The root causes of unavailability and delay to innovative medicines in smaller EU markets:

Reducing the time before patients have access to innovative medicines

1. Introduction[1]

EFPIA has looked for many years 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 2023, the average time to reimbursement for innovative treatments across the European Union (EU) and European Economic Area (EEA) countries has reached 578 days.[2] There are significant differences in the time taken prior to national reimbursement. The industry shares concerns about these delays and recognises that delays and the unavailability of medicines harm patients. These concerns are important context for the debate regarding the impact of the EU's planned revisions to the General Pharmaceutical Legislation and whether these will improve access to medicines for patients in the EU.

To address differences in availability, we need to understand the underlying causes. Over the past five years, EFPIA has documented the root causes 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 W.A.I.T. analysis.[3] These are rooted in the medicines access systems and processes in the EU member states and the corresponding impact on commercial decision-making (Table 1). They range from a slow regulatory process to late initiation of market access assessment, to duplicative evidence requirements, to reimbursement delays, to local formulary decisions. As the root causes are multifactorial, they can only be solved by different stakeholders working together.

Table 1: The root causes of delays and unavailability

Category	Potential root causes
1. The time prior to marketing authorisation	• The speed of the regulatory process • Accessibility of medicines prior to marketing authorisation
2. The pricing and reimbursement process	• Initiation of the process

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

2 The Patient W.A.I.T. Indicator 2024 Survey. Note: Only one date was submitted in total for Malta, so it is excluded from the range and average calculation.

3 EFPIA (2024) The root causes of unavailability of innovative medicines and delay in access: Shortening the wait. Available at: https://www.efpia.eu/media/xsmfuf4h/root-causes-of-unavailability-and-delay-efpia-cra-2024.pdf [accessed January 2025]

	• The speed of the national timelines and adherence
3. The value assessment process	• Misalignment on evidence requirements • Misalignment on value and price • The value assigned to product differentiation and choice
4. Health system constraints and resources	• Insufficient budget to implement decisions • Diagnosis and supporting infrastructure
5. The subnational approval process	• Multiple layers of decision-making process

Source: The root causes of unavailability of innovative medicines and delay in access: Shortening the wait

Even with the significant focus given to reducing access inequalities by the industry and policymakers, there has been little progress in improving availability, with the same smaller countries reporting low rates year on year. European countries share many of the same issues – for example, the regulatory process is jointly undertaken for those in the EU – but there is a concern that smaller markets have additional or specific challenges in addition to those previously described in the existing Root Causes studies.[4] This report complements the Root Causes paper and considers whether there are issues specific to the smaller markets that have not been previously documented and whether targeted solutions are required.

2. Evidence on unavailability and delays in smaller markets

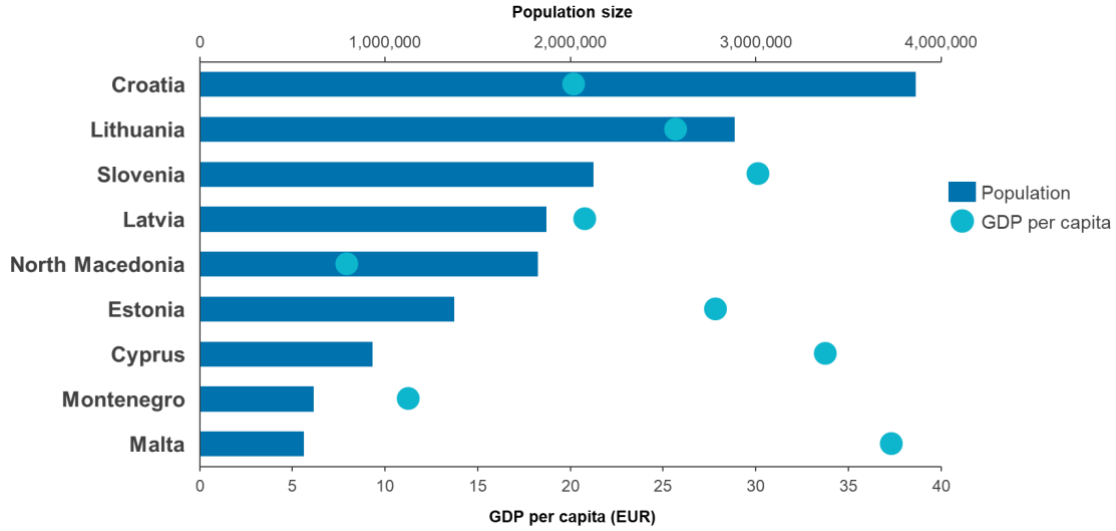
To investigate this, we chose to focus on seven EU countries (which share the same EU regulatory process): Croatia, Cyprus, Estonia, Latvia, Lithuania, Malta, and Slovenia; and two non-EU countries (included to examine the impact of local regulatory processes in smaller markets): Montenegro and North Macedonia.[5] These represent a range of smaller markets, all with availability of innovative medicines below the median in Europe and with population sizes below 4 million people. However, from the outset it is important to recognise that although they may have commonalities, there are also significant differences and each country is unique: for example, the population size varies from 3.9 million in

4 EFPIA (2024) The root causes of unavailability of innovative medicines and delay in access: Shortening the wait. Available at: https://www.efpia.eu/media/xsmfuf4h/root-causes-of-unavailability-and-delay-efpia-cra-2024.pdf [accessed January 2025]

