The root cause of unavailability and delay to innovative medicines: Reducing the time before patients have access to innovative medicines

Executive Summary[1]

The unprecedented speed of innovation exhibited over the last five years and the promise of the industry pipeline[2] provides an important opportunity to improve outcomes for patients. There is common agreement that the value of innovation is only realised when patients benefit from advances in treatment. However, a significant number of medicines are not available across all European Union (EU) markets.[3]

EFPIA for many years has looked at the length of time it takes for medicines to be made available. As illustrated by the most recent data in the Patient W.A.I.T. Indicator Survey in 2022, the average time to reimbursement for innovative treatments across EU and European Economic Area (EEA) countries has reached 517 days, ranging from 128 days in Germany to 1351 days in Malta. There are patient access inequities within Europe, with significant differences across countries in the number of products that are available at a point in time and that the time taken prior to national reimbursement also varies significantly from one country to another. The industry shares concerns about these delays and recognises that delays and the unavailability of medicines harm patients. Moreover, there is need to address delays as European economies and healthcare systems continue to recover from COVID-19.

Over the past three years, EFPIA has documented the root cause of access inequality and found there are 10 interrelated factors that explain unavailability and delay (defined as length of time from European marketing authorisation to availability at Member State level) to innovative medicines, building on the WAIT analysis.[4] These are rooted in the medicines access systems and processes in the EU member states and the corresponding impact on commercial decision-making. They range from a slow regulatory process to late initiation of market access assessment, to duplicative evidence requirements, to reimbursement delays, and local formulary decisions. As the root causes are multifactorial, they can only be solved by different stakeholders working together.

1 Terminology: This paper has adopted the terminology used in the updated W.A.I.T. analysis. Definitions are in the glossary.

2 See EFPIA Pipeline Review 2022 Update, IQVIA project report, August 2022. Accessible at: https://www.efpia.eu/media/676661/iqvia_efpia-pipeline-review_final-report_public-final.pdf

3 This paper focuses primarily on root cause of delay for centrally approved products by the EMA. It should be noted that there are non-centrally approved medicines for which many of these root causes would also apply.

4 https://www.efpia.eu/publications/downloads/efpia/the-root-causes-of-unavailability-and-delay-to-innovative-medicines/

Table 1: The root causes of delays and unavailability

Category	Potential root causes
The time prior to marketing authorisation	1. The speed of the regulatory process 2. Accessibility of medicines prior to marketing authorisation
The price and reimbursement process	3. Initiation of the process 4. The speed of the national timelines and adherence
The value assessment process	5. Misalignment on evidence requirements 6. Misalignment on value and price 7. The value assigned to product differentiation and choice
Health system constraints and resources	8. Insufficient budget to implement decisions 9. Diagnosis, supporting infrastructure and relevance to patients
The sub-national approval process	10. Multiple layers of decision-making process

The industry considers that the root causes of unavailability and delay could be addressed through collaborative work with Member States, European Commission and other stakeholders on proposals to improve availability and reduce delays. These must start from the beginning of the process, including proposals to speed up the regulatory process, delivering safe and high-quality diagnostics, vaccines and treatments to patients as fast as possible. The industry welcomes the commitment to address regulatory barriers. However, these will not improve patient access to innovative medicines by themself. EFPIA and its members have worked on a series of concrete access proposals to improve patient access to innovative medicines and reduce inequalities across Europe. These include inter alia:

- **A commitment from the industry to file pricing and reimbursement applications in all EU countries no later than 2 years after EU market authorisation, provided that local systems allow it**. This commitment reflects the joint ambition of industry and society to make innovation for unmet health needs available for patients and health systems across Europe as soon as possible.
- **The creation of a portal where marketing authorisation holders (MAH) can provide timely information regarding the timing and processing of pricing and reimbursement (P&R) applications in the various 30 European countries,** including the reasons why there is a delay in the P&R decision or why the MAH has not filed in a particular market.
- **A conceptual framework for Equity-Based Tiered Pricing (EBTP)**, to ensure that ability to pay across countries is considered in the prices of innovative medicines, anchored in a principle of solidarity between countries, to reduce unavailability of new medicines and access delays.

- **Novel payment and pricing models**, when used appropriately and tailored to the situation, can accelerate patient access, allowing payers to manage clinical uncertainty, budget impact and sustainability of the healthcare system, whilst providing sufficient incentives for innovation.[5,6]
- Contributing to achieving an **efficient system of European assessments of relative efficacy at time of launch** in the context of the implementation of the HTA Regulation.

The present report is the fourth edition of the root cause analysis first released in June 2020, which was used as a basis for discussion with several EU and national policy-makers and stakeholders. The present report takes stock of these discussions, updates the data and evidence and further articulates how policy proposals can address some identified hurdles in a collaborative and sustainable way.

1.1. Background and approach

The unprecedented speed of innovation exhibited over the last five years and the promise of the industry pipeline provides an important opportunity to improve outcomes for patients. Innovative medicines have already significantly increased survival, delivering treatments to patients with chronic diseases and those with previously untreatable cancers, treating genetic conditions for which there were no existing medicines and eliminating some infectious diseases.

There is common agreement that the value of innovation is only realised when patients benefit from advances in treatment. Everyone involved in healthcare – from patients to service providers, researchers to clinicians, pharmaceutical companies to payers – wants to see patients across Europe get access to new treatment options.[7]

The importance of addressing unavailability and delays was highlighted in the EU Pharmaceutical Strategy (see Box 1).

5 https://efpia.eu/media/554543/novel-pricing-and-payment-models-new-solutions-to-improve-patient-access-300630.pdf

6 https://www.efpia.eu/media/602581/principles-on-the-transparency-of-evidencefrom-novel-pricing-and-payment-models.pdf

7 https://www.efpia.eu/news-events/the-efpia-view/blog-articles/how-long-should-you-wait-for-a-new-medicine-europe-s-post-code-lottery/

Box 1: Discussion of root causes in the EU Pharmaceutical Strategy

> *"Innovative and promising therapies do not always reach the patient, so patients in the EU still have different levels of access to medicines. Companies are not obliged to market a medicine in all EU countries; they may decide not to market their medicines in, or withdraw them from, one or more countries. This can be due to various factors, such as national pricing and reimbursement policies, size of the population, the organisation of health systems and national administrative procedures resulting in smaller and less wealthy markets in particular facing these problems."*

Source: European Commission, EU Pharmaceutical Strategy[8]

The European Commission is currently preparing a revision of the EU Pharmaceutical Legislation. It is anticipated that this will include stepping up co-operation with and among Member States on the affordability of medicines. We understand that some of the proposals being discussed would require Marketing Authorisation Holders (MAHs) to market or supply all EU Member States within a fixed timeframe in order to satisfy requirements for regulatory data protection (RDP). For the reasons explored in this paper, primarily that the root causes of unavailability and delay are multifactorial (many of which extend beyond the control of MAHs), this requirement may be unattainable in practice.

Further, the industry has deep concerns regarding the use of regulatory tools designed for medicines authorisation being applied to address availability issues that are within the remit of Member States.[9] In most countries, the inclusion of the product on the reimbursement list will determine availability and access. Any requirement for MAHs to place a centrally authorised medicine on the market and provide a continuous supply in all Member States (including small markets) within a certain period from authorisation, or any provision allowing early entry of generics in the EU market if a centrally authorised medicine is not launched in all Member States within a given number of years of granting the marketing authorisation, could have the opposite effect on developing and commercialising innovation on several Member States' publicly funded markets, significantly reducing patient access to innovation.

The industry shares the concern about these delays, recognises that delays and the unavailability of medicines harm patients, and agrees that there is a need to act urgently to address these longstanding issues. The purpose of this paper is to explain the different factors that could explain unavailability and delay for patients across the EU and the degree to which these are supported by the most recently available data. On the basis of a common understanding, and focusing on the needs of patients, collaborative solutions can be found that address the issues raised in the report.

8 Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and The Committee of the Regions, Pharmaceutical Strategy for Europe COM/2020/761 final

9 RDP is an important form of protection for all products where strong patent protection is no longer available because of a long and challenging development process, or in the case of repurposed molecules for instance. A reduction of RDP could have a material impact on investments decisions and sends the wrong signals in terms of Europe's innovation agenda and global competitiveness.

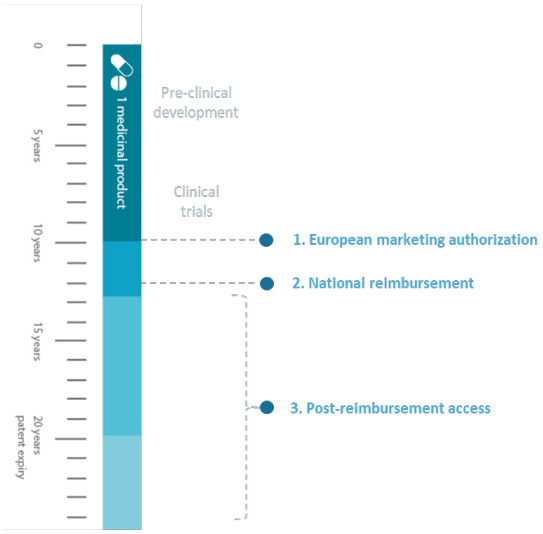
1.2. What do we mean by availability and delay?

In the European Union, once a new treatment has gone through a process of ten years of research and development on average, three further milestones have to be reached before patients have access to it (see Figure 1):

- A European marketing authorisation needs to be granted, confirming the quality, safety and efficacy of the therapy.
- Authorities within countries have to secure national (and regional) reimbursement of the therapy under an insurance or reimbursement scheme, in order to secure the adequate provision of medicines to all patients. In some cases, products may be available without reimbursement on the private market, but this does not ensure wide access to the patient population.
- Once reimbursed, innovations need to reach the people they are intended for and should be used in accordance with their labels, the latest scientific insights and relevant treatment guidelines (post-reimbursement access).

This paper focuses on availability and delays – so we focus on the first two milestones.

Figure 1: Milestones that must be reached to bring innovative therapies to patients



Milestone 1: European marketing authorization

A European marketing authorization is granted when the European Medicine Agency (EMA) positively evaluated:

- ✓ Quality: Is the quality of the manufacturing process up to standards?
- ✓ Safety: Is the therapy safe?
- ✓ Clinical efficacy: Is the therapy effective?

This regional authorization takes away the requirement to seek marketing authorization for new medicines from each member state separately.

Milestone 2: National reimbursement

European countries need to make evidence-based decisions on public healthcare expenditures. To inform reimbursement decisions for innovative oncology therapies, typical questions that need to be answered by national HTA bodies are:

- ✓ Medical need: Does this therapy address a health need?
- ✓ Relative clinical effectiveness: Is it more effective than current therapies?
- ✓ Cost-effectiveness: Is the price a good reflection of the added value?
- ✓ Budget impact: Can we afford the overall costs of this therapy?

This is done separately by each country. How countries make these decisions varies, leading to significant disparities in patient access throughout Europe.

