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# EU and US Pricing and Reimbursement for Innovative Medicines

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## Introduction

In both the European Union (“EU”) and the United States (“US”), there is an increasing focus on showing value for innovative medicines. While the mechanisms differ, this demand stems from the same developments - decreasing funds available to payers and increasing prices of innovative medicines. The payers’ responses are similar as well: proposals to limit prices and restrict availability and requiring proof of value of the innovative medicine before there will be an agreement to pay for it at any level.

Finite health care resources, particularly since the financial turmoil of 2007/2008, and the rising cost of new technologies, notably some of the costly new treatments for some rare cancers and other rare diseases<sup>1</sup>, have led payers to conclude that not all new pharmaceuticals can be reimbursed and resulted in turn in a multiplicity of new mechanisms for reimbursement decisions.

## EU - Member State Autonomy

The primacy of the Member States in pricing and reimbursement decisions in relation to medicines expenditure is long established: “*Union action shall respect the responsibilities of the Member States for the definition of their health policy and for the organization and delivery of health services and medical care... and the allocation of the resources assigned to them...*” (Article 168(1) of the 2009 Lisbon Treaty on the Functioning of the European Union – the “Treaty”).

However Article 168(7) of the Treaty confirms that EU action may “...*complement national policies...*” by taking “...*any useful initiative to promote such coordination, in particular initiatives aiming at the establish-*

*ment of guidelines and indicators, the organization of exchange of best practice, and the preparation of the necessary elements for periodic monitoring and evaluation*”.

This means that Member States of the European Union (EU) are free to set the prices of medicinal products and to decide on the treatments that they wish to reimburse. This is subject however to the Transparency Directive (Council Directive 89/105/EEC) (the “Directive”). The Directive aims to ensure that national pricing and reimbursement decisions are made in a transparent manner and do not distort the functioning of the EU Internal Market. These controls are however relatively high level in concentrating largely on setting time limits for pricing and reimbursement decisions, requirements for objective criteria and a requirement for an appeal mechanism. They do not address the merits of the decision nor do they envisage many of the price and reimbursement mechanisms that we discuss below. Over the past few years the EU sought to pass new legislation to bring the Directive up to date but this initiative was recently abandoned on political grounds.

The freedom of EU Member States in this area has led to prices varying greatly between Member States. A UK Department of Health, price analysis in 2009 among 11 Member States of 150 pharmaceuticals demonstrated a 25% difference between the lowest and highest-prices. It was noted in the US prices are significantly higher than any of the 11 Member States.

In part the differences have been shown to be a consequence of a positive link between per Member State income per capita and spending on pharmaceuticals per capita.

However, Member States use a variety of tools, both on the supply side (both for determining prices and reimbursement) and on the demand side (encouraging healthcare professionals to be mindful of cost or requiring patients to pay a share of the costs of their medicines).

As a consequence of these differences, distributors and others in the supply chain may purchase pharmaceuticals in Member States with lower prices and re-sell them in another where prices are higher (“parallel trade”). Attempts by the industry to rein in such EU trade have generally been rejected by the Court of Justice of the European Union as contrary to the core EU principle of the free movement of goods, notwithstanding that most of the difference in price is taken by the traders.

There are three broad categories of Member state interventions:

- Methods to control the prices of medicines (especially where still in patent). These include direct price regulation, reimbursement controls or profit or regulation of allowable profits and rates-of-return. External referencing pricing is used in all EU Member States except the UK and Sweden, whereby the Member State sets the national price of a medicine by reference to the prices of that medicine in other Member States, with the Member State in question adopting either the average or even the lowest price.
- Controls on prescribing (whether through financial and non-financial incentives or penalties), dispensing (including policies encouraging or enforcing generic substitution or limiting pharmacy margins) and cost-sharing demands on patients.

- Reimbursement strategies for new medicines (especially high-priced products) commonly based on health technology assessment to determine whether a new product provides value for money in relation to existing comparators. Such an assessment is used to determine whether such new medicine should be reimbursed. Where the benefit is uncertain, schemes such as risk-sharing agreements have been introduced whereby, for instance manufacturers are only paid in for patients where the treatment proves effective.