5 The choice of countries is always somewhat arbitrary, but in this case is consistent with some of these countries working together to look at policy solutions to improve availability. "Minister says proposal for voluntary procurement of medicines welcomed by EU counterparts" https://www.cbn.com.cy/article/2024/12/12/810872/minister-says-proposal-for-voluntary-procurement-of-medicines-welcomed-by-eu-counterparts/

Croatia to 560,000 in Malta,[6] and GDP per capita varies from €37,400 in Malta to €8,000 in North Macedonia.[7]

Figure 1: Population and economic size of the selected smaller markets



Source: Eurostat and World Bank

While there are annual fluctuations in the data on availability and delay in these markets, the overall picture has not changed substantially since 2019. Comparing results on the proportion of recent approvals by the European Medicines Agency (EMA)[8] that are available in each country shows us that there are significantly different rates of availability across smaller countries (Figure 2), with Slovenia demonstrating the highest rates, largely in line with the EU average, and Malta and North Macedonia consistently showing the lowest rates. Many countries exhibit fluctuations in availability over time; however, availability has generally improved over time in countries such as Latvia and Cyprus.[9]

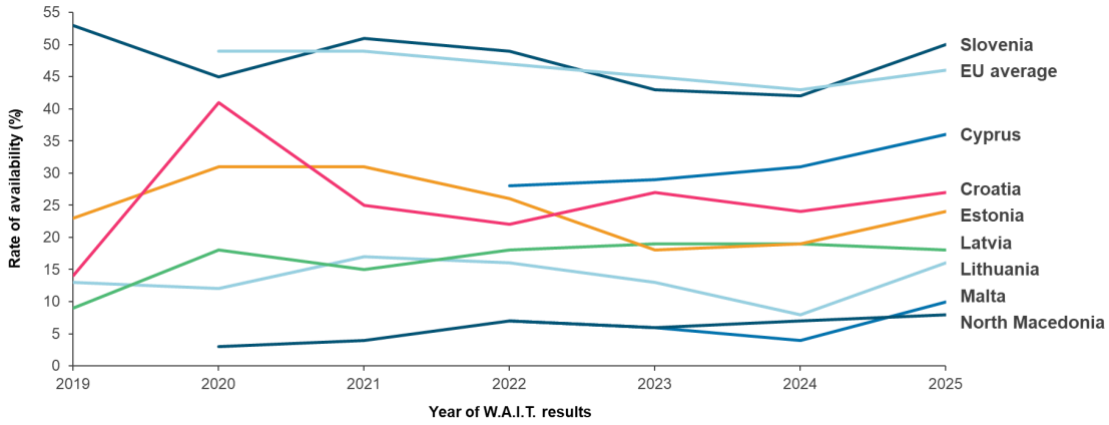
6 Eurostat, Population (national level) database, 2024. Available at: https://ec.europa.eu/eurostat/databrowser/view/tps00001/default/table?lang=en&category=t_demo.t_demo_pop [accessed January 2025]

7 World Bank, GDP per capita (current LCU), 2023. Available at: https://data.worldbank.org/indicator/NY.GDP.PCAP.CN [accessed January 2025]

8 The W.A.I.T. Indicators capture data on the availability of innovative medicines that have recently received European Union central approval in their first indication.

9 Data are not available for all countries in every W.A.I.T. survey as some countries have been added over time. Montenegro is not included in the W.A.I.T. survey.

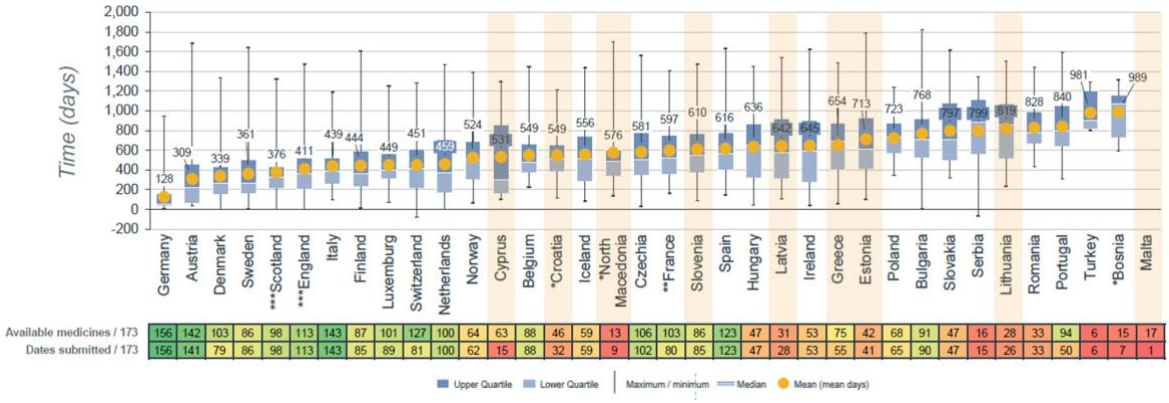
Figure 2: Rates of availability of innovative medicines in smaller markets[10]



Source: The Patient W.A.I.T. Indicator Surveys[11]

Common across most of the smaller markets is that there are clear delays in availability (Figure 3). Comparing trends in rates of availability versus time to availability shows that there are some commonalities (Slovenia and Croatia generally score higher on both metrics than the other smaller markets) but also some outliers (for example, North Macedonia has one of the poorest rates of availability, but medicines that are available have been reimbursed relatively quickly).