Milestone 3: Post-reimbursement access

Once reimbursed, innovations must reach the people they are intended for and must be used well. This requires:

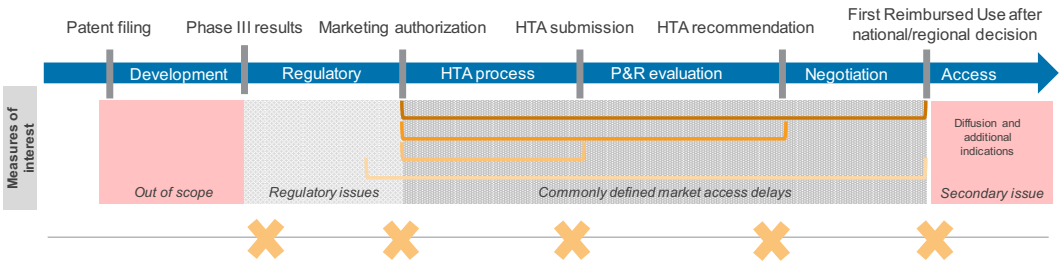
- ✓ Administration: Finalization of administrative procedures and allocation of budget
- ✓ Integration: Adequate health system infrastructure and oncology care pathways
- ✓ Prescription: Prescriber awareness
- ✓ Use: Patient access to the right expertise (geographical, financial, awareness)

Source: EFPIA 2020

It is important to distinguish between a number of different time points (Figure 2):

- The length of time between application for and the granting of marketing authorisation
- The length of time from market authorisation to application for pricing and reimbursement
- The length of time from application for P&R to decision on value assessment
- The length of time from decision on value assessment to reimbursement decision

Figure 2: Types of delay in the availability of medicines

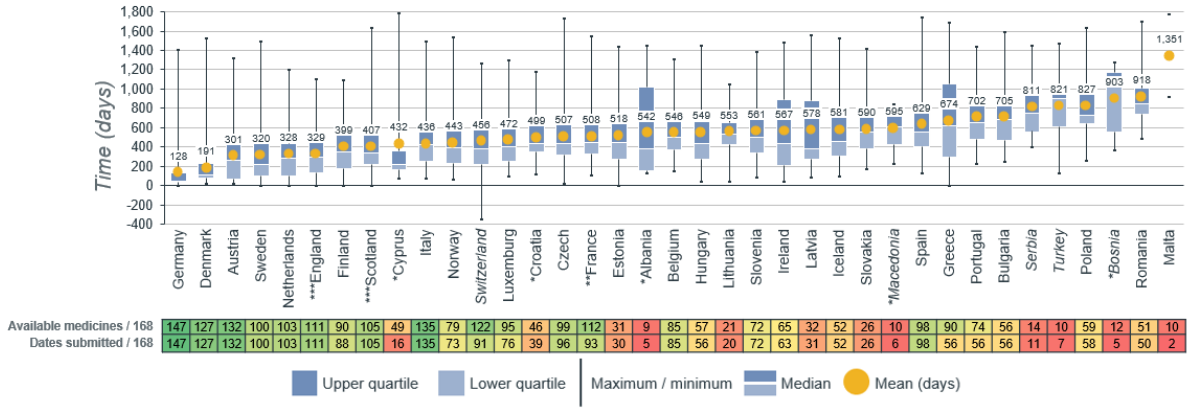


Source: EFPIA

1.3. What is the evidence on unavailability and delays?

EFPIA for many years has looked at the length of time it takes for medicines to be reimbursed. As illustrated by the most recent data in the Patient W.A.I.T. indicator 2022 survey (in Figure 3 below), the average time to reimbursement for innovative treatments across EU and European Economic Area (EEA) countries continues to be as long as 517 days, ranging from 128 days in Germany to 1351 days in Malta.

Figure 3: Mean time to availability in days (2018–2021)



Source: The Patient W.A.I.T. Indicator 2022 Survey

Patients in certain European countries can wait more than ten times longer than patients in other countries to get access to the same medicine. There are some common patterns: typically, patients in Northern and Western Europe get access to new treatments between 100 and 200 days after market authorisation has been granted, whereas patients mainly in Southern and Eastern Europe wait between 600 and 1000 days. This means that at any point in time, availability of medicines varies dramatically across Europe (as shown in Figure 4 below).

This has become more evident as data from more countries has been incorporated into this analysis, now that it enters its fourth year. When this analysis was first published in 2020, time to availability ranged from 127 days in Germany to 823 days in Poland (a difference of 696 days).[10] Now, with data available from Malta for the first time, we see this gap almost

10 EFPIA & CRA (2020) "The root cause of unavailability and delay to innovative medicines" Available at: https://www.efpia.eu/media/554527/root-causes-unavailability-delay-cra-final-300620.pdf [Accessed 2023]

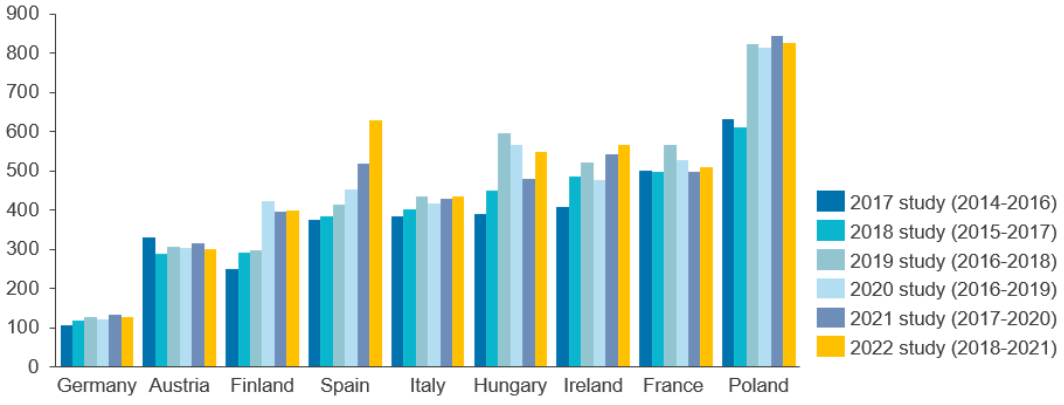
double to 1,223 days of difference between the fastest and the slowest countries in terms of speed of access to new medicines.

Figure 4: Comparing access across European countries

Source: The Patient W.A.I.T. Indicator 2022 Survey

It is important to consider whether delays are getting longer or shorter over time. If we look across all innovative medicines, there is little evidence that delays are reducing – in fact the contrary (see Figure 5).[11]

Figure 5: Comparison of delay over time (mean delays in days)

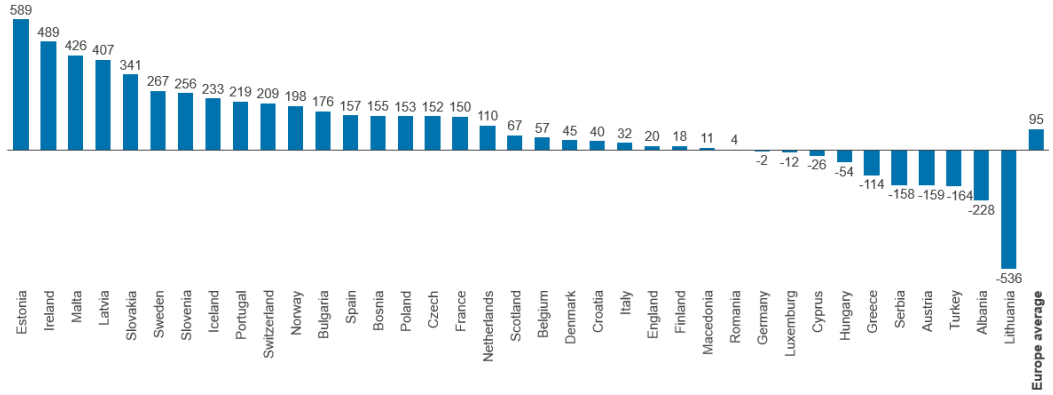


11 This will vary by therapeutic area. According to academic analysis, median times from marketing authorisation to first use of cancer medicines were shorter for medicines launched between 2010 and 2014 versus sample-wide (2000–2014). Time to Entry for New Cancer Medicines: From European Union–Wide Marketing Authorization to Patient Access in Belgium, Estonia, Scotland, and Sweden. Ferrario, A. Health Policy Analysis. *Value in Health* 21(7): 809–821, 01 July 2018

Source: The Patient W.A.I.T. Indicator 2022 Survey

There is also evidence that shows systematic differences between different types of medicines. Although access to oncology medicines appears to be improving, access to orphan medicines continues to vary considerably across EU member states, with long delays and low availability in Central and Eastern Europe (Figure 6).

Figure 6: Difference in the median time to availability for all medicines vs orphan medicines (2018 - 2021)



Source: The Patient W.A.I.T. Indicator 2022 Survey. Note: Positive values mean orphan are slower than all medicines by this number of days.

The analysis set out is broadly consistent with the Organisation for Economic Co-operation and Development (OECD) analysis of the availability of oncology medicines. This found significant differences in availability, with the largest percentage of product/indications approved in Denmark and Germany (91% and 88% respectively). Malta had the lowest percentage of pairs approved and covered 46%.[12]

The observed variation in the length of the delay even within a single sub-region of Europe is also consistent with findings in the literature. A recent academic study investigated access time for new oncology medicines in high-income European countries (Germany, UK, France, the Netherlands, Belgium, Norway and Switzerland) and found that this varied from 125 days to 1415 days. The number of reimbursed oncology medicines in each country ranged from 67% to 100%.[13]

Even within one country, patients can get access to some medicines almost immediately and wait years for others. For example, in Sweden the shortest delay to oncology medicines was 0 days and the longest 1120 days, in Scotland the variance was 105 days to 1337 days, and in Spain 132 days to 1400 days.

12 OECD (2020) "Addressing challenges in access to oncology medicines". Available at: https://www.oecd.org/health/health-systems/addressing-challenges-in-access-to-oncology-medicines.htm [Accessed March 2023]

13 Post, C., Van Laarhoven, H.W.M. and Hollak, C. (2022) Time to access to novel anticancer drugs in Europe, a case study in seven European countries. *Journal of Clinical Oncology* 40(16): 1586.

Although it is not possible to look at every therapeutic area using the W.A.I.T data long delays and variances across countries can also be observed in other therapy areas.[14]

1.4. What are the factors that could explain unavailability and delay?

The cause of delays and unavailability has been the subject of debate for many years. Policymakers and non-governmental organisations (NGOs) have often pointed out that industry uses approaches such as launch sequencing to determine the speed at which products get to market and it appears to be a commercial decision. The industry has often argued that the long, complex practice of applying for reimbursement often delays access to medicines. In reality, there are many interconnected factors that could explain unavailability and it is not possible to untangle their impacts with perfect precision. For example:

- In some markets, even if a product is reimbursed and available it is not in practice used on the market (see Section 1.6). Given this, it is unsurprising that other manufacturers might choose to avoid the cost of applying for reimbursement.
- In other markets, it is a requirement that a product is already reimbursed in a series of other comparable countries.[15] Again, it should be no surprise that application for reimbursement is delayed until access on these markets is achieved.

In other words, the environment affects commercial decisions. This paper seeks to untease these factors. EFPIA has identified 10 factors from 5 different perspectives: the time prior to market authorisation; the pricing and reimbursement process; value assessment criteria; health system constraints and resources; and delay from national to regional approval (Table 2).

Table 2: The root causes of unavailability and delay

Category	Potential root causes
The time prior to marketing authorisation	1. The speed of the regulatory process 2. Accessibility of medicines prior to marketing authorisation
The price and reimbursement process	3. Initiation of the process 4. The speed of the national timelines and adherence
The value assessment process	5. Misalignment on evidence requirements 6. Misalignment on value and price 7. The value assigned to product differentiation and choice

14 For example, in diabetes we see that some therapeutic classes have experienced particular challenges: SGLT-2 inhibitors only gained reimbursement in France in 2020, 8 years after EMA approval; in Poland, it took 12 years for long-acting insulins to be reimbursed after their first EMA approval. EFPIA and PwC analysis (2023) [unpublished]

15 Greece: article 22 of Law 4633/2019: medicines with patent protection are subject to health technology assessment (HTA) in Greece only if they are reimbursed in 5 other countries with HTA process from the following list: Austria, Belgium, France, Germany, Denmark, Spain, Netherlands, Italy, Portugal, Sweden and Finland.