In this review we focus on the third of these categories as it is in this area where there are more developments and which show interesting parallels with the unfolding US experience.

## US – The Role of Insurance Plans

In the US, as in the EU, the success of a new pharmaceutical or biological product is largely dependent on the extent to which government and private insurance plans reimburse health care providers that purchase the products. Unlike the EU, insurance plans typically offer separate coverage for self-administered prescription drugs dispensed by pharmacies, such as oral medications or creams, and drugs that are administered by health care professionals in an outpatient setting, for example by injection or infusion. Although the rules and policies governing payment pursuant to these distinct benefits may differ based on mode of delivery and channel of distribution, cost control measures and their impact on the market for new drugs is similar. Physician preferences as well as patient demand may be influenced by breakthrough therapies, but the market for these drugs is increasingly impacted by managed care reimbursement policies.

As a general rule, pharmacies do not influence the selection of unique, branded products, but acquire them to meet a need, that is, to fill a particular prescription. Thus, prescribing practices drive these sales. However, for the majority of patients who are covered by health plans, their payment policies effectively determine what is sold. The amount paid a pharmacy for a prescription depends on the structure of the health plan's pharmacy benefit and decisions of its Pharmacy and Therapeutics ("P&T") Committee.

## Managed Care in the US

Plans manage prescription costs through use of a formulary, which lists the drugs the plan will cover and restrictions it will place on

payment for the drug. A formulary is designed to deter a beneficiary from accessing an expensive drug through coverage denials and conditions on payment that limit choice. Accordingly, P&T Committees conduct clinical and cost effectiveness analyses to determine the content of their formularies. The Department of Defense ("DoD") formulary decision-making process for TRICARE, the military health care program, is somewhat open. DoD publishes the meeting minutes of its P&T Committee and Beneficiary Advisory Panel meetings, which are required by regulation. 32 C.F.R. §199.21(g). However, most P&T decisions are not transparent.

Common managed care techniques to control costs include:

- Managed formularies in which the number of covered drugs in a therapeutic class is limited and preferred drugs have lower co-payment requirements. Through this technique, plans essentially commoditize products by minimizing clinical differentiators and making cost the predominant factor in their coverage determinations.
- Step edits in which the patient must first try a lower cost alternative before the plan will pay for the more expensive drug.
- Prior authorization, which conditions reimbursement of a drug on approval by the plan. Plans are increasingly subjecting new, expensive therapies to prior authorization, based on clinical assessments, comparative effectiveness, and cost benefit analyses. Often, prescribing physicians are required to support their patients' medical need for the drug. Such an administrative burden has the intended effect of influencing what the physician prescribes.

Pharmacies are often reluctant to purchase products that may be dispensed infrequently due to payment restrictions. In order to overcome these impediments to sales of new drugs, manufacturers provide support to physicians to facilitate prescription authorizations and offer direct subsidies to privately insured patients in the form of co-payment assistance. As high-priced specialty pharmaceuticals and personalized medications become more prevalent, cost control techniques will likewise increase, leading to greater tension between beneficiaries and the plans that pay for their medications. It remains to be seen whether there is sufficient competition for enrollees among plans to reverse this trend.

The influence of managed care policies on the market for innovative drugs is particularly keen for physician-administered drugs,

because clinics and physician practices generally finance the cost of the treatment, acquiring product and chasing payment. These providers are increasingly unwilling to pay high prices at the risk of inadequate payment. Drugs and biologicals administered by physicians are covered by Medicare Part B, the government program that provides an outpatient medical benefit to the elderly, and many of these products are high priced innovative therapies for treatment of cancer and other diseases and conditions affecting an older population. Current Medicare Part B physician payment rules reflect the influence of payment policies for drugs and the impact of these policies is increased when private plans follow Medicare rules. Payment for a single source drug or biologic under Medicare Part B is based on the weighted Average Sales Price (ASP) for that product plus an additional 6% of the ASP. Social Security Act ("SSA") § 1847A(b)(1),(4). Because providers are reimbursed their cost, this formula tends to create an incentive to buy the higher priced product. For that reason, and to encourage the acquisition of biosimilars, the Affordable Care Act neutralized the incentive by creating a hybrid payment method for biosimilars in which providers receive the same amount over cost regardless of which product they select – a physician acquiring a less costly biosimilar receives the same profit without having to finance the higher cost. SSA § 1847A(b)(8).