Figure 3: Mean time to availability in days (2020–2023) in European countries[12]



Source: The Patient W.A.I.T. Indicator 2024 Survey[13]

10 Note: Montenegro is not included in the W.A.I.T. Indicator Survey. Malta and Cyprus were included for the first time in 2022. North Macedonia results should be interpreted within the context that rates of availability are reported by W.A.I.T. in context of EMA approvals, but North Macedonia makes its own marketing authorisation decisions, which may differ from those of the EMA. More generally, the geographic scope, methodology and reporting on the W.A.I.T. Indicators has evolved over time, and hence caution should be applied when making year-on-year comparisons.

11 IQVIA (various) EFPIA Patients W.A.I.T. Indicator 2018–2024

12 Malta is not included as no dates were submitted. Montenegro is not included in the W.A.I.T. Indicator Survey. North Macedonia is not covered by central EU marketing authorisation, so time to availability is calculated using the local authorisation date.

13 IQVIA (2024) EFPIA Patients W.A.I.T. Indicator 2024 Survey

3. What are the additional factors that could explain unavailability and delay in smaller markets?

To identify the additional factors explaining availability and delay in smaller markets, we undertook a literature review that included academic, think tank and government publications, we held a series of workshops with national trade associations, and we conducted interviews with country managers within EFPIA member companies.

Building from the existing evidence base of root causes of unavailability and delay across Europe, we focused this analysis on describing *additional* factors that can help to understand availability of medicines in smaller markets. This includes a deep-dive on three of the root cause categories:

- **The pricing and reimbursement process**
- **The value assessment process**
- **Health system constraints and resources**

We also analysed the time before marketing authorisation for the selected non-EU countries.[14] We did not look in detail at the subnational approval process as it does not help us to understand the specific challenges impacting smaller markets.

3.1. The time before marketing authorisation (ex-EU countries)

This analysis primarily focuses on the steps required for patients in smaller countries to get access to new medicines. The time to European marketing authorisation is therefore not a relevant issue, as there is a centralised process that applies to all EU markets, including smaller markets. For North Macedonia and Montenegro, we need to consider that they have their own regulatory processes, and pharmaceutical companies must file separately for national marketing authorisation.

The evidence from Montenegro is that the regulator (CALIMS) typically approves innovative medicines within one year following EMA approval.[15,16] This is consistent with local regulatory processes contributing to additional delays. There is no automatic recognition of EMA decisions. However, there have been efforts to increase the efficiency of the marketing authorisation step by aligning the local requirements with the EMA, such that manufacturers can leverage their EMA submissions to streamline dossier preparation time and local regulators can conduct accelerated reviews by referencing the published EMA decision. Nonetheless, this requires that the submission for marketing authorisation in North Macedonia and Montenegro occurs after the positive opinion from the Committee for Medicinal Products for Human Use (CHMP) at an EU level. CALIMS must issue a decision

14 EFPIA (2024) The root causes of unavailability of innovative medicines and delay in access: Shortening the wait. Available at: https://www.efpia.eu/media/xsmfuf4h/root-causes-of-unavailability-and-delay-efpia-cra-2024.pdf [accessed January 2025]

15 AmCham Montenegro (2020) Position paper: Value and access to innovative medicines in Montenegro. Available at: https://www.amcham.me/wp-content/uploads/2023/07/Position_paper_value_and_access_to_innovative_medicines_in_montenegro.pdf [accessed February 2025]

16 A product-by-product comparison of regulatory approvals in North Macedonia and Montenegro is not possible due to lack of data transparency.

within 210 days of receiving an application for marketing authorisation, or within 150 days if the product has already obtained EU marketing authorisation.[17]

3.2. The pricing and reimbursement process

After marketing authorisation is granted, every country in Europe has a distinct pricing and reimbursement (P&R) process with requirements falling on marketing authorisation holders and national health authorities. In the smaller markets, we find that there are often barriers affecting the speed of initiation of this process, and that there are country specific requirements. After initiation of the process, the timeline for reaching a decision on price and reimbursement conditions is also typically longer in smaller European markets than in larger markets. We have found new evidence of factors contributing to this delay in some of these smaller markets, including health technology assessment (HTA) capacity constraints, lack of transparency or ability to monitor the outcomes of decision-making processes, and lack of adherence to regulations on P&R timelines.

Initiation of the process

The initiation of the P&R process is typically the responsibility of the marketing authorisation holder. However, this varies across the countries considered.

In all of the selected EU countries, it is only possible to start the P&R process after the marketing authorisation decision has been published by the European Commission. In North Macedonia, price setting begins in parallel with marketing authorisation, although the price is officially approved after national regulatory approval.

In several of the smaller markets, professional medical associations or the payer can also request the initiation of the P&R process for innovative medicines; this is the case in Estonia and Slovenia, for example. In Estonia, the Health Insurance Act previously stipulated that only healthcare providers or professional medical associations could submit proposals to amend the list of inpatient healthcare services reimbursed by the Estonian Health Insurance Fund.[18] This has since been amended in recent years, and marketing authorisation holders can now also submit proposals for their own medicines to be included. However, this is a contributory factor when considering historical data on availability and delays.

It is also the case that in smaller markets, companies often lack a local legal entity and hence operate through local distributors and consultants who have the necessary presence and expertise to file the submission on their behalf. This does not change the filing requirements but may affect the business case to launch a new medicine (discussed further below).