Health system constraints and resources	8. Insufficient budget to implement decisions 9. Diagnosis, supporting infrastructure and relevance to patients
The sub-national approval process	10. Multiple layers of decision-making process

Source: EFPIA

We now turn to the evidence on what causes unavailability. As set out in the OECD analysis, this needs to be considered carefully, all stakeholders should jointly work to improve availability but should not expect availability to be 100%: "Broad access to all […] medicines is often assumed to be ideal, but is not essential. For example, if several medicines are potentially available for a given indication, procurement methods may result in only some of them being available, without disadvantaging patients."[16]

1.5. Root causes of unavailability and delay

1.5.1. The time prior to marketing authorisation

The first set of root causes to investigate relate to delay prior to marketing authorisation. The granting of a centralised marketing authorisation by the European Medicines Agency (EMA) covering all EU countries takes away the requirement to seek marketing authorisation for new therapies from each member state separately; however, the centralised process that is used for most innovative medicines still takes time.

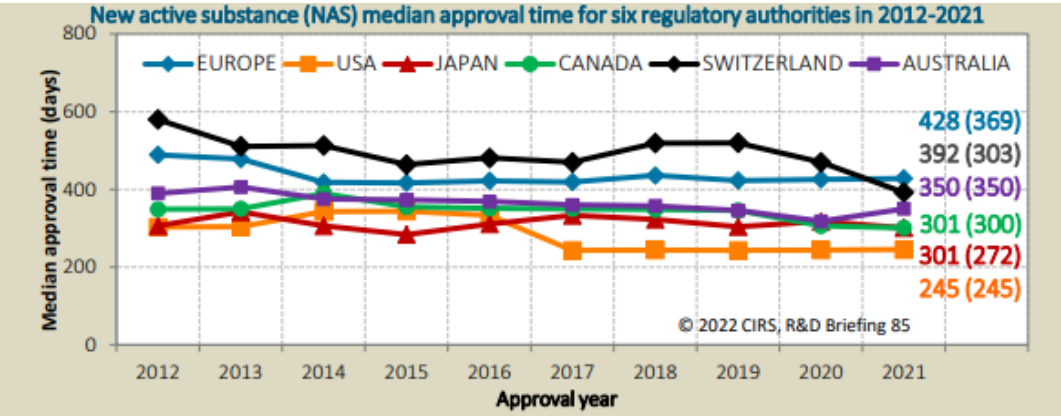
The speed of the regulatory process

Although this is not captured in EFPIA's W.A.I.T. indicator, the time from application to granting of marketing authorisation has been examined in many different papers. Looking at recent evidence on new active substances it is clear that the European regulatory process is slower than some international processes, particularly that of the US (Figure 7 below).[17]

16 Addressing Challenges in Access to Oncology Medicines, Analytical Report. OECD, April 2020.

17 This does vary by pathways. As reported in Rodier et al. (2019), The overall median approval time taken by the EMA for all the approved new active substances was about 423 days in 2019 compared to the official timelines of 210 days, with an average of 270 days for accelerated assessments, 481 days for conditional approvals and 281 days for high priority medicines. Rodier, Céline, Magdalena Bujar, Neil McAuslane, and Lawrence Liberti. 2019. New Drug Approvals in Six Major Authorities 2009-2018: Focus on Facilitated Regulatory Pathways and Orphan Status. London, UK.

Figure 7: Comparison of length of time of market authorisation process



Source: https://cirsci.org/wp-content/uploads/dlm_uploads/2022/06/CIRS-RD-Briefing-85-6-agencies-v2.3.pdf

Many studies have focused on cancer medicines. By looking at the findings of similar analyses over time, we observe that the speed of the regulatory approval process in Europe consistently lags behind that in other regions.

- For 29 cancer drugs approved by the EMA between 2006 and 2011, median approval time was shorter in the United States (US) (6.0 months) than in Japan and Europe (15.0 and 13.3 months, respectively). Breaking down the 13.3 months, this is composed of "active review" time (6.6 months), clock-stops (4.2 months) and administrative time (2.1 months). This contrasts with the US, where the entire 6.0 months of the process is composed of "active review" time. Authors also found that companies file for MA earlier in the US than in the EU, but that this is relatively short (1.7 months).[18]
- Similar patterns were observed in another study focusing on 16 tyrosine kinase inhibitors (TKIs) approved by the US Food and Drug Administration (FDA) between 2001 and 2012. This found that whilst the average time spent on review and approval differed between the US (205.3 days) and the EU (409.6 days), the active review time was similar in both jurisdictions (205.3 days in the US and 225.4 days in the EU), and companies filed for MA in both geographies within a mean of 31.2 days of each other. The differences in total time are attributed to longer clock stops in the EU during the review process to collect additional information from sponsors, and the time from recommendation by the advisory opinion, and the decision of the European Commission.[19]
- For 37 cancer medicines approved between 2005 and 2013, the time from date of filing for MA to approval was much longer for the EMA and Health Canada than for the FDA, by an average of 6.7 months and 6.4 months, respectively. Submissions

18 Hartmann, M., Mayer-Nicolai, C. and Pfaff, O. (2013) Approval probabilities and regulatory review patterns for anticancer drugs in the European Union. *Critical Reviews in Oncology/Hematology* 87(2): 112–121

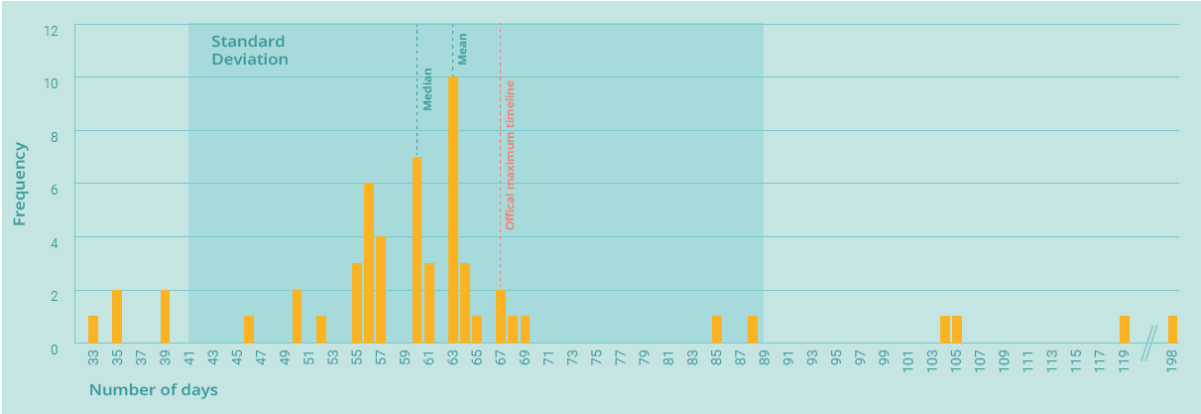
19 Shah, R. R., Roberts, S. A. and Shah, D. R. (2013) A fresh perspective on comparing the FDA and the CHMP/EMA: approval of antineoplastic tyrosine kinase inhibitors. *British Journal of Clinical Pharmacology* 76(3): 396–411

to the FDA were also made on average 12.9 and 28.4 months earlier than submissions to the EMA and Health Canada, respectively.[20]

- A study with a broader geographic scope reported that median approval times for oncology drugs and immunomodulators between 2015 to 2019 were the longest for Swissmedic (450 days) followed by the EMA (419 days), the Australian Therapeutic Goods Administration (TGA) (352 days), Health Canada (345 days), the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) (284 days) and the FDA (239 days).[21]
- The latest evidence suggests these trends remain unchanged: a 2022 study found that between 2010 and 2019, the FDA approved 95% of new oncology therapies before the EMA, with a median delay to market authorisation in Europe of 241 days. The EMA's median review time was found to be 226 days longer than the FDA's. 72% of applications were filed with the FDA first, and 23% were first filed with the EMA; Looking at the median, applications were filed with the FDA 20 days earlier than with the EMA.[22]

For other categories of medicine, the difference may be smaller but the FDA is still faster than the EMA.[23] The studies described attribute a portion of the delay in Europe to the period between the CHMP opinion and the EC decision (as shown in Figure 8).

Figure 8: Overview of timelines between CHMP opinion and EC decision



20 Samuel, N. and Verma, S. (2016) Cross-comparison of cancer drug approvals at three international regulatory agencies. *Current Oncology* 23(5): 454–460

21 The Centre for Innovation in Regulatory Science (CIRS), 2020

22 Lythgoe, M. et al. (2022) Cancer Therapy Approval Timings, Review Speed, and Publication of Pivotal Registration Trials in the US and Europe, 2010-2019. JAMA Netw Open 5(6): e2216183.

23 For example, "EMA and FDA comparison shows faster, and higher, approval rates in the US" https://www.shakespearepharma.com/ema-and-fda-comparison-shows-faster-and-higher-approval-rates-in-the-us/; and Zeukeng, M., Seoane-Vazquez, E. and Bonnabry, P. (2018). A comparison of new drugs approved by the FDA, the EMA, and Swissmedic: an assessment of the international harmonization of drugs. *European Journal of Clinical Pharmacology*, 10.1007/s00228-018-2431-7, 74, 6, (811-818)

Source: Vintura (2021)[24]. Timelines reflect all oncology therapies evaluated by the CHMP between 2016 and 2020 (new molecular entities only).

Some argue that this reflects that Europe is losing ground in terms of priority of regulatory approval and this will only get worse in the future.[25] However, even today there is often a significant delay caused by the marketing authorisation process.

Accessibility of medicines prior to marketing authorisation

In reality, it is possible for patients to access medicines prior to marketing authorisation in some countries.[26],[27] Funded early access schemes represent temporary reimbursement pathways that ensure direct patient access to new promising treatments prior to regulatory approval, where there is a clear unmet need.[28]

Some countries have introduced early access schemes specifically aimed at providing immediate patient access for products prior to a full marketing authorisation (MA) being granted. Some countries, such as France and England, have introduced a more systematic approach. For example, in France, products with high unmet need can be granted an "autorisation d'accès précoce" (AAP)[29] prior to receiving a conditional MA approval. Although the AAP was only introduced in 2021, it is not a new system, but a reform of the rules on early access to unauthorised medicines that were first introduced in France in 1992.

More recently, somewhat comparable schemes have developed in other markets. For example, England's "early access to medicines scheme" (EAMS). Unlike the French AAP scheme, the company that applies for EAMS must provide the medicine free of charge to the National Health Service (NHS) until the full marketing authorisation is granted. Those patients who receive a free medicine during this EAMS period will continue to do so up to

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24 Vintura (2021) "Every Day Counts, Improving regulatory timelines to optimise patient access to innovative oncology therapies in Europe". Available at: https://www.efpia.eu/media/636486/improving-regulatory-timelines-to-optimise-patient-access-to-innovative-oncology-therapies-in-europe.pdf [Accessed March 2023]

25 For example, global regulatory timelines are changing over time – over the last 10 years. EMA's have stayed relatively flat (increased a little during the last year) while Japan PMDA, US FDA and China NMPA have dramatically reduced their review timelines over the decade.

26 It is also possible that where a new indication for an existing product is not (yet) approved or covered, access this may be possible through off-label prescribing.

27 Formally, Hungary, Latvia, Austria, Germany, Denmark, Finland, the Netherlands and Sweden do not require price obtainment from the competent authority before "market launch", according to EFPIA's Market Launch and Withdrawal Survey (May 2020). This is not the case in other countries. Indeed, there is a requirement to apply for reimbursement status before market launch is in effect in Italy, Czechia, Spain, Slovenia, and Portugal.

28 In addition, most countries have named patient compassionate use programs which might be offered to patients with life-threatening or seriously debilitating conditions or an area of unmet clinical need. These have recently been documented in Access to medicines in Europe: Delays and challenges for timely patient access, Bregtje Kamphuis, Anna-Maria Fontrier, Olina Efthymiadou, Jennifer Gill, Hana Salyga and Panos Kanavos | November 2021

29 This was introduced in July 2021 through the Social Security Financing Law for 2021 (LFSS 2021) and replaced the Autorisation Temporaire d'Utilisation or "ATU". When it is granted pre-marketing authorisation, the AAP replaces the cohort ATU.

the point of a positive funding policy (e.g. Health Technology Assessment (HTA) guidance, national funding policy, local funding arrangements).[30]

1.5.2. Delay between marketing authorisation and application for reimbursement

Once a medicine has a marketing authorisation, there can still be a delay before the start of the reimbursement process. This can be for multifactorial reasons: for example, because some countries want to wait for the formal EMA decision and/or reimbursement decisions in other countries before they start their own reimbursement processes.

