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Being patient: what delays access to new drugs in Europe?

On average, the first citizen to access a new drug in Belgium will wait 13 months longer for it than someone prescribed the same drug in Germany or the UK, despite an EU-wide licensing process. This suggests that country-specific drug regulation—the 'fourth hurdle' faced by drug manufacturers—may go a long way to explaining launch delay across Europe

Variation in the availability of new drugs across Europe presents an economic puzzle.[1] While there is general economic harmonisation in other measures, the disparity in the availability of different drugs can be stark. For example, a survey undertaken by Eurordis in 2004, on the availability of 12 new drugs licensed for sale throughout the EU within the first year of their launch, found that Denmark was the only country where all 12 were available to patients.[2]

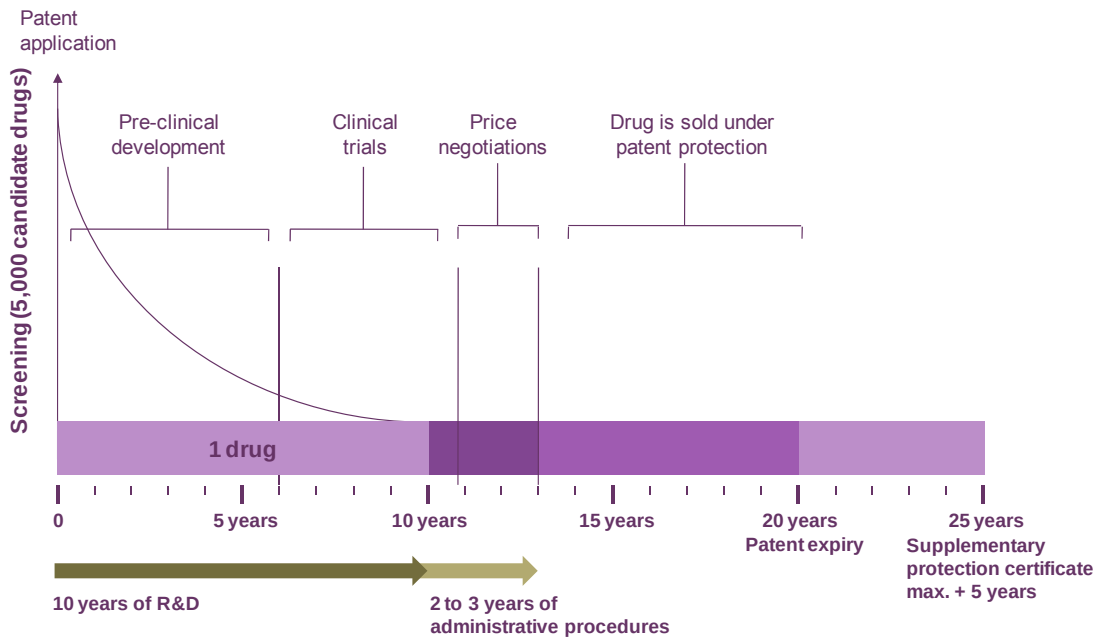
This is even more surprising given that the licensing of drugs for national use, known as 'marketing authorisation', is generally awarded in all European countries at the same time. This means that variation in countries' preferences to adopt new, arguably more risky, treatments cannot fully explain the observed launch delays, and suggests a significant role for country-specific drug regulation—the 'fourth hurdle' faced by drug manufacturers in Europe.

The life cycle of a drug

Prior to the first sale of each new drug, there is a long and costly development and production process, which can be broken down into three stages: pre-clinical development; clinical trials; and price negotiations—as illustrated in Figure 1.

Pre-clinical development and clinical trials relate to research and development (R&D), the longest and most costly part of the process (estimated to cost on

Figure 1 The life cycle of a drug



Source: Oxera.

average €1 billion in 2007).[3] This takes around eight years, but the durations of clinical trials can be quite variable, continuing until the licensing authority considers that sufficient evidence has been shown to demonstrate a drug's safety and efficacy.

Since 1995, when both a centralised marketing approval process and a mutual recognition programme were introduced, marketing authorisation for each drug has usually been granted simultaneously across Europe. Indeed, for biotechnology drugs, marketing authorisation in EU Member States is available only via this centralised procedure.[4] In Europe, therefore, the variation in drug availability cannot be fully explained by variation in the duration of clinical trials. Instead, country-specific entry costs, including local price regulation of pharmaceuticals, are likely to be the key drivers.