There are also countries where additional requirements need to be satisfied before manufacturers can file for P&R. This does not typically take the form of formal rules that prohibit filing, but instead an informal preference for filing only after there are sufficient results from other countries. In many of the smaller markets, payers have a strong preference to only begin the national assessment and decision-making process when there

17 CInMED (n.d.) Law on Medicines. Available at: https://cinmed.me/wp-content/uploads/2023/01/Law-on-medicines-Official-Gazette-of-Montenegro-080-20-unofficial-translation.pdf [accessed March 2025]

18 Estonian Parliament (2019) Health Insurance Act (RaKS). Available at: https://www.riigiteataja.ee/akt/113032019136 [accessed January 2025]

are published assessments available from major European markets, so that the local P&R process can be carried out in a more efficient and less duplicative manner.[19] There is often a preference for English language reports; hence, countries may wait for England's NICE, Scotland's SMC, or Ireland's NCPE[20] to publish their assessments before conducting a local evaluation.

Given the challenges with submission, we also see that manufacturers and health authorities frequently leverage the use of alternative access schemes (AAS) as a precursor to the full submission for formal reimbursement. So, the initial focus on the marketing authorisation holder is to achieve access through the AAS. Given the small patient populations in these markets, named patient programmes can act as a substantial means for patient access to be achieved ahead of the P&R process being initiated. For example, in Cyprus, a country with only 950,000 people, physicians are able to request named patient access to EMA-approved innovative medicines before the manufacturer has filed a local submission for P&R and been formally reimbursed, which can take years[21] (as a result of challenges described in the next section).

The speed of national timelines and adherence

In all of the selected countries, we found a defined P&R process with some guidance on key requirements for manufacturers. Perhaps inevitably, given the smaller size of these countries, the size of the national agencies involved is significantly smaller than in larger EU countries. The length of time taken for agencies in smaller EU markets to reach decisions on P&R should, in theory, reflect the EU Transparency Directive (European Commission, 1988) which sets a strict maximum time of 180 days for reaching a national P&R decision. We find that in practice, many of the smaller markets almost always find it challenging to meet this timeline. In some markets this is exacerbated by the nascency of the decision-making bodies. For example, in Cyprus, the National Health Service (GeSY) was only introduced in 2019 (just before the COVID-19 pandemic), and so decision-making processes are still maturing and navigating initial challenges.[22] The new process has also introduced the requirement for Cyprus-specific therapeutic protocols to be developed, which adds time and complexity to the incorporation of new medicines into the system. However, it should also be noted that some smaller markets, such as Slovenia and Croatia, demonstrate success in conducting timely P&R processes, with the Slovenian authorities recently increasing the headcount of their Health Insurance Institute in order to clear a backlog of P&R applications. We did not, however, find any evidence of marketing

19 The introduction of EU Joint Clinical Assessment may replace the preference for completed national HTA reports in the future and offer similar efficiency gains.

20 Malta has historically sourced medicines from the UK. Following Brexit, medicines are now typically sourced from Ireland (which has lower rates of availability and greater delays in availability of innovative medicines than the UK, as shown in W.A.I.T.). "The availability of medicines post-Brexit in Malta" (2024) Available at: https://www.regulatoryrapporteur.org/pharmaceuticals/the-availability-of-medicines-post-brexit-in-malta/653.article [accessed January 2025]

21 The Patient W.A.I.T. Indicator 2024 Survey finds the average time between marketing authorisation and availability in Cyprus is 531 days. The time can reach as high as 1,300 days for some medicines.

22 Petrou, P. (2021) The 2019 introduction of the new National Healthcare System in Cyprus. *Health Policy* 125(3): 284–289

authorisation holders (MAHs) being discouraged from filing for P&R due to capacity requirements.

We did find concerns about the lack of transparency of these processes and lack of ability for manufacturers or physicians to understand at what stage of the process specific medicines are, or when a decision can be expected. Notably this is a concern in Malta, Cyprus, North Macedonia, and Montenegro, where manufacturers report filing medicines for reimbursement and then not hearing back from authorities with a request for more evidence or to enter into pricing negotiations for up to several years after the submission was made. In Malta, of 259 medicines submitted to GLFAC for clinical assessment between 2014 and 2019, only 131 were reviewed by the second committee focusing on affordability (ACHCB). Only 95 were ultimately approved for the public formulary.[23] The status of decisions on other submitted medicines is not transparent.

There are also issues with the publication of updated positive lists (an issue that has largely disappeared in larger European markets), with several smaller markets only publishing updates to the positive reimbursement list on an annual or ad hoc basis. In North Macedonia, the positive list is updated irregularly, with previous reports of a gap of up to seven years between publications. This creates delays in availability of medicines that have been determined to address local unmet needs and have demonstrated cost-effectiveness to the system.

3.3. The value assessment process

Value assessment is a complex and often resource-intensive process in many European countries, and this can be exacerbated in smaller markets. Each of the smaller markets considered has its own unique value assessment process with distinct evidence requirements, but most also have requirements on budget impact assessments. We find that amongst the smaller markets, there are some largely common challenges arising from the size of these markets (relating to small patient populations and lack of availability of local epidemiological data) and some challenges that arise from each country's preferred mechanism(s) for managing their limited pharmaceutical budget (which result in misalignment of value from price, or affect the value placed on the availability of particular medicines).