On the other hand, use of an average commercial price as a surrogate for actual cost of an expensive drug is unfair to smaller practices that lack purchase power and may not recoup their entire acquisition cost. It also tends to create downward price pressure as customers seek to avoid paying more than the average price, which has the effect of continuously ratcheting down prices. In order to recoup their investment, manufacturers of new drugs must price them high at launch due to the inevitable price erosion. This situation is exacerbated when a billing code encompasses multiple products. Recently, the Centers for Medicare and Medicaid Services (CMS) decided to assign the same billing code to all biosimilar products referencing the same biological product, which means physicians will be paid the same rate based on a weighted average selling price of all the biosimilar products covered by the billing code, regardless of what they actually paid. 80 Fed. Reg. 41686, 41961-41962 (July 8, 2015). Although CMS to date has assigned unique billing

codes to innovator products, assigning multiple products to a billing code based on therapeutic equivalence has been an effective means of reducing their selling price.

### US Price Controls

Federal government programs also control costs through mandatory discounts and rebates that significantly reduce manufacturers' realization on drugs purchased or reimbursed with federal dollars, and penalize price increases after launch, which encourages manufacturers to price their products higher initially. See, e.g., SSA §1927, 42 U.S.C. §1396r-8 (Medicaid Drug Rebate Program); Veterans Health Care Act §603, 38 U.S.C. §8126 (federal procurement programs). These price controls apply not only to copycat drugs but also to orphan drugs where the market is small and potential sales are limited, and breakthrough therapies requiring years of development. In some cases, manufacturers are required to provide discounts to primary and secondary insurers and in other cases they are required to provide discounts on both purchase and reimbursement transactions on the same unit. Further, the mandatory discounts are a floor. Competitive pricing for formulary position begins at that level. For example, DoD conducts class reviews in which it solicits contingent discounts and rebates above the mandatory minimum based on awarded formulary position. Similarly, State Medicaid programs compete contracts for supplemental rebates above the national mandatory rebate amount. Consequently, manufacturers introducing new drugs into the market must take these mandatory price reductions into account when establishing the launch price and projecting revenue.

### Health Technology Assessment ("HTA")

HTA (commonly described as "value-based assessment or "value-based pricing"), and often referred to in the US as "healthcare effectiveness and outcomes research" ("HEOR"), is used to make pricing and reimbursement decisions in a growing number of Member States. It involves the use of economic techniques to assess the value of new and existing medicines whereby a drug's cost-effectiveness as against its comparator will determine the price premium over its existing product and hence the pharmaceutical's price.<sup>2</sup>

It commonly involves an analysis of one or more of cost-effectiveness, cost-benefit,

cost-utility and/or cost-minimization depending on the outcome measures to be evaluated and the relative cost of comparators. The resulting of cost effectiveness and cost utility analysis is often represented as an incremental cost-effectiveness ratio (ICER) in Euros or Pounds per Quality Adjusted Life Year (QALY), which is a combined measure of quality of life and length of life as a result of an intervention and then enables a determination as to its level of therapeutic benefit and cost, in relation to its comparators.

In the EU, this will be then considered against an upper limit of what the health care provider is prepared to pay for an additional unit of benefit such as a 'QALY'. Depending on the Member State concerned, the assessment may be a more or less direct tool for price setting and reimbursement. The UK combines rate-of-return controls with HTA appraisals which some consider to be a 'perfect storm' of cost containment!

The evidence accepted by Member States and the weight afforded to it will vary between Member States. This inevitably results in differences in prices and coverage decisions across the Member States so that patient access to such medicines also varies across the EU. This can be aggravated when manufacturers refuse to launching a product in a low price market, given the risks of external price referencing to that price.