European pharmaceuticals price regulation

To allow pharmaceutical companies to recover the sunk costs of R&D, innovative drugs are protected by patents from the competition posed by generic (biochemically equivalent) substitutes. However, the pharmaceutical company is very rarely completely free to determine the sale price of a new drug. First, it may face price competition from therapeutically equivalent, but not biochemically equivalent, drugs (where these exist). For example, a number of different drugs can be effective at lowering cholesterol, all classified as 'statins' but developed under different patents.[5] Alternative treatment approaches can also be an effective constraint on a pharmaceutical company's price-setting ability. In the case of diabetes, for some people, exercise and a careful diet can provide similar benefits to medication. Second, national authorities also often impose some additional controls on national drug prices.

National drug price regulation has two main objectives:

- to limit national drug prices and control national healthcare expenditure. In 2008, total expenditure by European statutory health insurance systems reached €120 billion,[6] covering between 10% and 25% of each country's total healthcare expenditure;[7]

- to promote equal access to drugs for all national citizens. Where drug prices are high, access may be restricted to citizens more able to pay, either directly or through purchasing more comprehensive insurance policies.

Unlike in other price-regulated industries, drug prices are not typically set in line with 'costs'. Instead, value-based approaches are used, whereby the value of the drug—often measured in terms of the cost efficiencies or efficacy advantages that it provides over existing treatments—underlies the regulated price. One reason not to focus on the direct costs involved in developing and bringing a particular drug to the market is to avoid the complex issue of allocating the joint costs of R&D. For each drug that reaches the market, it is estimated that at least 5,000 other potential drugs will 'fail' at some point during the medical testing stages.[8] Although these failed drugs do not provide the full set of benefits of successful drugs, by expanding the frontier of medical science they still provide wider benefits to the industry and society, for which some remuneration should be rewarded. Moreover, if firms are unable to recover the cost of R&D for unsuccessful drugs, they could be forced to leave the market.

Within Europe, the common styles of drug price regulation can be categorised as follows.

- **International (external) reference pricing**: the drug price is capped at either the average or the minimum price of a selection of other, generally European, markets. For example, in Greece the drug price is capped at the lowest EU price, and must be available within at least two of the following countries: France, Switzerland, the UK, the USA, Sweden and Germany.

- **Therapeutic reference pricing**: the drug price is set with reference to the price of therapeutic substitutes. This is the usual way in which drug prices are set in the Netherlands, but is only possible where a therapeutic class of drugs exists.

- **Profit controls**: the total profits earned by pharmaceutical companies are capped. This is the approach taken in the UK, where drug prices are not directly regulated but ex post price cuts may be imposed.

- **Detailed benefit evaluation**: the drug price is set with reference to the expected benefit of the drug, which is determined from clinical evidence but may require further clinical trials. This is required, for example, for some drugs in Switzerland.[9]

It is common for a national regulator to adopt more than one approach. Sometimes this depends on how 'innovative' the drug is—for example, in 2003 France introduced a fast-track scheme for 'life-saving' drugs.[10] In the UK, where launch drug prices are not directly regulated, certain drugs are referred to the National Institute for Clinical Excellence (NICE) for guidance over their use under National Health Service (NHS) reimbursement, and may not be approved for NHS use if the price is too high.[11]

How can drug price regulation affect the availability of drugs?

Experience shows that care is required in implementing drug price regulation. The G10 Medicines Group, a temporary European Commission sub-committee established in order to investigate how innovation and the provision of drugs in the EU could be improved, concluded:

> The price negotiating systems and reimbursement structures in a number of Member States can lead to significant delays[12]

A consideration of the incentives and constraints that pharmaceutical companies face can help to understand why price negotiations can result in such delays.

The decision to launch a drug in any market once it has been developed depends on whether the expected profits from future sales in that market are sufficient to cover the expected cost of local entry. The expected cost of entry should be interpreted as the opportunity cost of entry—ie, it should not be restricted to the direct monetary costs of local entry. For example, when the firm has sufficient resources to enter only one market at a time, or when parallel exports[13] reduce the volume of sales abroad, the opportunity costs will include any forgone sales in other markets. There are therefore three mechanisms through which drug price regulation can affect the availability of drugs in each market:

- by reducing the expected price of local drug sales;
- by increasing the cost of, and timescales for, entering the regulated market;
- by increasing the opportunity cost of entering the regulated market by reducing the expected price of drug sales in other markets.

This suggests that in countries where drug price regulation is less stringent (ie, where expected prices are higher and the cost of entry is lower), drugs are more likely to be available. Indeed, statistical analysis confirms this to be the case. For example, when considering the launch of 375 new drugs in 15 countries, including nine EU Member States, Danzon and Epstein found that higher competitor prices (which represent the impact of local regulation on the expected launch price) significantly increased the probability of a drug being available.[14]

This also suggests that regulation in one market might negatively affect the availability of drugs in other markets. As explained below, where one market references the prices of another, or (parallel) imports its drugs, this can discourage entry into the referenced/exporting market.