Misalignment on evidence requirements

The misalignment that exists among industry, regulators, and HTA bodies, but also among HTA bodies in different European countries, is well documented.[24] On top of this, there are additional evidence-related factors that contribute to delays in availability of medicines in smaller markets.

The first of these is logistical. Given the small population sizes in these markets, there may not be local data to complete the budget impact analysis that is required by most countries for the introduction of a novel medicine, particularly if that medicine is indicated in a small

23 Abraham, K. & Franken, M. (2023) A SWOT analysis of the complex interdependencies of the Maltese reimbursement processes. *Health Policy* 4(100095)

24 EFPIA (2024) The root causes of unavailability of innovative medicines and delay in access: Shortening the wait. Available at: https://www.efpia.eu/media/xsmfuf4h/root-causes-of-unavailability-and-delay-efpia-cra-2024.pdf [accessed January 2025]

patient population. In some countries, this problem is exacerbated by a lack of robust health data infrastructure, and in others the necessary data exists but is held by the health authorities and is not accessible for manufacturers to use when preparing their P&R submissions (for example, this is reported in Cyprus, Lithuania, Croatia, and Estonia).

Another evidence challenge can be described as both a symptom and a cause of unavailability of innovative medicines in smaller markets: because these markets generally are slower to adopt innovative medicines (as shown in W.A.I.T.), the local standard of care in the country may not align with the international standard of care. When pharmaceutical companies are designing comparative clinical studies, they base this on a global assessment of the relevant standard of care in a given indication. If the smaller European markets have not yet reimbursed that comparator, they face difficulties when assessing the efficacy of a novel medicine that used that comparator in its clinical studies. In some countries, this creates a need for post-hoc indirect treatment comparisons (ITC) to demonstrate value relative to the local comparator, which can be methodologically challenging and reduces likelihood of reimbursement. Some of the smaller markets have recognised this as a challenge and accept simpler ITC methodologies.

In some smaller markets, there can also be uncertainty regarding how the official guidelines and regulations on evidence requirements and decision criteria have been interpreted in the context of specific reimbursement decisions. This has been noted in markets such as Croatia and Montenegro, where detailed reimbursement appraisals are not published for each new medicine and hence it is not always clear which criteria and associated evidence have driven the decision in practice. This could contribute to delays as it may necessitate requests for additional information during the negotiation process, or lead to negative reimbursement decisions without transparent rationale (which may deter the submission of new applications for reimbursement).

Misalignment on value and price

Most countries in the scope of this study use some form of HTA, but there is significant variation in whether the process has flexibilities for different types of innovative medicines. A particular challenge in the methodology used in Estonia is that there are strict ICER thresholds (€20,000 per quality-adjusted life year (QALY) for chronic treatments, €40,000 per QALY for end-of-life treatments) that are defined with a more restrictive definition of value and more limited recognition of the particular context of specific patient groups or diseases than other countries typically use – for example, not taking into account disease severity. Unusually, the cost-effectiveness calculation also considers VAT (at 9%) as part of the cost of the medicine; this differs from larger HTA markets, such as the UK, which exclude VAT from all economic evaluations.[25] Estonia also lacks any ICER flexibility for orphan medicines; this contrasts with other countries in Europe, including neighbouring Latvia (which uses a context-specific threshold of €300,000 per QALY for orphan medicines).[26]

25 NICE (2023) NICE health technology evaluations: the manual. Available at: https://www.nice.org.uk/process/pmg36/chapter/economic-evaluation-2 [accessed February 2025]

26 Vončina, L. et al. (2023) Review of Latvia's Pricing and Reimbursement System and its Lists of Reimbursed Medicines. Available at: https://www.vm.gov.lv/lv/media/13686/download?attachment [accessed January 2025]

Even once there is alignment on the value of a new medicine in a given country, a subsequent challenge arises when trying to align that value with the country's ability to pay. We find that in the smaller markets this can generate further delays, not only at the list price setting stage but also from subsequent application of measures intended to contain pharmaceutical spend, such as confidential discounts, tenders and use of clawbacks, all of which ultimately misalign the determined value of a medicine with its net price. For example, in North Macedonia, after a decision on the P&R conditions for a new medicine is reached, a tender must be established for that International Nonproprietary Name (INN). This can delay patient access and generate uncertainty, as tenders are only renewed annually. In Malta, single-winner tenders are established at an ATC4 level. The result of this is another process before the product is available, and that the resulting price is not aligned to the value assessment process. Ultimately this prevents patient access to new medicines that are not able to secure the winning bid.

One tool that can be used to both manage the risk related to expenditure on a medicine and ensure that price is aligned with value is managed entry agreements (MEAs). However, these are challenging to implement in many smaller markets for two reasons: (1) the lack of data availability and accessibility to support the design and implementation of MEAs, and (2) a lower level of willingness from HTA bodies and payers to enter into such agreements. The data availability challenge was described above in the context of limited data to support even standard budget impact modelling, let alone more sophisticated contracts. The willingness challenge is not present in all markets, and indeed we see payers in some smaller markets demonstrating openness to finding innovative solutions to ensure medicine availability (such as in Croatia and Slovenia). In other countries, such as Malta and Montenegro, typically only simple confidential discounts can be negotiated. The willingness and capacity for countries to enter into MEAs may also depend on the type of MEA: for example, an OECD study found publicly available evidence of 22 MEAs in Lithuania, but only one of these was performance-based.[27] There is also a lack of integration between the MEAs and the P&R process in smaller markets. In North Macedonia, although MAHs can negotiate MEAs with the expert commission for concluding special agreements, which sits within the Ministry of Health (MoH), these MEAs are not considered within the reimbursement decision. This disconnect between pricing decisions and reimbursement reduces the utility of MEAs for both the MAH and the MoH, meaning they are not implemented in practice.