Even after the process is initiated, the length of the P&R process varies from country to country. Although the EU Transparency Directive (Directive 89/105/EEC) has set 180 days as the maximum timeline for member states to make P&R decisions, in practice this may be much longer due to clock stops or a lack of adherence.

Initiation of the process

In a minority of markets, there is immediate access after marketing authorisation, at least for some products. For example, in Germany the standard process provides manufacturers with a temporary period of free pricing that enables access to a medicine that has been authorised by the EMA, almost from day one, avoiding the delay resulting from an ongoing HTA assessment and pricing negotiations.

However, in many markets the P&R process does not start automatically; this requires a submission by the company or decision by those in the assessment process. This depends on the rules: the process in some countries is possible prior to marketing authorisation, but in others this requires a positive opinion from the EMA Committee for Medicinal Products for Human Use (CHMP), or even a formal decision from the EC or a publication in the Official Journal of the EU before a dossier can be submitted or is assessed. In some cases, countries even await decisions from other countries, whilst in others the national processes can only start when a cohort of other countries have finalised their decisions at national level.[31]

In other cases, the process is dependent on other stakeholders. This is changing for the better in some countries. For example, in Estonia, applications to the inpatient service list were previously made by clinicians and manufacturers were in principle not able to initiate this process.[32] However, the amendment of list of health services within Estonia's Health Insurance Act now has added the service involving the administration of a medicinal product may be initiated by the holder of the marketing authorisation of the medicinal

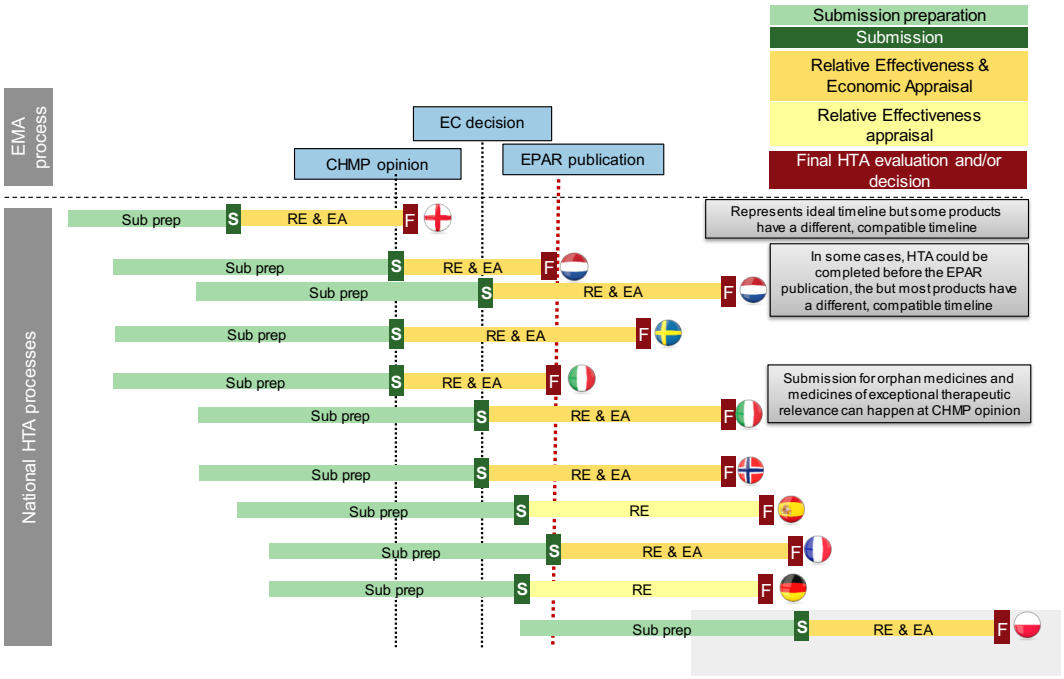
30 Office for Life Sciences. Gov.uk (2016). Guidance on Early access to medicines scheme (EAMS): task group and principles. 10 May 2016. https://www.gov.uk/government/publications/early-access-to-medicines-scheme-eams-how-the-scheme-works/early-access-to-medicines-scheme-eams-task-group-and-principles.

31 For example, in Czechia, as maximal pricing and reimbursement levels are based on referencing to other EU countries, the availability on at least three EU member states' markets is necessary for P&R application. EFPIA Market Launch and Withdrawal Survey. In Bulgaria, manufacturers can submit their dossier to undergo HTA only when a positive recommendation has been issued by the UK, France, Germany or Sweden (Malinowski et al. 2020).

32 Time to Entry for New Cancer Medicines: From European Union–Wide Marketing Authorization to Patient Access in Belgium, Estonia, Scotland, and Sweden. Ferrario, A. Health Policy Analysis. *Value in Health* 21(7): 809–821, 01 July 2018

product.[33] Another example can be seen in Scotland, where manufacturers are proactively invited to submit newly approved indications to the Scottish Medicines Consortium after the country has conducted horizon scanning.[34] Illustrative timelines for the HTA process in different European countries are shown in the figure below.

Figure 9: Time until the reimbursement process can be initiated



Source: EFPIA; EPAR refers to European public assessment report

This shows that in some countries the process can start significantly before the marketing authorisation (England), whilst in others there is a delay even after publication in the EU Journal. Leaving to one side the impact of national rules, two other factors need to be taken into account.

1. A significant amount of research has been undertaken to understand the degree to which delayed application is caused by external reference pricing. The intuition for this is clear: if a country references the price of medicines in much lower income countries, able to pay a much lower price, companies will be encouraged to launch medicines in the high price country first. This will avoid lower prices cascading from one country to another. A series of reports for the Commission have documented this effect.[35]

33 Riigi Teataja (2022). Health Insurance Act. Available at https://www.riigiteataja.ee/en/eli/520012014001/consolide

34 Time to Entry for New Cancer Medicines: From European Union–Wide Marketing Authorization to Patient Access in Belgium, Estonia, Scotland, and Sweden. Ferrario, A. Health Policy Analysis. *Value in Health* 21(7): 809–821, 01 July 2018

35 Kanavos, P., Fontrier, A., Gill, J., & Efthymiadou, O. (2020) Does external reference pricing deliver what it promises? Evidence on its impact at national level. *Eur J Health Econ* (21): 129–151. Retrieved January 29, 2020, from https://link.springer.com/article/10.1007/s10198-019-01116-4

2. Equally, the application for P&R is a time-consuming process. Every country requires the development of a tailor-made dossier in local language and compliance with local rules. Although companies often have specialised groups to manage this process, it is still necessary to prioritise internal activities. This issue is exacerbated for smaller companies that have not gone through the process before and companies that have not launched a new medicine for some time (as shown in Figure 10 below where larger companies have higher levels of availability). As with any commercial decision, and applicable to many sectors of industrial production, we would expect companies to take into account the commercial size of the opportunity to determine where to put their resources. This is not just about industry resources; HTA bodies do not have limitless capacity.[36] For that reason, companies are often inclined to not start an application until authorisation to enter the European market has been confirmed.

Figure 10: Percentage of products available in EU countries, segmented by company size

Sorted by total availability % according to EFPIA W.A.I.T. (2018 – 2021 cohort)

Country	Top-20 global pharma N=78	Other biotech and SME companies N=86	Large company delta % above or below the country average reported in W.A.I.T.
Germany	97%	85%	7%
Denmark	92%	67%	13%
Austria	89%	67%	12%
Italy	88%	68%	11%
Switzerland	88%	59%	15%
Netherlands	91%	48%	22%
England	76%	58%	10%
France	71%	59%	6%
Sweden	83%	40%	23%
Finland	79%	35%	23%
Scotland	67%	44%	12%
Czech	79%	32%	25%
Belgium	79%	29%	26%
Spain	68%	38%	16%
Norway	72%	31%	22%
Portugal	67%	35%	17%
Greece	67%	31%	19%
Slovenia	70%	27%	23%
Luxembourg	66%	29%	19%
Ireland	61%	25%	19%
Hungary	64%	18%	25%
Bulgaria	47%	14%	18%
Cyprus	54%	5%	26%
Iceland	42%	11%	17%
Poland	39%	13%	14%
Estonia	41%	11%	16%
Romania	34%	14%	11%
Croatia	41%	5%	19%
Slovakia	29%	15%	7%
Russia	37%	7%	16%
Latvia	30%	6%	13%
Lithuania	30%	5%	13%
Turkey	21%	8%	7%
Serbia	20%	2%	9%
Bosnia and Herz.	18%	1%	9%
Macedonia	14%	0%	8%
Malta	7%	7%	0%
Kazakhstan	9%	4%	3%
Albania	5%	1%	2%

Source: EFPIA Patients W.A.I.T. (launched 2022), IQVIA analysis of company size, top-20 pharma defined by 2022 Q4 MAT total sales (Rx only) globally

In 2022, EFPIA members committed to the creation of a European Access Portal where marketing authorisation holders (MAH) can provide timely information regarding the timing and processing of P&R applications in the various EU-27 countries, including the reasons

36 O'Rourke, B. et al. (2019) The 'Top 10' Challenges for Health Technology Assessment: INAHTA Viewpoint. *Int J Technol Assess Health Care* 2020 36(1): 1–4. doi: 10.1017/S0266462319000825. Epub 2019 Nov 28

why the MAH has not filed in a particular market.[37] This is not the focus of this document, and findings from European Access Portal will be published separately.

The speed of the national timelines and adherence

Most European countries have a set of rules around the timelines for decision-making on national pricing and reimbursement, but even when countries have such rules in place, compliance can be challenging. This results in delays and unpredictability of timelines.

The length of time taken should reflect the EU Transparency Directive (European Commission, 1988). The purpose of this directive is to ensure the transparency of measures that regulate P&R of medicinal products. It sets a strict maximum time of 180 days for reaching a national P&R. This timeline starts from the moment a dossier is submitted and excludes time needed by companies to provide additional information ("clock stops"). The Transparency Directive puts the responsibility in the hands of national governments, whereas it is a responsibility of all stakeholders to allow for reasonable interactions in order to ensure evidence-based decision-making within this time frame.

Many Member States also have legislation specific to speciality medicine or rare diseases. In Italy, for example, the national P&R process for orphan drugs should conclude within 100 days as per Italian law.[38] In reality, it takes on average 477 days for new orphan medicines to become available to patients in Italy.[39]

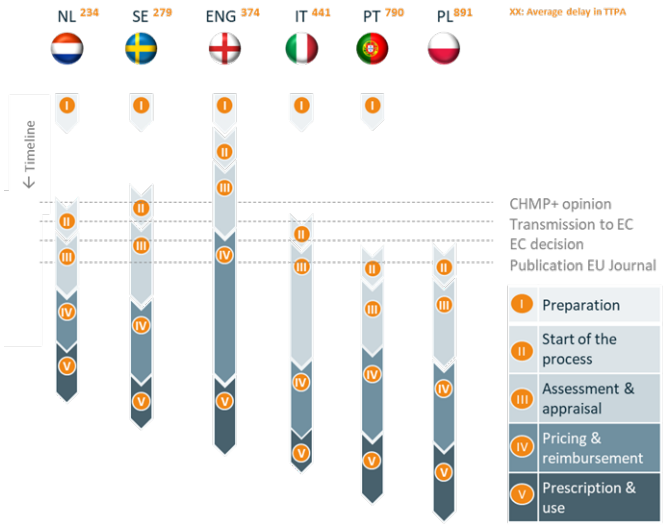
There is relatively little data on the time taken from the start of the national P&R process to its conclusion. The data from the Time to Patient Access study for the six case study countries is below (Figure 11). This shows that even after taking into account delayed initiation, there are significant differences across countries. This is consistent with the OECD analysis, which was able to separate the delay initiation of the process from the length of time taken from application for reimbursement to approval for reimbursement for a selection of European countries.