Over time, if the expected (opportunity) cost of entry falls, or the regulated price rises, an initial decision by the pharmaceutical company not to launch in a particular country might be reversed. When this is the case, access to the drug in this market is delayed relative to other markets. Two reasons for why the opportunity cost of entry to a country might decrease over time are as follows: the launch is delayed; and the fixed cost of entry falls. These are explained in detail below.

The launch is delayed

In the presence of parallel trade and external price referencing, delaying launch in a low-price market can reduce the opportunity cost of local entry.

At present, parallel trade is an issue specific to Europe, where patent rights are exhausted at a regional (as opposed to a national) level.[15] This means that a drug sold in any EU Member State can be freely traded throughout Europe without the consent of the originating pharmaceutical company, reducing the extent to which a pharmaceutical company can price-discriminate between EU Member States. The benefits of parallel trade continue to be strongly debated, and a summary of the potential welfare effects was provided in a previous issue of *Agenda*.[16] One cause of concern relevant here is the negative impact on drug availability in the exporting market: to limit parallel trade, the pharmaceutical company may choose to delay the launch of a drug in low-price markets until either the price in higher-price markets has fallen, or non-price barriers to parallel trade have been established, as follows.

- Drug prices may fall from their initial launch price level due to subsequent regulation. For example, in Germany, drug prices are regulated only after the drug has been classified, which can take up to two years. Alternatively, drug prices may fall due to increased competition from additional therapeutic substitutes or (after patent expiry) generic substitutes.

- Non-price barriers that pharmaceutical companies have adopted in order to limit parallel trade include differentiating the packaging between countries—for example, providing health and safety information only in the destination country's language (EU law requires the parallel importer to provide health and safety information in the local language); and marketing the drug with different brand names in different countries.[17]

External price referencing is common both inside and outside the EU, and creates an incentive for pharmaceutical companies to delay launch in low-price, reference markets until after prices in referee markets

have been agreed. By agreeing prices in referring markets first, the pharmaceutical company hopes to maintain price differentials between markets and increase returns from drug sales.

The negative impact of parallel trade and external price referencing on the availability of drugs in exporting and reference markets has been found in a number of independent analyses.[18] For example, the aforementioned research by Danzon and Epstein found that the median launch lags for Greece, Spain and Portugal (which are common sources of parallel pharmaceutical exports in the EU) range between 21 and 34 months—double the delay observed in the UK, Germany, Sweden and the Netherlands (which are common destinations for pharmaceutical imports). This pattern confirms the intuition that a firm will launch last in low-price markets, to minimise the impact from any external price referencing of such markets abroad.

The fixed cost of entry falls

Over time, the fixed cost of launching a particular drug in a particular market may fall.

Launching a drug usually involves country-specific price negotiations, which can present an additional bureaucratic hurdle for the pharmaceutical company. With greater launch experience, particularly with local regulators, this hurdle may decrease over time. There is some statistical research supporting this hypothesis. For example, Kyle finds that pharmaceuticals invented by firms that are active in many countries are likely to reach more markets.[19]

To encourage the use of the drug, the pharmaceutical company may consider it appropriate to promote the benefits of the drug to prescribing doctors. Due to economies of scale in marketing, it is likely to be more cost-efficient for a pharmaceutical company to undertake such activities for multiple drugs simultaneously. This creates an incentive for the firm to delay the launch of one drug until a second drug has also achieved marketing authorisation. This is another reason why the fixed cost of launch might decrease over time.

Other factors might also explain why delaying the launch of drugs in certain markets can be more cost-efficient for a pharmaceutical company. For example, the existence of credit constraints on pharmaceutical companies is likely to result in their launching in markets in the order of their expected profitability.

A potential for European-wide drug price regulation?

With expenditure on pharmaceuticals reaching 25% of national healthcare expenditure in some European countries, the importance of managing drug prices should not be understated, particularly when public spending is under pressure.[20] However, the potential adverse effects of drug price regulation on the availability of drugs domestically emphasises the importance of careful consideration when implementing national regulation. In particular, the national regulator needs to trade off any cost savings from lower drug prices against the potential for forgone health benefits from fewer or delayed drug launches. Where the new drug provides cost efficiencies over existing treatments, it might even be the case that drug price regulation could result in delays without an overall reduction in total healthcare expenditure.