The value assigned to product differentiation and choice

In the context of finite and often very limited pharmaceutical budgets, countries also vary in how much value they place on the availability of particular medicines. Countries may have very few patients with a particular condition or may favour different approaches to treating that condition than those used in other countries. In Slovenia, determination of the local medical need for a new medicine by a scientific committee is a necessary step before reimbursement negotiations can begin.

27 Wenzl, M. and Chapman, S. (2019) Performance-based managed entry agreements for new medicines in OECD countries and EU member states: How they work and possible improvements going forward. Available at: https://www.oecd.org/en/publications/performance-based-managed-entry-agreements-for-new-medicines-in-oecd-countries-and-eu-member-states_6e5e4c0f-en.html [accessed January 2025]

Establishing the epidemiologically driven need for a new medicine is particularly relevant in smaller markets when it comes to rare diseases. For example, Malta has a population of only 550,000. The number of patients with a given rare disease is very likely to be fewer than 50, or fewer than 10 in the case of ultra-rare diseases.[28] This may affect the extent to which new rare disease medicines are prioritised in the P&R process and budget allocation decisions (and the extent to which alternative access schemes represent a more effective alternative to standard P&R pathways).

We also see variation in the ways in which countries choose to manage the availability of multiple medicines within a therapeutic area or drug class. For example, in Malta, after a positive HTA evaluation, the MoH will then list the new medicine on the Government Formulary List (GFL). The Central Procurement Supply Unit is responsible for procurement of medicines on the GFL, which typically takes the form of single award tenders at the therapeutic class level, with price as the key criterion. Therefore, irrespective of the determined value of an innovative medicine, the manufacturer will be required to bid the lowest viable price in order to secure any patient access. As these tenders are conducted at the class level, there are often multiple innovative medicines and generic medicines competing within the same lot, and patients will only gain access to the one winning product. The resulting contracts can last up to four years. This approach demonstrates prioritisation of price competition and cost containment over access to a wide range of medicines and enablement of choices in shared physician and patient decision making.

3.4. Health system constraints and resources

A common characteristic of the selected smaller markets is the constrained healthcare budget that they are operating with, relative to larger or wealthier European countries. The mechanisms by which policymakers in each country choose to control pharmaceutical expenditure within those limited healthcare budgets can contribute to unavailability and delays in availability of innovative medicines.

Insufficient budget to implement decisions

Many of the smaller markets in scope of this study spend less on healthcare and on pharmaceuticals per capita than the EU average (Figure 4). Therefore, irrespective of positive outcomes from HTA evaluations, payers may lack budget to reimburse all innovative medicines. This inevitably contributes to delays in availability, which is observed in many of the smaller markets:

- In Lithuania, when a medicine receives a positive decision from the P&R process – involving an assessment of comparative efficacy, comparative effectiveness and cost-effectiveness, budget impact analysis and price negotiation – the product will then need to be moved to a positive waiting list until budget can be allocated for its reimbursement. The positive waiting list currently contains 82 medicines that have been positively appraised but are awaiting reimbursement.[29] The waiting time is reportedly 12–14 months on average, but there are instances where medicines

28 Using the EMA's definition of an orphan medicine (one that treats a condition affecting fewer than 5 in 10,000 people): https://www.ema.europa.eu/en/human-regulatory-overview/orphan-designation-overview

29 Evaluation of applications for inclusion of new medicines in the List of Reimbursable Medicines or expansion of reimbursement conditions; current situation as of October 1, 2024.

have been on the waiting list for years; the current list includes one medicine that was submitted in 2013. This delays availability of many medicines beyond the official end of the P&R decision-making process.

- In Latvia, the challenge has been similar in the past, but there are signs that this could be improving: in 2025, €21.6 million has been set aside for improving access to medicines, partially by increasing the number of reimbursed innovative medicines.[30] To manage the allocation of the budget, the National Health Service (NHS) makes decisions on what innovative medicines to reimburse via prioritisation criteria. However, there are many different criteria, with no indication as to their relative weight and importance.[31]
- In Malta, the healthcare budget is insufficient to procure all medicines on the GFL; therefore, there is political prioritisation for certain indications and medicines. The Minister of Finance, in collaboration with the Minister of Health, senior health officials and the chief medical officer, highlights these in the annual national budget speech, and this dictates where budget is allocated and the products which the Central Procurement and Supplies Unit (CPSU) prioritises with its limited annual procurement budget.[32,33]
- In Montenegro, although the positive reimbursement list is updated three times a year, as per national regulations,[34] there is not always sufficient budget to include all new medicines that have been filed for reimbursement. In some instances, the reimbursement list has been updated on schedule but no new medicines have been added to the list (the only updates being to the maximum wholesale price of previously listed medicines).