37 EFPIA (2022) "Addressing patient access inequalities in Europe: The Industry commitment to file pricing and reimbursement applications across Europe and the European Access Portal." Available at: https://www.efpia.eu/media/677156/addressing-patient-access-inequalities-in-europe.pdf [Accessed March 2023]

38 Prada, M., Rossi, L. and Mantovani, M. (2020) Time to reimbursement and negotiation condition in Italy for drugs approved by the European Medicines Agency during the period 2014-2019. *AboutOpen* 7(1): 89-94

39 *The Patient W.A.I.T. Indicator 2022 Survey*

Figure 11: Start of the national process in the six-case study countries



Source: Time to Patient Access, Ventura (July 2020)

Exacerbating the impact of the structural differences between national P&R processes on these delays, countries also have varying levels of resources to support the P&R process. For example, the number of staff at HTA agencies in Europe ranges from zero full-time equivalents (FTEs) to over 600 FTEs.[40]

It has been pointed out by a number of different authors that tailored approaches for different types of medicines can improve speed of access.

- In some markets there is immediate access of medicines that are dispensed in the hospital, but the national reimbursement process applies to medicines dispensed in community pharmacies. However, as specialist medicines have become an ever-larger part of the healthcare budget, more restrictions have been applied, as illustrated by the case of the Netherlands.[41]
- In other cases, there are different channels for different types of medicine. For example, Deticek *et al*. (2018) found that the most successful countries in terms of rapid availability of orphan medicines were Germany, Norway, Finland, Sweden, and France. These countries have specific mechanisms to improve patient access to these medicines and to grant full or substantial reimbursement from public resources.[42]

40 European Commission (2018) "Commission Staff Working Document Impact Assessment: Strengthening of the EU Cooperation on Health Technology Assessment (HTA)". Available at: https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:52018SC0041&rid=8 [Accessed March 2023]

41 How is patient access to high-cost orphan drugs changing? https://www.remapconsulting.com/patient-access-to-high-cost-orphan-drugs-remap-consulting/

42 Detiček, A., Locatelli, I. and Kos, M. (2018) Patient Access to Medicines for Rare Diseases in European Countries. *ISPOR Value in Health*. 21(5): 553-560.

1.5.3. Delays due to the value assessment process

A part of the P&R process is the value assessment process. Misalignment on evidence is reported as one of the most prominent and complex delaying factors. Misalignment takes place not only between industry, regulators, and HTA bodies, but also occurs between regulators and HTA bodies, as well as among different HTA bodies. Misalignment can be found in all assessment criteria including patient population, comparators, trial design, end points, and statistical analysis. Even once there is agreement on evidence, there can be a significant debate on whether this justifies the price of the medicine. Finally, different countries have adopted different approaches to class competition and the value of choice.

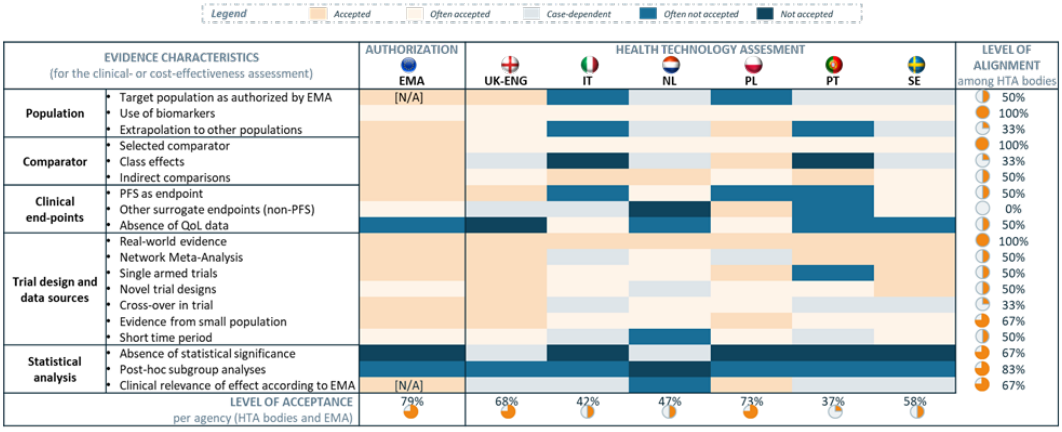
Misalignment on evidence requirement

Once the P&R process is initiated, one of the reasons that the national timeline gets extended are clock stops, requests for information or rejections during the HTA process. Different countries have different requirements for the evidence, during the assessment process, and this represents a challenge, as (1) evidence is developed at a global level and hence developing additional country specific evidence can be time-consuming, and (2) the evidence requirements are not always predictable (even with early dialogue processes that have developed in Europe over the last five years).

To illustrate the differences in evidence requirements we can compare the evidence requirements of EMA and the HTA bodies in the six case study countries from the TPA project (see Figure 12). Based on desk research and interviews with agency representatives, for each agency the research assessed whether 19 different characteristics would be accepted as convincing evidence.

The level of alignment is highest for the use of biomarkers and real-world evidence (RWE), for example. These elements are “often accepted” by all HTA bodies. The level of alignment is lowest when HTA bodies are asked for acceptance of surrogate endpoints other than progression-free survival (PFS). As illustrated in Figure 12, every agency looks at the use of surrogate endpoints in a different way: these are accepted in Poland and often accepted in Sweden; not accepted in the Netherlands and often not accepted in Portugal. England and Italy determine acceptance on a case-by-case basis.

Figure 12: Evidence requirements vary between agencies, prolonging national discussions and decision-making



Source: Time to Patient Access, Ventura (July 2020)

The grey colour code reflects acceptance on a case-by-case basis. The blue colour code ("often not accepted") and lighter orange colour ("often accepted") also reflect a certain level of unpredictability. This is consistent with findings in the literature which indicate that only around 40% of HTA agencies globally have guidelines that make specific reference to the consideration of surrogate endpoints.[43]

Misalignment of value and price

Next, even if there is agreement on the evidence regarding the value of a medicine, different countries have different levels of income and hence ability to pay. Decision makers are faced with the enormous challenge of striking a balance between fast patient access, uncertainty about real-world value, and a reasonable price reflecting the (potential) value.

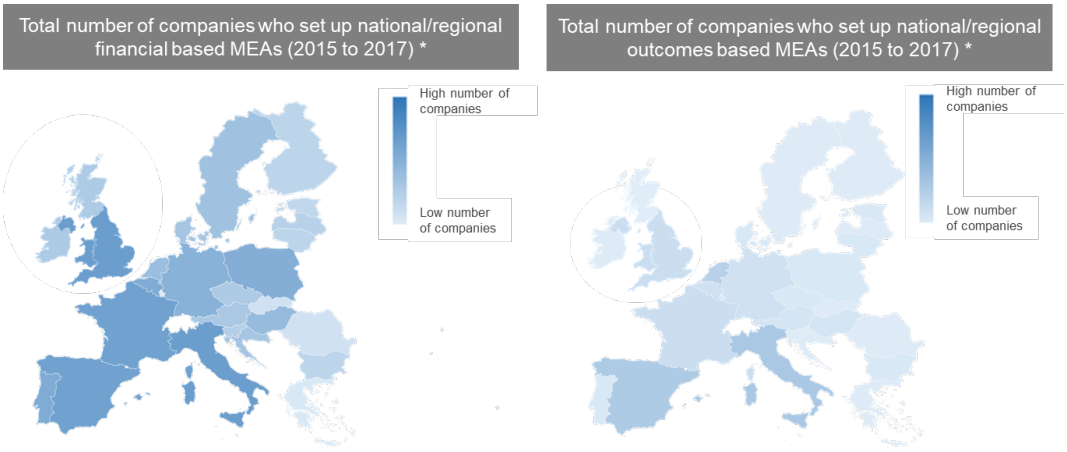
There is clearly also a debate around delays and price. Looking at a simple correlation we find that there is a positive relationship between price indices and availability. This is, however, too simplistic, as high-price countries may have quicker diffusion and greater usage; so, there are many confounding factors. The limited number of studies that have tried to unpick the relationship between delay and price have not found a meaningful result. Ferrario (2018) found expected prices do not affect the speed of launch, although pointed out this may be due to limited variation in prices across the four study countries.[44]

However, there is broad consensus that prices need to reflect the ability to pay. Where prices are higher than the perceived value or affordability, there is an inevitable delay as the price is negotiated. This is clearly complicated by external reference pricing (discussed above); this means that the agreed price needs to take into account how this price will be used outside of the country, in addition to whether it aligns with the assessment of value by the national HTA body. Where it is possible to use flexible contracts to align price and value, this should reduce delays. However, the ability to agree novel payment mechanisms varies considerably around Europe. This is particularly the case in Central and Eastern Europe, where we observe the largest delays.

43 Grigore, B. *et al.* (2020) Surrogate Endpoints in Health Technology Assessment: An International Review of Methodological Guidelines. *PharmacoEconomics* 38: 1055-1070.

44 Time to Entry for New Cancer Medicines: From European Union–Wide Marketing Authorization to Patient Access in Belgium, Estonia, Scotland, and Sweden. Ferrario, A. Health Policy Analysis. *Value in Health* 21(7): 809–821, 01 July 2018

Figure 13: The use of managed entry agreements (MEAs) across Europe



Source: EFPIA "MEAs and innovative pricing models: Real world experience" Final Report 2018

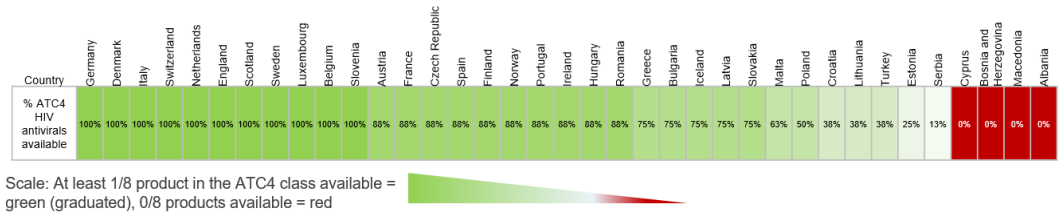
The value assigned to product differentiation and choice

The value that countries place on a particular medicine also varies. Countries may have different numbers of patients with a particular condition (some countries may have very few); and approaches to treatment may vary, with some countries favouring surgical approaches rather than therapeutic interventions. So clinical and epidemiological factors affect the degree to which countries have an unmet need and therefore the degree to which these are prioritised in P&R process and value assessments.

There is another dimension to consider, related to physician choice and the value of competing medicines. Different countries take different approaches to determine the value of class competitors. Some countries believe that physicians should have access to all the products on the market, in order to provide patients with the best products for them and to allow physicians clinical freedom. Equally, competition between innovative medicines is encouraged in some markets, with the follow-on products in a class being encouraged as this can lead to competition and better value for the payer. Other countries have favoured an approach of choosing a preferred product – sometimes through a rigid procurement process that allows them to select a single manufacturer at least for a period of time. If this is the case, is it unsurprising that we see access to only a subset of the products. To examine this, IQVIA has examined a series of ATC4 therapeutic classes. It is not surprising that as the number of ATC4 options decreases, more countries approve all authorised options.

Given that the number of options vary in different ATC4 classes, we would therefore expect to see differences in availability of products. This is validated by the evidence if we look at Figure 14, percentage of HIV antivirals (J5C9) available in each country. Although availability varies significantly across the European countries, the vast majority of countries have access to at least one product in the class.