There is relatively little EU coordination at present but the European Network of Health Technology Assessment ("EUnetHTA") is developing a role as the umbrella organization for the 100 or so HTA bodies across Europe. EUnetHTA's core model is to provide a framework for HTA assessment in an efficient, structured and systematic way. Formed in 2006, its gestation was slow but it has now been endorsed by the EU directive on cross border healthcare (Directive 2011/24/EU), establishing a framework for its future aims. EUnetHTA's future role in European healthcare is uncertain with some commentators suggesting that it could pave the way for a centralized HTA agency.

In the U.S., there has been a similar demand among state government and private insurer payers, as well as physician groups, to limit prices, show value through HEOR, and restrict availability of high cost innovative medicines. In the absence of a centralized purchasing and HTA entity in the US, there have been a variety of reactions. These include efforts to tie the pricing of drugs to a showing of how well they perform, efforts by private insurers and state governments to

stop covering certain drugs or to impose stringent limits on their availability for prescription for patients, which have been met with litigation challenging the legality of such restrictions, and suggestions by State Medicaid directors that the federal government impose price controls for certain high cost specialty drugs.<sup>3</sup> The type and scope of HEOR and health economics information that manufacturers can properly disseminate to payers consistent with FDA restrictions, however, remains unclear and controversial, and likely will be the subject of judicial challenges as well in the event of new FDA guidance and enforcement actions.

### Risk-sharing Agreements

For some new and expensive medicines, limited evidence may make assessment difficult, for instance where there uncertainty as to the optimal doses or indications or the patients most likely to benefit. "Risk-sharing" or "performance-based" agreements have been developed, in both the EU and the US, to afford payers a degree of certainty and allow patients access to innovative medicines. Through such agreements, payers may typically seek to manage uncertainty as to clinical value and cost-effectiveness.

These agreements include:

- A medicine being reimbursed on a conditional basis as against pre-defined criteria and if the product fails to meet these targets, the manufacturer may incur price changes or rebates. Alternatively the uncertainty as to value could mean that the payer only agrees to reimbursement in limited cases. If a budget is also fixed and then exceeded the manufacturer may then be liable to return the excess. Alternatively, there may be pre-defined outcomes for individual patients and the manufacturer would bear the costs if those desired outcomes are not achieved.
- The medicine being reimbursed under controlled circumstances, while further evidence is gathered, for example, as to the most appropriate patient populations or the cost-effectiveness of the product. The development within Europe of 'adaptive pathways,' whereby products for unmet needs will undergo an iterative and pre-planned process of an initial approval for a well-defined patient subgroup being extended to a larger patient population as uncertainty is reduced through the collection of post-approval data, will pose reimbursement challenges to Member State payments.

- Disease management or ‘beyond the pill’ deals whereby the manufacturer becomes responsible for the management of treatment of certain patients and offering the payers overall patient management savings in return for a favorable price or coverage.
- Product range deals whereby agreement on a price or reimbursement of an innovative new product may be counter-balanced by reductions or discounts in the prices of others of the company’s products.

In the US, similar contractual risk-sharing arrangements have become increasingly common between manufacturers and private payers. In the absence of a centralized payer for negotiations, manufacturers have also needed to confront potential price discrimination issues among purchasers by reason of certain types of discounts and rebates. In order to gain market acceptance of a high-priced new therapy, as in the EU, manufacturers in the US are offering agreements in which payment is tied to performance based on specific metrics. These agreements are particularly helpful where P&T Committees want clinical data for a longer period of time than is available. For manufacturers, the risk of guaranteed performance is an attractive alternative to lower prices that may impede return on investment in new drugs. This issue has been exacerbated by the increasing demand by payers for most-favored-nation (MFN) clauses protecting them from the potential of not receiving discounts or rebates provided subsequently to other buyers.

