessment framework.

The process of assessing the value for money of a medicine is broadly a four-step assessment:

1. **Comparative efficacy from clinical trials of the medicine** (as compared to alternative treatments for the same condition). The quality of the data is scrutinized, as to the clinical trial design, the inclusion/exclusion criteria, the randomization procedure etc.
2. **Comparative effectiveness from real-life data on use of the medicine.** If an added benefit is observed in clinical trials, it may or may not be pertinent to real-life medical practice. The following conditions are scrutinized: i) the statistical effect size of the additional benefit of the medicine showed in a clinical trial (i.e. is the effect sufficient to be clinically important or does it present a significant improvement for the patients?), ii) the transferability of the clinical trial data across jurisdictions or regions, and iii) the transferability from a clinical trial model to real life. If a medicine doesn't show significant benefit after these two steps, the value will be considered equal or lower than that of the comparator treatment. If it is so, no premium price can be granted. However, if the benefit is shown, value for money can be further assessed by comparing the extra benefits to the extra costs of the new medicine.
3. **Cost-effectiveness.** This method compares the drug's effectiveness benefit against the cost consequences of using the drug (e.g. cost per Life Year Saved, per Quality Adjusted Life Year (QALY), per success, per relapse avoided etc.). Cost per QALY has been increasingly adopted by most HTA organizations over the recent years. Because the (real-life) effectiveness of a new intervention is often unknown at its market launch, this approach remains quite theoretical. Nevertheless, it is commonly considered rational to set a maximal threshold for the Incremental Cost-Effectiveness Ratio

Box 1. The Importance of Affordability

In the US, payers pay for certain oncology products \$ 80,000 to increase life expectancy by 1.2 months. By simple extrapolation, survival gain of 1 year would be valued at \$ 800,000. In the country, 550,000 patients die from cancer annually. If new drugs are developed that extend life by one year, \$ 440 billion would be needed to purchase this drug for all patients. This amount seems unaffordable, even for the richest countries. Therefore, it seems that beyond assessing what is the value of the additional health benefit a new medicine, we need to be concerned about what is the affordability of the payer to fund this new medicine.

(ICER) per QALY gained for funded interventions. However, this approach may lack consideration for the payer’s affordability (Box 1).

4. **Budget Impact.** This stage determines if the intervention is affordable in the current budget and if not, what is the additional budget needed to reimburse this new drug or what actions should be undertaken to make it affordable. Some countries do not consider budget impact as they believe it is redundant with the efficiency assessment, as the ICER threshold is expected to reflect/be adjusted on the country’s affordability. This remains debatable. Following the exemplary value assessment framework presented above, the payers may wish to estimate what is the right price for the medicine in question. In the institutionalised health care payer settings, the value-based pricing is currently considered to be the most promising model, but the methodology is only emerging and it remains to be seen if it will be implemented successfully.

The Link Between HTA and Pricing & Reimbursement Conditions

Negative HTA recommendation for use of a medicine translates into sub-optimal MA in various ways. The impact on price can be through direct reduction of the price by the payer, price-volume agreements or co-payments (e.g. in Germany). The impact on reimbursement is by reducing the maximum percentage of reimbursement (e.g. in France).

Further, restrictions can be applied on the scope of prescription of a drug. Partial restriction consists in defining a population of patients or an indication that is narrowed as compared to the MAu of a drug. The full restriction means that a drug will not be included in formularies or in guidelines (e.g. in Canada, UK). Pre-authorization of prescription for a medicine by the payer or by a specialist medical center are further means of ensuring that the drug is only prescribed to the patient population strictly defined by the payer. Finally, Market Access Agreements discussed in section 7 are contracts between the manufacturers and the payers that aim at obscuring the real medicine price or that allow a temporary premium price until stronger evidence on drug’s effectiveness or safety is developed.

Non-HTA Tools That Affect Drug Pricing

HTA is a laborious process and it’s often unclear how to link HTA recommendations to the price of a medicine. Reference pricing is a benchmarking model of setting prices of medicines by comparing them to the prices of the same medicine in other countries or by comparing them to prices of existing medicines in the same therapeutic area or with a similar mechanism of action in the same country. These methods are described below.

External Reference Pricing

External Reference Pricing (ERP) (also referred to as “External Price Referencing”, “International Price Benchmark”, “External Price Benchmark”, “External Price Linkage” or else “International Price Linkage”) has rapidly become a widespread cost-containment tool. It is used among European countries, as well as by other countries such as Brazil,

Jordan, South Africa, Japan, Turkey, Canada and Australia that refer to the European drug prices in order to establish their own.