Figure 14: Number of products available in a therapeutic class (the example of HIV antivirals)



Source: EFPIA Patients W.A.I.T. (launched 2022), IQVIA ATC4 class (J5C9, HIV antiretrovirals, n=8)

A similar result is seen in other therapeutic areas, including Hepatitis C, PD-L1s, and Her-2 inhibitors**.**

The number of products available in a therapeutic class is therefore likely to reflect the value that different countries put on competing products – and the degree to which payers perceive a loss due to lack of choice.

1.5.4. Health system constraints and resources

The fourth category of root causes relates to the health system, its funding and infrastructure. To understand availability and delay we need to take into account health system constraints and resources, particularly insufficient budget to implement decisions, and the infrastructure for diagnosis.

Insufficient budget to implement decisions

Within Europe, we clearly have countries with very different levels of income, with GDP per capita varying from €13,000 to €132,000 per annum.[45] They also have made different decisions regarding the amount that they invest in healthcare. The data from the OECD clearly shows the European differences in economic context:

- Relative healthcare spending as a percentage of overall GDP is twice as high in Germany or France (12.8% and 12.4% respectively) as in Romania (6.3%).[46]
- Relative pharmaceutical expenditures as a percentage of overall GDP is over four times higher in Greece and Bulgaria (2.9% and 2.8%, respectively) as in Denmark and the Netherlands (0.65% and 0.7% respectively).[47]
- Absolute healthcare spending ranges from approximately €6,800 per capita in Germany respectively to €1,900 per capita in Romania (OECD, 2020).[48]

45 OECD. (2022). Gross domestic product (GDP). Available at: https://data.oecd.org/gdp/gross-domestic-product-gdp.htm [Accessed March 2023]

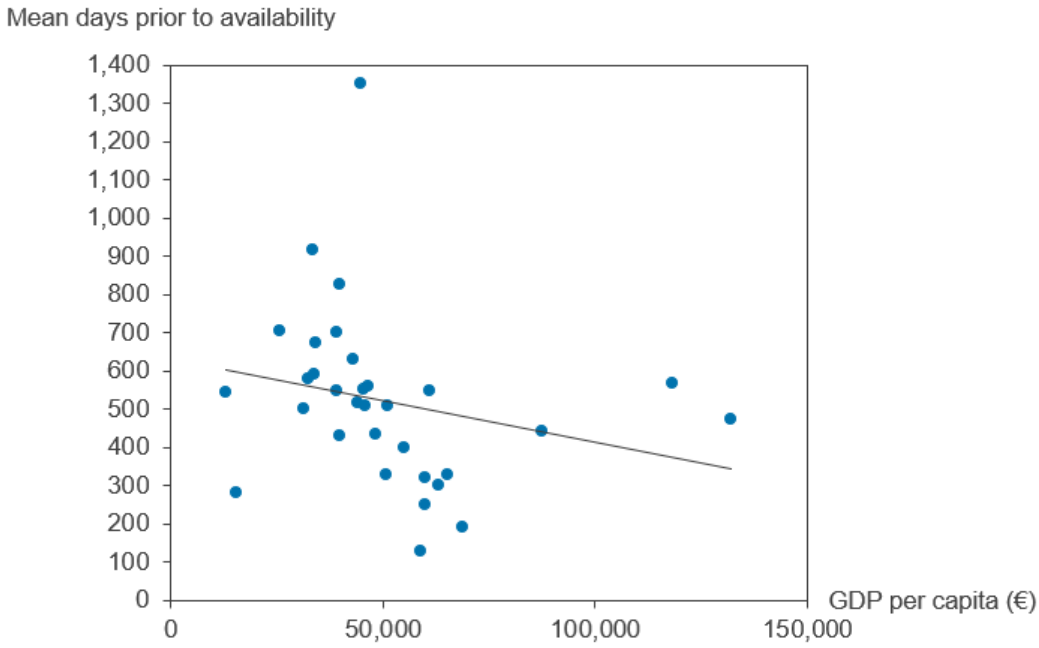
46 OECD. (2021). Health Spending. Available at: https://data.oecd.org/healthres/health-spending.htm#indicator-chart [Accessed March 2023]

47 OECD. (2021). Pharmaceutical Spending. Available at: https://data.oecd.org/healthres/pharmaceutical-spending.htm [Accessed March 2023]

48 OECD. (2021). Health Spending. Available at: https://data.oecd.org/healthres/health-spending.htm#indicator-chart [Accessed March 2023]

Given the difference in income and spending on healthcare and medicines, it is unsurprising that the prioritisation of health technologies varies across European countries. Given variance in healthcare priorities, it would be surprising if we saw the same access to different forms of healthcare.

Figure 15: Relationship between time to availability (delays) and GDP per capita



Source: The Patient W.A.I.T. Indicator 2022 Survey, OECD 2022

As shown in the figure above, we do find a negative relationship between income and delays (although there are clearly many other factors as well). This result is consistent with the broader economic literature. Indeed, there are many papers showing that the impact of the size of the market remains, even after taking into account many other factors. For example, Costa-Font (2015) observed a significant and robust market size effect that decreases the launch time of new pharmaceutical products as market size increases.[49]

Diagnosis, supporting infrastructure and relevance to patients

The existing health infrastructure is a barrier to access in many European countries. For that reason, even after reimbursement, healthcare systems may face difficulties absorbing and using a new therapy in the most optimal way due to the need for high quality health facilities, diagnostic centres and health personnel.

In reality, there are many barriers in the infrastructure that mean applying for reimbursement for a medicine in some markets is not realistic. This is particularly true for highly specialised or orphan medicines:

- Accurate and timely diagnosis is dependent on the availability of accessible screening and diagnosis programs and services, which itself depends on the

49 Costa-Font, Joan, McGuire, Alistair and Varol, Nebibe (2015) Regulation effects on the adoption of new medicines. *Empirical Economics* 49(3): 1101–1121. ISSN 0377-7332

infrastructure and expertise (e.g. number of geneticists) available.[50] The degree to which countries have adopted widespread screening or targeted diagnosis of at-risk patients varies significantly.

- Even where diagnosis programs exists in a country, access to diagnostic testing can be limited: for example, a recent study found that uptake of multi-biomarker testing for precision oncology varies from 0% to over 50% across European countries (Figure 16).[51] Country-level studies have identified the absence of public funding for testing as the main barrier to uptake.[52] There is a need for appropriate reimbursement for (newly approved) diagnostics.
- Diagnosis requires investment in reimbursement of diagnostics and appropriate investment in testing facilities, but also requires investment in physician education (and a focus on paediatricians) and an effective referral process.
- Given the small number of patients needing highly specialised or orphan medicine, it is best to concentrate expertise in Centres of Excellence (CoEs), but these are not evenly developed across European markets.

Figure 16: Access to precision oncology biomarker testing in Europe

(A) Single biomarker test access (B) multi-biomarker test access (C) biomarker test quality

Source: Normanno et al. (2022)[53]

For many countries the availability of scientifically robust epidemiological data for individual rare diseases varies greatly, if it is available at all.[54] This can create a vicious cycle where the lack of epidemiological country-specific data contributes to a lack of appropriate health resource prioritisation decisions, and little attention being given to the need to develop rare

50 Dharssi, S., Wong-Rieger, D., Harold, M. and Terry, S. (2017). Review of 11 national policies for rare diseases in the context of key patient needs. *Orphanet journal of rare diseases* 12(1): 63

51 Normanno, N. *et al.* (2022) Access and quality of biomarker testing for precision oncology in Europe. *European Journal of Cancer* 176: 70-77.

52 Mestre Ferrandiz, J. et al. (2023) Biomarkers as a driver of Precision Medicine in Oncology

53 Normanno, N. *et al.* (2022) Access and quality of biomarker testing for precision oncology in Europe. *European Journal of Cancer* 176: 70-77.

54 Manuel Posada De La Paz, Domenica Taruscio, Stephen C. Groft (2017). Rare Diseases Epidemiology: Update and Overview. Springer International Publishing (Verlag)

disease diagnosis programs. The lack of a developed coding nomenclature for rare diseases also creates challenges, particularly for healthcare systems to map out their specialised healthcare services and budget impact.[55]

As a result – given that the number of patients for rare diseases may be very low, and finding these patients may be difficult – ensuring appropriate use and pharmacovigilance is challenging and the commercial viability of applying for reimbursement does not currently exist.

Given this, it is unsurprising that for some orphan medicines the availability across Europe is unfortunately low. Even where products are not available on the national reimbursement list, the industry works with other stakeholders to ensure access for patients. There is evidence on the use of compassionate use programmes across Europe.[56]

1.5.5. Delay from national to regional approval

Most of the studies on availability and delays focus on time to national reimbursement. In reality, there are multiple layers of decision-making processes. In some countries, reimbursement decisions need to be made at all levels from national level to regional level and to then local hospital level, thus prolonging the time before patients can access treatments.

Multiple layers of decision-making processes

European countries have different ways of organising their decision-making processes. Some countries such as Iceland and Croatia organise price negotiations, assessment, appraisal and budget allocation on a national level. Other countries organise these decisions partly at a national level and partly at a regional level. In most European countries, price negotiations, assessment and appraisal take place on a national level but budgets are allocated by healthcare insurers (a single payer institution or different health insurers) or on a hospital level (WHO, 2018).

To illustrate this, many papers examine the situation in Italy. For example, a recent paper found that for the regional access, both the timing and the number of drugs available for patients were widely different from region to region. The mean best regional time (defined as the average number of days after AIFA market authorisation as published in the GU and the first purchase date in the first Italian region) was 29 days. The longest regional time (the number of days between GU and the first purchase in the last region for which data are available to date (July 2016)) was 293 days.[57] More recent analysis has shown that there has been little improvement over the last five years. Even when a national price applicable across all the regions is agreed, it still has to go through 20 different processes locally from Lombardy in the north to Sicily in the south before it is available to patients. This can take anywhere from 6 to 9 months depending which region the patient lives in.

55 Rath, A., Bellet, B., Olry, A., Gonthier, C. and Aymé, S. (2014) How to code rare diseases with international terminologies? *Orphanet journal of rare diseases* 9(1): O11

56 Balasubramanian, G. An overview of Compassionate Use Programs in the European Union member states, *Intractable Rare Dis Res.* 2016 Nov; 5(4): 244–254. doi: 10.5582/irdr.2016.01054

57 Rada, M. (2017) Timeline of Authorization and Reimbursement for Oncology Drugs in Italy in the last three years.

Although the academic literature has focused on Italy, this applies to many markets in Europe.

1.6. Availability is not access

Even once a medicine is on the public reimbursement list and has navigated any regional process, this does not mean that patients have access to medicines. The TPA[58] project identified remarkable differences in the use of new oncology therapies once reimbursement is in place. Based on an assessment on access in sixteen countries, twelve months after reimbursement, for thirteen recently launched therapies, the average access ranged from 61% to 0.3%.

There are many additional barriers that affect usage of medicines:

- An additional delay on top of the P&R period is attributed to the time between the P&R decision and the publication in the national gazette (journal). For example:
    - This is necessary for final access in Belgium, adding an additional level of bureaucracy and a delay of two to three months.
    - In Italy, there is often a delay between the point a reimbursement decision for a new medicine is made and the final step of the national P&R process: publication of this decision in the *Gazzetta Ufficiale* (GU – the Official Gazzette).
    - In Hungary, although officially the reimbursement decision for a new medicine should be taken within 90 days, the reimbursement list is only updated ad hoc.[59] Inclusion on the reimbursement list is required for any medicine to be used in both the inpatient and outpatient sectors.[60]
    - In Bulgaria, although the reimbursement list is updated on a predictable schedule, this only occurs once per year, in January.[61] This means that if the P&R process for recently launched medicines does not conclude by December of any given year, reimbursement will be delayed by another full year.
- Clinical guidelines do not always include the most recent therapeutic innovations. This is evident even in larger Western European countries: for example, in France, HAS guidelines for diabetes have not been updated since 2013, despite the reimbursement of many new medicines and drug classes in that time.[62] The

58 Vintura (July 2020) "Every Day Counts" Available at: https://www.efpia.eu/media/578013/every-day-counts.pdf

59 Kawalec, P. *et al*. (2017) Pharmaceutical Regulation in Central and Eastern European Countries: A Current Review. *Front Pharmacol* 8:892.