### National Budgets and Unlicensed Medicines/Indications

In certain circumstances in the EU the national payers including national healthcare administrations, HTA/ cost effectiveness bodies, social insurance bodies and other governmental agencies, will seek to avoid paying for an expensive new products entirely and instead will sanction or encourage the use of cheaper alternatives – sometimes including either unlicensed medicines or off-label use of medicines for other indications, notwithstanding the availability of the new, licensed preparation.

Notable examples include the following:

- In 2012 France amended the law allowing its authorities to recommend for solely economic reasons off-label use where licensed alternatives existed.
- In 2014 Italy similarly allowed the authorities to make recommendations on cost grounds as to the safety and efficacy of a

given medicine for off-label use.

- In the UK, the National Institute for Health and Care Excellence (NICE), appraised the cost-effectiveness of Avastin® (bevacizumab) against Lucentis® (ranibizumab) in the treatment of wet age-related macular degeneration although the former has only been licensed for oncology indications. NICE has indicated that it plans to continue off-label comparators in the future despite on-going criticism of such practices. Similar comparisons have been carried out by the authorities in Austria, France, Germany and Norway.

These practices appear questionable in the light of three key EU legal principles:

- Article 168(1) of the Treaty states that “*a high level of human health protection shall be ensured in the definition and implementation of all Union policies and activities*” which commits the EU to adopting and enforcing a strict medicines approval system. For Member States to be allowed to put cost before patient safety under these circumstances has been argued to run contrary to this objective.
- EU law provides that medicinal products must receive a Marketing Authorization (MA) before being marketed and used to treat a specific condition. Article 5.1 of Directive 2001/83/EC provides that, at the option of the Member State, a medicine may be excluded from the need for a marketing authorization in order to fulfill special needs, in response to a bona fide unsolicited order from a physician. The cost of treating a patient with a medicine authorized for a given disease is not a relevant criterion to promote unlicensed use. This was confirmed in the case of *Commission v Poland Case C 185/10*, in which the Court of Justice stated that as a “*general principle...the protection of public health must unquestionably take precedence over economic considerations*”. Any decisions to prescribe a medicine off-label should be the concern of the treating physician based solely on the medical needs of the individual patient.
- This question is particularly acute as regards to orphan drugs: the promotion of off-label use would remove the benefit of the 10-year market exclusivity and jeopardize the efforts to encourage pharmaceuticals companies to invest in orphan drugs. Regulation (EC) No 141/2000 (the Orphan Regulation). The recitals provide that it is “*necessary to stimulate the research, development and bringing to the*

market of appropriate medications by the pharmaceutical industry” and under Regulation 9 of the Orphan Regulation “*Member States shall communicate to the Commission detailed information concerning any measure they have enacted to support research into, and the development and availability of, orphan medicinal products or medicinal products that may be designated as such.*”

### Equivalence Policies in the US

In the US, private plans have been broadening their view of therapeutic equivalence, including off-label use of existing products, to expand alternative therapies and competition for preferred formulary status. For example, by enlarging the concept of therapeutic class and minimizing clinical outcomes as differentiators, plans create competition in which cost effectiveness may outweigh clinical effectiveness. Plans that favor dispensing of generic drugs are also able to exclude new drugs without generic equivalents. In some cases, a new drug may not be covered if it is deemed equivalent to an over the counter medication. Similarly, if an older drug has a generic equivalent for a particular indication and the FDA approves a New Drug Application for a new indication for the same or similar formulation, the market may be limited, because health plans may not cover the new, more expensive drug that is priced to recoup research and development for the new indication. Instead, plans will pay for prescriptions of the generic drug used off-label.

Although government plans like Medicaid have historically used a more restricted view of therapeutic equivalence for coverage and payment purposes, and provided more access to new drugs, that has begun to change. For example, there is political pressure to change the Medicare Part D regulations to give the plans more flexibility in structuring their formularies. This pharmacy benefit program for the elderly is implemented through private plans under contract with the government that are subject to regulation. For a drug to be covered by a Medicare Part D Plan, it must be a prescription drug approved by the FDA, used for a medically accepted indication, meaning the use is supported by citation in one of the compendia specified in statute or agency guidance, and not excluded by statute (*e.g.*, drugs used for cosmetic purposes). 42 C.F.R. §423.100. Although Part D Plans have dis-

cretion in how they structure their formularies, currently, certain rules apply.