There has been increasing coordination between EU Member States in terms of pharmaceuticals regulation. This was marked by the creation in 2005 of the High Level Pharmaceutical Forum to examine the potential efficiency gains within a European high-level platform, which in 2008 provided ten recommendations for the market.[21] The work of the Forum was supported by three expert working groups, one of which—the Pricing and Reimbursement Working Group—focused on the potential for efficiencies in EU country-specific drug regulation.

Since national drug price regulation is not costless (often involving resource-intensive cost-effectiveness evaluations) and can have adverse effects on drug availability in other markets, stronger international coordination might lead to welfare improvements.

[1] This article focuses on new innovative drugs, defined as those for which the drug developer receives patent protection, as opposed to new generic drugs for which there is no patent protection.
[2] *Eurordis Newsletter* (2006), April. Available at http://www.eurordis.org/content/improving-patient-access-orphan-drugs-europe. The sample considered drugs with 'orphan' status. This status provides drug developers with additional competition protection and clinical trial tax breaks to encourage the development of treatments for rare diseases.
[3] €1.059 billion (in 2005 prices). DiMasi, J.A. and Grabowski, H.G. (2007), 'The Cost of Biopharmaceutical R&D: Is Biotech Different?', *Managerial and Decision Economics*, **28**, pp. 469–79.
[4] Cohen, J., Faden, L., Predaris, S. and Young, B. (2007), 'Patient Access to Pharmaceuticals: An International Comparison', *European Journal of Health Economics*, **8**, pp. 253–66.
[5] Sweetman, S.C. (2009), 'Cardiovascular drugs', in S.C. Sweetman (ed), *Martindale: The Complete Drug Reference* (36th ed.), London: Pharmaceutical Press, pp. 1155–434.
[6] Efpia (2010), 'The Pharmaceutical Industry in Figures'.
[7] OECD Health Data 2010, available at http://www.oecd.org/document/16/0,3343,en_2649_34631_2085200_1_1_1_1,00.html.
[8] See http://www.efpia.eu/content/default.asp?PageID=361.
[9] Office of Fair Trading (2007), 'Pharmaceutical Price Regulation Scheme: Annexe K', February.
[10] The fast-track system is available to all drugs categorised as ASMR I-III—ie, life-saving, disease-modifying or otherwise offering clear therapeutic advantages over existing drugs.
[11] NICE was established in 1999 to end the unfair 'postcode lottery', in which access to certain treatments under the UK NHS varied between (regional) Primary Care Trusts (PCTs). Since 2002, all PCTs have a statutory obligation to fund any prescribed, NICE-approved treatments.
[12] European Commission (2002), 'High Level Group on Innovation and Provision of Medicines in the European Union: Recommendations for Action', May.
[13] When a drug is imported into a market without the permission of the pharmaceutical company holding the intellectual property rights, such exports are commonly referred to as 'parallel exports'.
[14] Danzon, P. and Epstein, A. (2008), 'Effects of Regulation on Drug Launch and Pricing in Interdependent Markets', Working Paper 14041 NBER, May.
[15] US proposals to constrain drug prices have considered the adoption of external referencing and drug importation.
[16] Oxera (2008), 'Shades of Grey: Arguments For and Against Parallel Trade in Pharmaceuticals', *Agenda*, October.
[17] Kyle, M. (2007), 'Strategic Responses to Parallel Trade', NBER Working Paper Series, w12968, March.
[18] These include Danzon, P. and Epstein, A. (2008), 'Effects of Regulation on Drug Launch and Pricing in Interdependent Markets', Working Paper 14041 NBER, May; Danzon P., Wang, Y. and Wang, L. (2005), 'The Impact of Price Regulation on the Launch Delay of New Drugs—Evidence from Twenty-Five Major Markets in the 1990s', *Health Economics*, **14**, pp. 269–92; Kyle, M. (2007), 'Pharmaceutical Price Controls and Entry Strategies', *The Review of Economics and Statistics*, **89**:1, pp. 88–99, February.
[19] Kyle, M. (2007), 'Pharmaceutical Price Controls and Entry Strategies', *The Review of Economics and Statistics*, **89**:1, pp. 88–99, February.
[20] OECD Health Data 2010, available at http://www.oecd.org/document/16/0,3343,en_2649_34631_2085200_1_1_1_1,00.html.
[21] European Commission (2008), 'High Level Pharmaceutical Forum 2005–2008', October.

If you have any questions regarding the issues raised in this article, please contact the editor, Dr Gunnar Niels: tel +44 (0) 1865 253 000 or email g_niels@oxera.com

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