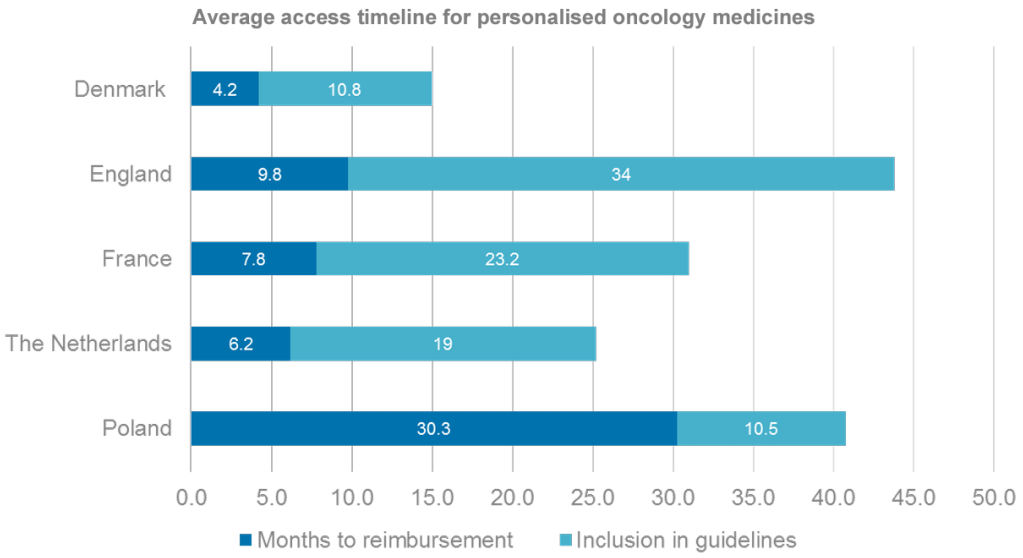
60 WHO (2018) "Medicines reimbursement policies in Europe" Available at: https://www.euro.who.int/__data/assets/pdf_file/0011/376625/pharmaceutical-reimbursement-eng.pdf [Accessed March 2023]

61 Kawalec, P. *et al*. (2017) Pharmaceutical Regulation in Central and Eastern European Countries: A Current Review. *Front Pharmacol* 8:892.

62 Haute Autorité de Santé (2013) "Stratégie médicamenteuse du contrôle glycémique du diabète de type 2" Available at: https://www.has-sante.fr/jcms/c_1022476/fr/strategie-medicamenteuse-du-controle-glycemique-du-diabete-de-type-2 [Accessed March 2023]

absence of clinical guidelines has the potential to lead to delays for two reasons: first, a new medicine may not be picked up in horizon scanning, leading to a delay in decision-making by HTA bodies; and second, prescribers may hold back from starting to use new therapies due to a lack of clarity on the positioning of the new therapy in the treatment pathway. This is illustrated below for new personalised oncology medicines (Figure 17).

Figure 17: Average access timeline for personalised oncology medicines



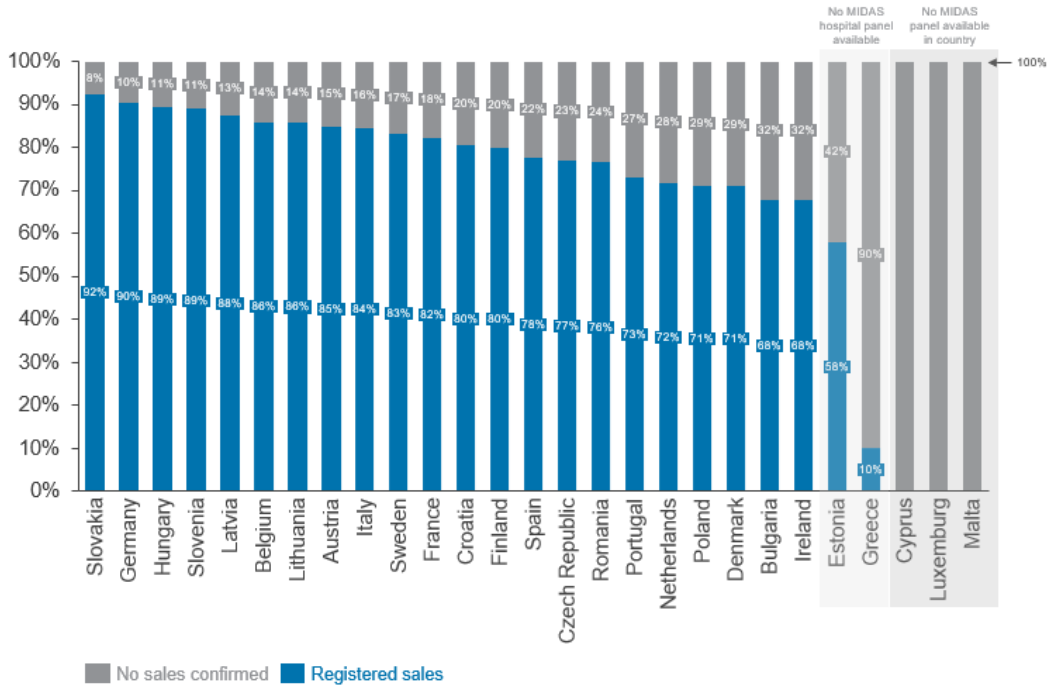
Notes: Average access timeline from first-in-class PM in NSCLC, Melanoma and Ovarian Cancer (gefetinib; crizotinib; vemurafenib; pemprolizumab; olaparib)

Source: EBE Personalised Medicine Report (2018)[63]

In other cases, a medicine is on the reimbursement list, but budgets are not allocated for its use or it is not recommended. As a result, even once the full process is complete and a medicine is potentially available on the market, there is no guarantee that it can be used. For example, patients have access to only 76% of the products that are available in Romania (see Figure 18). Given this experience, it is not surprising that not all companies choose to apply for reimbursement in these markets.

63 CRA, EBE, EFPIA (2018) "An evidence-based analysis to characterise the benefits of personalised medicines to patients, society and healthcare systems" Available at: https://www.efpia.eu/media/362039/cra-efpia-ebe-the-benefits-of-personalised-medicines-to-patients-society-and-healthcare-systems-final-slide-deck-2-july-2018.pdf [Accessed March 2023]

Figure 18: Percentage of available products with no recorded sales in the EU



Source: IQVIA MIDAS sales data 2015-2022. Analysis includes all available products (2018-2021). 'Sales' is defined as available in WAIT indicator and shows EU sales in IQVIA MIDAS. 'No sales' is defined as available in WAIT indicator and shows no EU sales in IQVIA MIDAS. No sales is defined as no sales found in IQVIA MIDAS data since 2015. Some countries in this analysis are not covered by IQVIA data, or do not cover the hospital channel (coverage is retail only).

1.7. The impact of delayed access to innovative medicines

Although there are many statistics on the percentage of medicines available or the length of time taken for a medicine to be made available, the real impact of delays is on patients, the healthcare system and society. It is difficult to quantify the impact of delays but there is no doubt this leads to:[64]

- Higher mortality and avoidable deaths
- Lost quality of life for patients but also their families and friends
- An impact on other healthcare costs, which could have been avoided with newer treatments, and a knock-on impact on other patients
- Loss of productive employment and ultimately a cost to the economy

The scale of the potential impact of reduced delays can be illustrated by looking at potential efficiencies. For example, recent analysis has estimated the potential to reduce the length of time between CHMP opinion and EC decision. If this could be reduced by 12 days this

64 Achieving equal and timely access to innovative anticancer drugs in the European Union (EU): summary of a multidisciplinary CECOG-driven roundtable discussion with a focus on Eastern and South-Eastern EU countries https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6863652/

would lead to 3,300 years of potential lives (YPL) saved. If this was increased to a 15-day reduction, the saving would increase to 4,200 YPL.[65]

1.8. Policy solutions to improve availability of innovative medicines

It is clear from this paper that the reasons behind the unavailability of medicines and delays are multifactorial. These are rooted in the medicines access systems and processes in the member states and the corresponding impact on commercial decision-making. These include a slow regulatory process, late initiation of market access assessment, duplicative evidence requirements, reimbursement delays, and local formulary decisions. It is also clear that there is a shared aspiration to "make sure that patients across Europe have new medicines and therapies in their countries quickly".[66] As the root causes are multifactorial, they can only be solved by different stakeholders working together. To bring different stakeholders together to discuss the root causes, consider different policy solutions and how these could work in practice, EFPIA has called for a High-Level Multi-Stakeholder Forum on Access to Innovation and made a series of commitments. This includes a commitment to file pricing and reimbursement applications in all EU countries no later than 2 years after EU market authorisation, provided that local systems allow it. This commitment reflects the joint ambition of industry and society to make innovation for unmet health needs available for patients and health systems across Europe as soon as possible. However, no single commitment, or indeed regulatory requirement, can address unavailability and delay and this needs to be part of a package of policy proposals.

Reflecting the different root causes, there are five areas where proposals are required:

Proposals to speed up the regulatory process, delivering safe and high-quality diagnostics, vaccines and treatments to patients as fast as possible

There is shared aspiration to reduce regulatory approval times in Europe and bring these in line with international best practice. [67] There are several areas for action within the existing legislative framework to address this: encourage the use of new types of clinical trials; allow greater use of data from real-world use; allow ongoing dialogue between the developer and the regulator about a treatment throughout the development continuum (dynamic regulatory assessment) and simplify how medicines and other healthcare products are regulated, e.g. by closing the gap for GMO and combination products compared to medicinal products and streamlining the biomarker validation process. The evaluation and the revision of the basic pharmaceutical legislation (Dir 2001/83 and Reg 726/2004) and consolidation with other regulations provides an opportunity to reinforce expertise-driven assessment and enable a more agile centralised authorisation framework; adapting the regulatory framework for selected technologies; providing the opportunity to test new approaches for complex or cutting edge medicines; potential streamlining and accelerating current procedures and enhanced digitisation replacing the paper patient information leaflets with electronic versions. It is also important to update the regulatory

65 Vintura, November 2021, Every Day Counts, Improving Regulatory Timelines to Optimise Patient Access to Innovative Oncology Therapies in Europe

66 As set out in the European Commission's Pharmaceutical Strategy Roadmap - https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12421-Pharmaceutical-Strategy-Timely-patient-access-to-affordable-medicines

67 Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and The Committee of the Regions, Pharmaceutical Strategy for Europe COM/2020/761 final

framework for variations to simplify and adapt it to keep pace with scientific development. This will benefit patients by decreasing the risk for shortages and ensuring swifter access to innovative medicines and optimise life-cycle management to ensure the availability of safe, effective and innovative treatments to patients in a timely manner.

However, the progress on regulatory efficiency could be undone by misguided policies that link regulatory incentives to evidence development, or the supply of medicines. This could have unintended consequences on early initiation or discontinuation of research projects, clinical development times and ethics, the location of clinical trials, marketing authorisation timelines, incentives for innovation overall and in different therapy areas.