The WHO Collaborating Centre for Pricing and Reimbursement Policies defines ERP as «the practice of using the price(s) of a medicine in one or several countries in order to derive a benchmark or reference price for the purposes of setting or negotiating the price of the product in a given country». Consequently, the change of price for a given product in one country affects the price in other countries.

Altogether, ERP methods and rulings are outlined with different levels of accuracy within the national pricing regulations. Portugal and Austria are examples of countries in which the legislation provides ample details on the use of ERP. German and Estonian laws provide much less guidance on the matter. On one extreme, Luxembourg resorts to ERP to determine the price of all newly marketed drugs. In contrast, Estonia, France and Germany resort to ERP in the case of innovative and publicly reimbursed medicines only.

Internal Reference Pricing

Benchmarking prices of existing medicines in the same therapeutic area or with a similar mechanism of action in the same country is used by some countries to set prices of new drugs. E.g. in Germany, when no additional benefit has been established in HTA of a newly approved medicine, it is allocated to a reference price group with pharmacologically and therapeutically comparable pharmaceuticals. All pharmaceuticals in this group will have the same price. In many European countries, an internal reference pricing system is in place for reimbursed generics, that is all products that contain the same off-patent molecule are priced at the same level.

1.6 Market Access Agreements

Definition

The high cost of novel treatments is a common cause of negative or restricted reimbursement decisions by healthcare payers. Such decisions can reduce or even eliminate MA for new products. Therefore, both the payers and the industry seek compromise in achieving MA for novel products.

The outcome of such negotiations can be called Market Access Agreements (MAA). MAA can be defined as “an agreement between two or more parties, who agree to the terms and conditions under which a product will get access to the market”. MAA specify, often in a confidential manner, the conditions under which a concerned treatment will be priced and reimbursed in a given population of patients.

Taxonomy

To simplify the nomenclature and taxonomy, MAA can be generally grouped into financial (Commercial Agreements, CA) or outcomes-based (Payment for Performance

Agreements (P4P) or Coverage with Evidence Development (CED): financial agreements are CA between two or more parties entering into a deal for goods acquisition; outcome-based agreements are part of an insurance or warranty facility: the payer agrees to a price under the insurance that the product will deliver a predefined health outcome in a given patient. This regroups two kinds of MAA: P4P and CED.

These two types of MAA are subdivided into two categories, MAA at the population level (certain types of CA, such as price-volume agreements, CED) and MAA at the individual patient level (certain types of CA, such as price cap per patient, free drug supply after a pre-defined treatment duration etc., P4P).

P4P are agreed by payers to avoid expenditure on treating patients who do not respond to a drug and who cannot be identified *ex ante*, by permanently linking the payment to drug's performance in individual patients. P4P is set to pay only for patients who achieve a pre-specified response to a drug.

In contrast, CED are temporary MAA where the payers agree to finance the new technology as a part of a well-designed study, in order to generate real-life evidence that will enable final price and reimbursement decisions. Such evidence may not be available at the time of drug launch because data from clinical trials do not reflect the real-life use, health outcome, dosage or duration of treatment, actual targeted patient population or the impact of the medicine in question on the use of other health care resources.

Finally, MAA can be a mix of two types of agreements, e.g. a simple price discount (CA) is often an element of P4P.

The Future of MAA

CA and P4P ensure drug cost reductions to payers while maintaining high list prices. The importance of high list prices for the industry pertains from the use of ERP globally. Therefore, maintaining high visible prices in the major pharmaceutical markets can help manufacturers ensure high prices in countries that use those countries to set prices of new drugs. In the future, the complex and burdensome P4P will likely be replaced by CA when payers need to reduce the cost or by CED when they wish to reduce uncertainty about drug's performance.

1.7 Market Access for Orphan Drugs

Definitions of Orphan Drugs

Orphan medicinal products, or "orphan drugs", constitute a class of drugs that have been developed specifically to treat a rare medical condition generally referred to as "orphan disease". As the name suggests, rare diseases occur in a very small population. Therefore, making orphan drugs profitable for the industry may require obtaining high prices for a low number of users. At present, there is no universal definition of rare disease and it differs among countries.

In the US, an orphan drug is defined in the *Orphan Drug Act* as: «Orphan drugs are used in diseases or circumstances which occur so infrequently in the USA, that there is no reasonable expectation that the cost of developing and making available in the USA a drug for such disease or condition will be recovered from sales in the USA for such drugs».

The limit of prevalence for a rare condition in the US is defined as the absolute number of 200,000 people in the population. In 1985 and 1990 the definition of orphan drugs was extended to products other than drugs like biologics, medical devices, and medical foods.