30 "Latvia to allocate EUR 21.6 million for improving access to medicines". Available at: https://www.navlindaily.com/article/23769/latvia-to-allocate-eur-21-6m-for-improving-access-to-medicines [accessed February 2025]

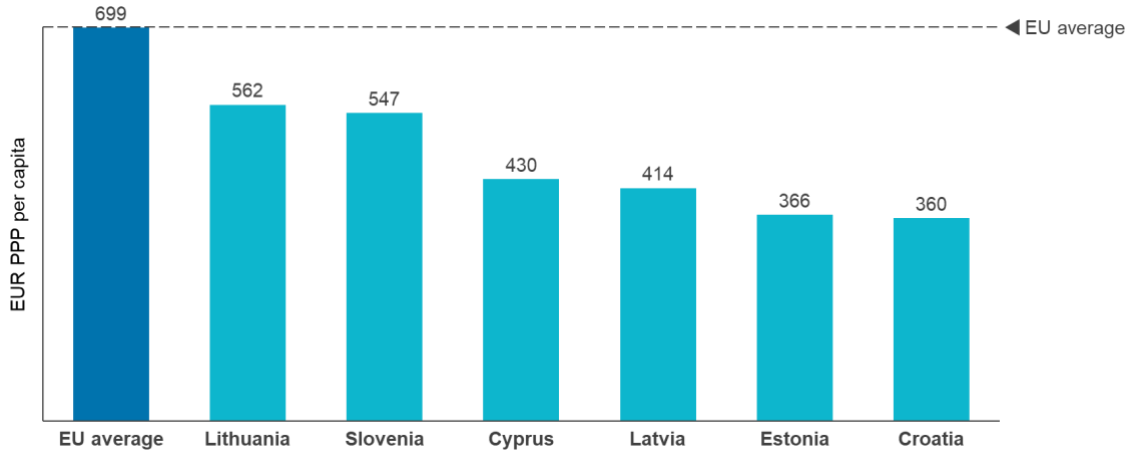
31 Vončina, L. et al. (2023) Review of Latvia's Pricing and Reimbursement System and its Lists of Reimbursed Medicines. Available at: https://www.vm.gov.lv/lv/media/13686/download?attachment [accessed February 2025]

32 Abraham, K. & Franken, M. (2023) A SWOT analysis of the complex interdependencies of the Maltese reimbursement processes. Health Policy 4(100095)

33 Abraham, K. & Franken, M. (2019) Prioritization of Drugs For Reimbursement In The Maltese Health System. Value in Health

34 REGULATION ON CRITERIA FOR THE DRAFTING, REMOVAL OR ADDITION OF ITEMS ON THE BASIC PAYMENT LIST. Available at: https://fzocg.me/wp-content/uploads/2023/05/Uredba-o-kriterijumima-za-stavljanje-odnosno-skidanje-lijeka-sa-osnovne-i-doplatne-Liste-ljekova.pdf [accessed March 2025]

Figure 4: Spending on pharmaceuticals and medical devices in smaller markets (2021)[35]



Source: OECD (2023)[36]

Smaller markets, with smaller healthcare budgets, are also taking different decisions regarding the proportional allocation of the healthcare budget to pharmaceuticals. Challenges also arise when pharmaceutical budgets shrink relative to the total capacity for expenditure on health. For example, when GeSY was established in Cyprus in 2019, the total budget was approximately €1 billion, and €200 million from this was allocated to pharmaceuticals. GeSY has matured over the past five years and the budget has grown to €1.7 billion; however, the pharmaceutical budget is expected to remain stagnant and not increase in line with the wider budget. This implies a de-prioritisation of access to new medicines relative to other competing health system priorities.

Despite many of these smaller markets facing challenges in budget allocation for reimbursement of innovative medicines, there has been some success in securing budget for specific types of medicine by setting out tailored access pathways that draw from distinct budgets. For example, in Croatia, rare disease drugs are funded through separate national budgets, which limits access delays for these products due to wider pressure on healthcare budgets; while in North Macedonia, there is specific funding allocated from the country's alcohol and tobacco tax.

Diagnosis, supporting infrastructure, and relevance to patients

Existence of appropriate health infrastructure to support access to reimbursed medicines is a challenge in many European countries, as has been extensively documented in the literature and summarised over the past five years in studies of the root causes of unavailability and delay.[37] Specifically in North Macedonia, predominantly only clinics

35 Note: 2021 data is not available for Malta. No data is available for North Macedonia and Montenegro as these are not OECD member countries.

36 OECD Health Statistics. Available at: https://www.oecd.org/en/data/datasets/oecd-health-statistics.html [accessed January 2025]

37 EFPIA (2024) The root causes of unavailability of innovative medicines and delay in access: Shortening the wait. Available at: https://www.efpia.eu/media/xsmfuf4h/root-causes-of-unavailability-and-delay-efpia-cra-2024.pdf [accessed January 2025]

within the capital, Skopje, have the infrastructure and medical expertise to administer innovative medicines. MAHs are able to provide access for these hospitals without undergoing the standard reimbursement process (see Section 4: Access without availability), which discourages MAHs from going through the more restrictive and less flexible broader P&R system.

The extent of the challenge in smaller markets is particularly evident for orphan medicines and precision oncology treatments that often require diagnostic testing infrastructure and a network of experts to diagnose and treat patients. A recent study by the European Society for Medical Oncology (ESMO)[38] found that Croatia, Cyprus, Latvia, Lithuania, Malta, North Macedonia, and Slovenia have no national or regional initiatives in place to support implementation of innovative molecular technologies, and that access to next generation sequencing (NGS) is generally poor across the smaller markets (Table 2).