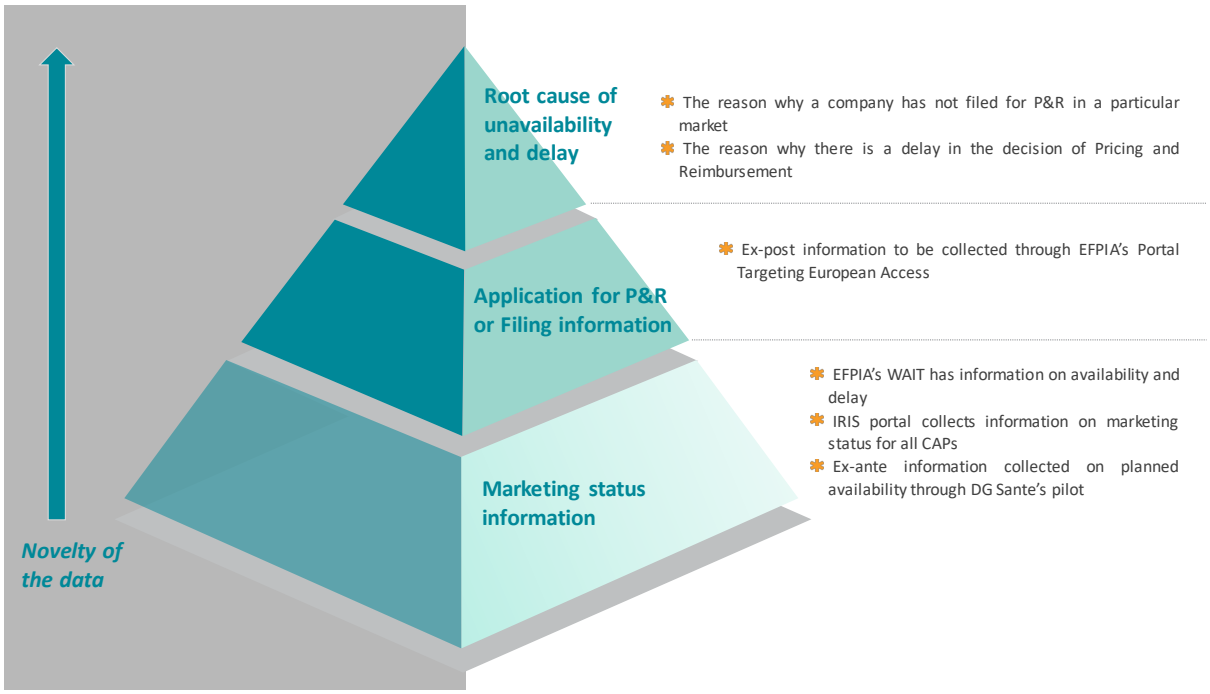
Proposals that aim to increase transparency of information regarding placing on the market of centrally approved products

The industry has launched a European Access portal where marketing authorisation holders (MAH) can provide timely information regarding the timing and processing of pricing and reimbursement (P&R) applications in the various EU-27 countries, including the reasons why there is a delay in the P&R decision or why the MAH has not filed in a particular market.

EFPIA already contributes to transparency on unavailability and delay with its yearly published Patient WAIT report, highlighting the delays to patient access across the EU, as well as this current report on the 10 most common root causes of unavailability and access delays. However, to better understand the root causes and monitor how they evolve, the industry has launched a European Access Portal.

Marketing authorisation holders of centrally approved product are requested to provide timely information regarding the timing and processing of P&R applications in the 30 European countries including the reasons why there is a delay in the P&R decision or why the MAH has not filed for P&R in a particular market.

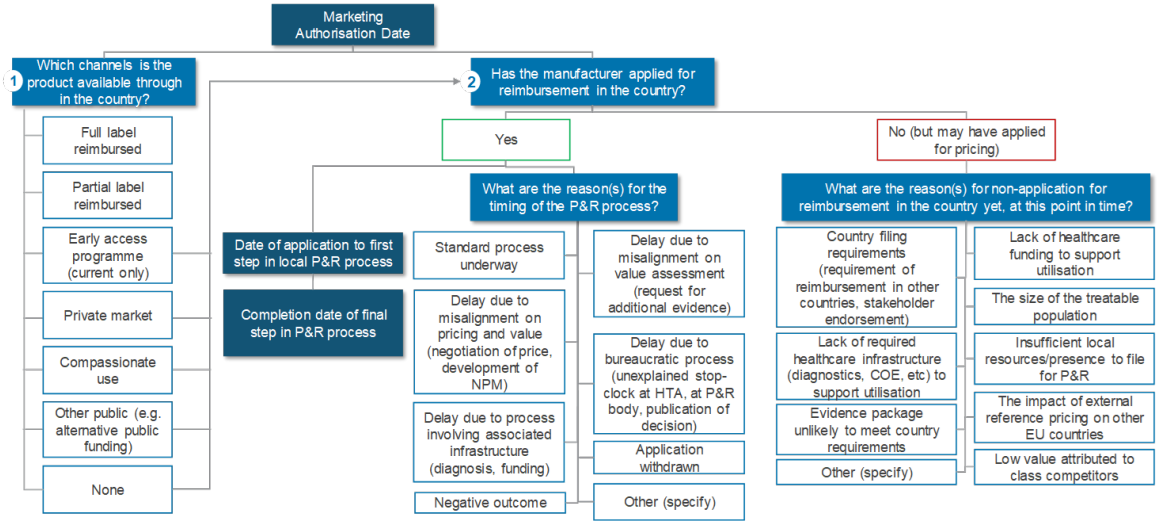
Figure 21: Potential for more granular data on unavailability and delay



Over 90% of EFPIA members with products eligible for inclusion in the Portal submitted data. This shows for the first time the percentage of products that have been filed or reimbursed following marketing authorization – finding that even including products that have only recently been approved, the majority have already been filed or reimbursed. And allows us to understand the reasons for this delay, quantifying the prevalence of root cause described above. The data from the Portal will only become richer over time allowing us to both monitor and understand in greater detail the reason for unavailability.

The first results from the Portal are being published separately. This will include aggregate data collected on timing of filing/no filing and root causes of individual products. Through regular reports it will be possible to track progress in lowering the hurdles causing unavailability and delay.

Figure 22: Data captured by the Portal



Even the preliminary results support the multifactorial causes of unavailability and document that it is a shared responsibility, requiring a shared solution.

Proposals to facilitate a process that allows prices to align with value and ability to pay

The industry is committed to supporting the development of **novel pricing and payment models**. When used appropriately and tailored to the situation, can accelerate patient access, allowing payers to manage clinical uncertainty, budget impact and sustainability of the healthcare system, whilst providing sufficient incentives for innovation.[68,69]

Although there are examples of novel pricing and payment models being used today, legal barriers, a lack of appropriate data infrastructure, and an unwillingness to adapt current

68 https://efpia.eu/media/554543/novel-pricing-and-payment-models-new-solutions-to-improve-patient-access-300630.pdf

69 https://www.efpia.eu/media/602581/principles-on-the-transparency-of-evidencefrom-novel-pricing-and-payment-models.pdf

systems often prevent their use. To help address these barriers, the industry proposes a set of guiding principles regarding the use of novel pricing and payment models:

1. Access Principle: Novel pricing and payment models should facilitate broad and timely patient access whilst balancing the sustainability of the healthcare system and incentives for innovation.
2. Value Principle: A high quality, methodologically robust and mutually agreed value-based framework is the foundation for novel pricing and payment models.
3. Collaboration Principle: Payers and companies should work together to anticipate where novel pricing and payment models are needed and ensure they are fit for purpose.
4. Transparency Principle: There should be transparency regarding the existence of the novel pricing and payment agreements and the outcomes data generated (with appropriate safeguards in place), while retaining confidentiality of commercial terms.
5. Infrastructure Principle: Stakeholders should work together to ensure the required data infrastructure is fit for purpose and legal frameworks are in place to enable access

The industry has an important role to play and commit to an open dialogue and collaboration with payers and policy makers to reach a win-win solution putting patients' interests first.

Proposals to improve the efficiency and quality of value assessment

The industry is committed to contributing to the creation of an **efficient system of European assessments of relative efficacy at time of launch** in the context of the implementation of the HTA Regulation.

HTA agencies currently reach different conclusions on the medical impact (relative efficacy and/or relative effectiveness assessment) of new pharmaceuticals, even though the data studied is predominantly the same for all markets – such as safety and efficacy data from registration trials. This is because HTA agencies adopt different approaches to rating and interpreting the data. This might apply to trial design, relevant endpoints, appropriateness of defined patient subgroups and treatment comparators. With the establishment of the legal basis of the EU HTA regulation, and the start of the implementation period (from January 12th 2025 the regulation will apply to oncology and ATMP products, followed by orphan medicinal products (OMPs) three years later, and all other Centrally Approved Medicines after five years.), there is an opportunity to establish an efficient system of European assessments of relative efficacy at time of launch but the EU HTA regulation will only deliver against its promise, if all stakeholders collaborate during the next coming years on implementing a future-proof system that delivers high quality outputs that are relevant for decision making in Member States.

Proposals to ensure equity of access and solidarity across EU member states

The industry is committed to participating in a **structured dialogue on conceptual framework for Equity-Based Tiered Pricing (EBTP)**. The objective is to ensure that ability to pay across countries is considered in the prices of innovative medicines, anchored in a principle of solidarity between countries, to reduce unavailability of new medicines and access delays.

Building on Value Based Pricing (VBP) as the foundation for pricing innovative medicines (where the pricing of medicines is based on the value they deliver to patients, healthcare systems and society), Equity Based Tiered Pricing (EBTP) is a framework for the pricing of medicines that takes into account a country's ability to pay with the objectives of improving patient access (defined broadly in terms of speed and availability) across Europe. The commitment of both Member States and industry is needed for EBTP to work in practice, and some of the current barriers to access and differential pricing need to also be addressed. This includes addressing how External Reference Pricing (ERP) is used and ensuring that non-extraterritoriality is observed. EFPIA members support an EBTP approach based on a concrete conceptual framework[70] with the following characteristics:

- To promote faster and greater access, companies would voluntarily commit to applying EBTP principles to specific innovative medicines.
    - The framework would include simple rules regarding the tiers and how this affects the price of medicines when EBTP is applied, but would leave room for individual companies to determine how this is applied.
- In order for prices to reflect value and be consistent with EBTP, companies will continue to negotiate with individual countries in order for prices to reflect the value that medicines deliver in that market. EBTP would set a framework for prices but the final price is dependent on company strategy and negotiations in the Member States. EBTP does not replace value assessment or value-based pricing.
- The resulting price must be commercially confidential. Given the need for price confidentiality, it will not be possible to publicly observe exactly how EBTP is working in practice. A process of verification would be required.

The proposed industry commitments would be contingent on the implementation of corresponding commitments from other parties necessary for the EBTP framework to achieve the intended impact.

1.9. Conclusion

The need for a dialogue on how to improve availability and reduce delays is clear. Although it is inevitable that availability will vary to some extent across European markets, patients in one part of Europe should not have to wait ten times longer for a new medicine than those in another part. Patients living with one condition in a country should not have to wait longer than patients living with a different condition. We need to work together to ensure that access to medicines is based on the patient's clinical need, not on their postcode. The industry has set out a number of commitments demonstrating how the industry can play a key role in addressing the issue of unavailability and delay.

70 https://efpia.eu/media/636825/a-shared-approach-to-supporting-equity-based-tiered-pricing.pdf

Glossary:

- **Access:** Refers to actual systematic usage of medicines.
- **Availability:** Inclusion of a centrally approved medicine on the public reimbursement list in a country. A medicine is available on the market if patients can receive the medicine under a reimbursement scheme. The availability date is the first date when doctors can prescribe / hospitals can administer the medicine to patients in the country, who will be able to benefit from reimbursement conditions applicable in the country (i.e. administrative procedures to be included in the positive reimbursement list have been completed, where applicable).
- **Time to availability:** The time to availability is the number of days between EMA marketing authorisation and the date of availability to patients.
- **Market launch:** This refers to whether a product is placed on the market for sale (not to its reimbursement by the national or regional authorities).