The EU orphan drugs regulation was implemented almost 20 years after the US regulation. As defined by the regulation EC No 141/2000, a product can be designated as orphan drug, if it is intended for the treatment, prevention or diagnosis of a disease that is life threatening or chronically debilitating; the prevalence of the condition in the EU is not more than 5 in 10,000 or it must be unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development; no satisfactory method of diagnosis, prevention or treatment of the condition concerned can be authorized, or, if such a method exists, the medicine is of significant benefit to those affected by the condition.

In 2005, France was the first EU country that established a national plan for orphan drugs that also included funding provisions. France hosts several European organisations that work in the field of orphan diseases, such as Eurordis, Orphanet portal, and the Orphanet Journal of Rare Diseases.

Spain was the second European country that published a national strategy for rare diseases in 2008. Some regions like Andalucía, Extremadura and Catalonia have created their own rare disease plans.

Further, the UK's National Institute for Health and Care Excellence (NICE) is developing new methodology to evaluate the so called ultra-orphan drugs, called Highly Specialised Technologies (HST). The use of the term ultra-orphan drug is restricted to drugs used to treat conditions with a prevalence of less than one case per 50,000 population.

The HTA Frameworks for Orphan Drugs and Ultra-Orphan Drugs

Different European jurisdictions focus on various HTA criteria for the evaluation of orphan drugs, such as cost-effectiveness, budget impact, disease severity, therapeutic need, social benefits etc. There is no universal HTA decision framework and the existing approaches are facing many challenges.

Standard HTA approaches that require data from RCTs are often relaxed when applied to orphan drugs. This is because there may be little data available, or the data may be of low validity or quality, even if the drug in question has been licensed for use. Because of the high unmet needs, despite the data paucity, higher levels of uncertainty on clinical efficacy, safety, incremental cost-effectiveness and budgetary impact may be allowed by decision makers and these drugs are reimbursed in certain countries.

These various approaches result in disparities in access to orphan drugs among countries. Interestingly, France and Italy focus on criteria such as proven clinical value, evi-

dence from cohort studies, and the degree of innovation, but do not require a formal cost-effectiveness analysis for regular and orphan drugs.

In contrast, in England and Wales, a threshold of ICER per QALY is the benchmark of medicine funding recommendations by NICE. For instance, one study showed that NICE gave only two positive recommendations on 43 EMA-approved orphan drugs, 69% of them were reimbursed in Sweden and 94% and 100% of them were reimbursed in Italy and France respectively. However, for ultra-orphan drugs, NICE would like to operate as a “broker” putting together all the stakeholders around the same table and looking for a reasonable price that would satisfy all parties, which should allow greater patient access to such products.

This illustrates a trend where countries that require standard cost-effectiveness analysis typically have a lower coverage of orphan drugs than countries that do not. Consequently, patients with rare diseases in countries which employ solely the cost-effectiveness approach may be deprived of access to orphan drugs.

As shown before, ICER-based decision making that focuses on the allocation of limited resources in order to maximize the health value generated may not be compatible with the pursuit of social equity. However, incorporating social values into the HTA framework requires more empirical research that measures the social preferences in a given society. For instance, people can share two notions of equity: horizontal equity (equal treatment of equals, implying that everyone in the society is equal by birth and spending health care budget on rare diseases is unfair) and vertical equity (unequal treatment of unequals, implying that people in the society are not equal by birth (e.g. in terms of their genetic make-up) and therefore are entitled to special treatments). From the utilitarian perspective of allocation of limited resources, funding of orphan drugs must support the vertical equity.

However, many orphan drugs would not be recommended for reimbursement even if societal perspectives were incorporated into funding decisions, because of their very high prices.

In the US, there are no formal HTA frameworks to assess the value of orphan drugs and the prices are unregulated. The high cost of orphan drugs is driven by the perceived need for a return on investment from a smaller than usual population of patients, lack of alternative treatments and the severity of the rare disease.

Further, pricing of orphan drugs has been described as obscure and the prices of orphan drugs in the US do not seem to correlate with the patient population sizes.

Therefore, more transparent pricing methods, such as ‘cost-plus’ or ‘rate of return’, could be considered when pricing orphan drugs. However, it’s complex to assess objectively what is the cost of developing a drug and how to account for the cost of unsuccessful candidate molecules that had to be discontinued without financial return to manufacturers.

Conclusion

Orphan drug incentives have stimulated the pharmaceutical industries to the development of research into diseases with significant unmet medical need. The revenue-gen-

erating potential of orphan drugs is similar for non-orphan drugs, even though patient populations for rare diseases are significantly smaller. Moreover, orphan drugs may be more profitable, when considered in the full context of developmental drivers including government financial incentives, smaller clinical trial sizes, shorter clinical trial times and higher rates of regulatory success. However, current orphan drug policies are unlikely to be sustainable, because they have led to high prices of orphan drugs and to limited coverage and restricted patient access when cost-effectiveness is the sole decision-making criterion. This calls for policy changes which are unavoidable in order to ensure sustainability of the health care systems.