- Formularies cannot be designed to discriminate against particular patient populations. As a safe harbor, Part D Plans can use the same classes and categories of drugs used in the United States Pharmacopeia (“USP”) Model Guidelines. Medicare Prescription Drug Benefit Manual, CMS Pub. No. 100-18, Chapt. 6, §30.2.1.
- Formularies must include two chemically distinct drugs in each class and category, unless only one drug is commercially available. Medicare Prescription Drug Benefit Manual, CMS Pub. No. 100-18, Chapt. 6, Appendix C, Att. I, §C.
- For certain protected categories, including certain immunosuppressants, antidepressants, antipsychotics, anticonvulsants, antiretrovirals, and antineoplastics, formularies must include all drugs in the category. Medicare Prescription Drug Benefit Manual, CMS Pub. No. 100-18, Chapt. 6, §30.2.5.

Since enactment of the Medicare Modernization Act, which established the Part D program, there have been proposals to relax these requirements to facilitate cost containment measures. Further, benchmark plans applicable to state exchanges implementing the Affordable Care Act are not subject to the same restrictions applicable to Medicare Part D, and exchanges have some discretion in determining the category to which a drug is assigned. How a drug is classified can

have a big impact on its price and utilization.

### Conclusion

Budgetary constraints and the rising cost of many new innovative medicines will continue to put great stress on the payment and reimbursement systems of both the EU and the US. Effectively addressing these twin pressures that are common to both will require joint exploration and exchange of approaches. Simple efforts to deny access by patients to often life extending and enhancing innovative medicines will be difficult to maintain in view of physician and patient opposition and the consequent lack of political will to do so. Imposition of price controls or drastic price reductions in reimbursement for innovative medicines risks significant adverse effects on pharmaceutical research and development and on addressing complex diseases for which there is no currently effective therapies.

Properly assessing the cost of innovative medicines in relation to how well they work for patients is thus imperative in addressing these twin pressures. Decrying prices of new innovative medicines in isolation is misguided and unhelpful. It is clear that, notwithstanding high costs, the overall economic effects of use of an innovative medicine may be positive for the healthcare system.<sup>4</sup> To develop both proper and broadly acceptable HTA and HEOR mechanisms, however, will re-

quire sustained and coordinated attention by manufacturers and payers in both the EU and the US to several fundamental issues:

- Development of broadly agreed-upon research methodologies for HTA and HEOR.
- Transparency in utilizing such methodologies by payers in interpreting the evidence.
- Broadening HTA and HEOR analyses to incorporate not only clinical or cost-effectiveness, but also factors of salient concerns to patients, including quality of life, workplace productivity, and adherence to treatment regimens.
- Sharing of HTA and HEOR evidentiary databases among payers and among regulatory jurisdictions to enhance consistency of access and reimbursement decisions.

With the aging of populations in the EU and US, cost pressures are likely to increase. To safeguard patient access to, and manufacturer development of, new innovative medicines, a coordinated and concerted effort to address pricing and reimbursement is imperative.

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1 See B. R. Hirsch, et al., “The Impact of Specialty Pharmaceuticals as Drivers of Health Care Costs,” 33 Health Affairs 1714 (Oct. 2014).

2 For a detailed review, see S. P. Mahinka, “Imperative: Cost Effectiveness Research,” LMG Life Sciences Guide 2013, at 18-21. See also US Government Accountability Office Report to Congressional Committees, “Comparative Effectiveness Research: HHS Needs to Strengthen Dissemination and Data-Capacity-Building Efforts” (March 2015).

3 See Inside Health Policy (Oct. 28, 2014).

4 See J.D. Chambers, et al., “Despite High Costs, Specialty Drugs May Offer Value for Money Comparable to that of Traditional Drugs,” 33 Health Affairs 1751 (Oct. 2014).