1.8 Early Advice

Medicine manufacturers have an opportunity to consult regulators and HTA bodies, early in the development process of a medicine as a part of specific early advice schemes. The authorities concerned by these schemes use various terms, such as “early dialogue” or “scientific advice”.

Such advice can help pharmaceutical companies establish what evidence these authorities will need in order to determine a medicine’s benefit-risk balance (in the marketing authorization process) and its “value-for-money” in real-life use (in the HTA process).

For instance, manufacturers can apply for parallel scientific advice from EMA and national HTA bodies at any stage of development of a medicine, whether the medicine is eligible for the centralized authorization procedure in the EU or not.

Further, the so called adaptive pathway is an accelerated scientific advice pathway of EMA for therapies indicated for serious conditions with high unmet needs. It requires that there is an iterative development with use of real-life data. It provides to the possibility to engage various stakeholders including regulators, HTA bodies and patient representatives in multiple discussions along the development pathway.

EMA has also developed a scheme for priority medicines called PRIME, in order to optimize the development and accelerated assessment of medicines of major public health interest. PRIME reinforces early dialogue and builds on regulatory processes such as scientific advice to optimize the generation of robust data and the accelerated assessment procedure to improve timely access for patients to priority medicines.

Further, individual EU countries have also implemented similar programs. The company needs to identify the appropriate timing to seek early advice. For instance, very early in the drug development (non-clinical/proof of concept stage), the company may seek clarifications/adjustments of general clinical trial design but limited patient data. They are likely to obtain a general response with a less specific advice. In contrast, later in the drug development (prior to phase III) the company can obtain more precise responses regarding clinical trial design and pharmacoeconomic questions. When phase III plans have been finalised, advice can still help to adjust design/statistical analysis plan of phase IIIb/IV studies.

Overall, the advice should be sought early enough to ensure that the company can integrate the advice in all phases of the development. However, if the advice is sought too early, population(s) and indication(s) may be dramatically affected by the advice from the HTA agencies. Therefore, end of phase IIB should be a reasonable time to request the advice.

In summary, the main goal of the early HTA advice is to achieve consensus between HTA bodies and the EMA (when relevant) on the global drug clinical development plan. Simultaneous feedback from HTA bodies and regulators can help companies to identify key areas of consensus and divergence between these different stakeholders.

1.9 Early Access Programs

Early Access Programs (EAPs) are country-specific regulatory processes which grant MA to unlicensed medical drugs to specific patients, under specific terms, provided that they fulfil specific criteria.

The EU, through the European Regulation 726/2004/EC, defines Compassionate Use as a treatment option that allows the use of an unauthorized medicine for patients who either have a disease for which no satisfactory authorized therapies exist or who cannot enter a clinical trial.

In the US, FDA regulations have allowed patients access to investigational drugs and biologics through Expanded Access since 1987. Expanded Access is a regulation that makes promising drugs and devices available to patients with serious or immediately life-threatening diseases. The FDA currently approves Expanded Access, on a case-by-case basis for an individual patient, for intermediate-size groups of patients with similar treatment needs who otherwise do not qualify to participate in a clinical trial, or for large groups of patients who do not have other treatment options available and sufficient information is known about the safety and potential effectiveness of a drug from ongoing or completed clinical trials.

EAPs can be divided into two main types of programs:

- **Nominative or named-patient EAPs** are typically initiated by physicians for an individual patient in great need of a medicinal product, which will be administered under the physician's responsibility. Companies usually have little influence on this type of EAP. However, companies can try to anticipate these demands and define in advance a set of criteria allowing safe access and administration to patients.
- **Cohort EAPs** are usually initiated by the manufacturer to allow access for a group of patients to an unauthorized medicinal product.

The different countries may refer to them differently but all the programs fall within this binary classification. The regulatory requirements for each programmer also vary.

Global EAP Trends

The majority of countries have both nominative and cohort EAPs (France, Italy, Spain, Denmark, Norway, Brazil, and South Korea). UK, Switzerland, Australia, Israel, and Turkey have nominative programs only and only Germany has a cohort program only. All the programs are under the remit of relevant government health authorities. Commercial provision of drugs/devices in EAP is possible in most of the programs and the price is usually set freely. In the remaining cases, the price is negotiated with relevant authorities. Reimbursement is usually conditional. Full reimbursement is only possible in France, Italy, Spain, and in the License Procedure in Sweden.

There is currently no evidence that these programs expedite the speed at which medicines receive market authorization. Similarly, EAPs do not guarantee market authorization and there is currently no aggregate evidence showing that EAPs will guarantee reimbursement/coverage after marketing authorization.

1.10 To Know More

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