Table 2: Availability of next generation sequencing (NGS) in smaller European markets[39]

	NGS panel (DNA) - small panel - Lung	NGS panel (DNA) - small panel - Breast	NGS panel (DNA) - small panel - Colon	NGS panel (DNA) - small panel - Prostate
Croatia				
Cyprus				
Estonia				
Latvia				
Lithuania				
Malta				
North Macedonia				
Slovenia				

Key: Always | Usually | Occasionally | Research | Never

Source: Bayle, A., et al. (2023)[40]

4. Access without availability

For the purpose of this study, availability has been defined as inclusion of a centrally approved medicine on the public reimbursement list in a country. This is typically through a P&R process that is started through a filing application (by companies or in some cases by medical professionals, as discussed above). As set out in the Root Causes paper, it is possible for patients to have access to medicines without availability (reimbursement) and

38 Bayle, A., et al. (2023) ESMO study on the availability and accessibility of biomolecular technologies in oncology in Europe. *Annals of Oncology*. 34(10): 934–945

39 Note: Montenegro was not included in the scope of this research.

40 Bayle, A., et al. (2023) ESMO study on the availability and accessibility of biomolecular technologies in oncology in Europe. *Annals of Oncology*. 34(10): 934–945

vice versa.[41] The industry has attempted to collect this information by looking at data on the utilisation of medicines and by collecting data on use of alternative access schemes through the European Access Hurdles Portal.[42]

Alternative access schemes (AAS) can be defined as routes by which manufacturers can make innovative medicines accessible to patients (either a subset or the full eligible patient population) without filing for reimbursement through the standard P&R process. AAS therefore do not result in what this report defines as "availability" (i.e. inclusion on a national reimbursement list), but rather they result in patient *access* to new medicines. Importantly, these are distinct from alternative funding sources for certain classes of medicines, such as described above for rare diseases in North Macedonia, and from tailored adjustments to the standard P&R process, such as increased ICER thresholds for orphan medicines in Estonia and Latvia. Such adjustments are made with the goal of supporting *availability* (i.e. the inclusion of the product on a national reimbursement list).

Focusing on AAS, unsurprisingly, we find that these are more important in many of the smaller markets than is typically the case across Europe. However, these take different forms (as outlined in Figure 5) and, as a result, demonstrate different levels of effectiveness in providing wide patient access to new medicines.

41 EFPIA (2024) The root causes of unavailability of innovative medicines and delay in access: Shortening the wait. Available at: https://www.efpia.eu/media/xsmfuf4h/root-causes-of-unavailability-and-delay-efpia-cra-2024.pdf [accessed January 2025]

42 CRA (2024) European Access Hurdles Portal: Results from the second year of data collection. Available at: https://www.efpia.eu/media/0m4pswzd/european-access-hurdles-portal-2024-cra-report.pdf [accessed January 2025]

Figure 5: Alternative access schemes in smaller markets[43]

	Alternative access scheme	Format	Applicable products or therapy areas	Funded?
Croatia	Compassionate Use	Physician-requested named patient programme	Severe diseases	No national funding; hospitals can choose to provide funding
Cyprus	Nominal Requests Committee	Physician-requested named patient programme	Severe diseases	Funded
Estonia	Compassionate Use	Physician-requested named patient programme	Severe diseases	Funded
Latvia	Compassionate Use	Physician-requested named patient programme	Severe diseases	Funded
Lithuania	Ultra-rare Disease Pathway	Physician-requested named patient programme	Ultra rare diseases	Funded
Malta	Direct Tendering	Drug class tenders	All	Funded
	Malta Community Chest Fund	Private funding from charitable organisation	Severe chronic illness, cancer, and rare diseases	Funded
	Exceptional Medical Treatment Pathway	Physician-requested named patient programme	Rare diseases (fewer than five patients in Malta)	Funded
Montenegro	Compassionate Use	Physician-requested named patient programme	Rare diseases	Funded
North Macedonia	Conditional Funding	Hospital-requested specific hospital programme	Innovative products	Funded
Slovenia	Compassionate Use	Physician-requested named patient programme	Severe diseases	Unfunded
	Named Patient Programme	Physician-requested named patient programme	Severe diseases	Funded

Source: CRA analysis

The most notable case of this is Cyprus, where until January 2025, a large proportion of innovative medicines were made available via the named patient basis route at the MoH, which had funding of €100 million (relative to the €200 million budget for medicines reimbursed via the standard pathway). This named patient programme does not require manufacturer filing, enables simpler and more efficient price negotiations, and sees a shorter delay to patient access. Given the long delays in the P&R process, this route provided faster access to patients. This has now been integrated into GeSY and hence managed as part of the overall pharmaceutical budget, so its role in the future is uncertain. Similarly, in North Macedonia the conditional funding pathway is often prioritised for innovative medicines since this facilitates faster patient access.

In some countries, such alternative access schemes provide a backstop to enable access. For example, in Malta, it is not necessary for medicines to have filed and been listed on the GFL to bid for a tender, creating the possibility for reimbursed patient access without filing and going through the standard reimbursement system. From the innovator's perspective, this channel has some significant issues, as the tenders are irregular and unpredictable, and they are winner-takes-all tenders (undertaken at ATC4 level). Given this, manufacturers could submit a bid and potentially lose to a lower-cost class competitor, or plan to submit a bid in the next round, but such attempts to provide access would not be

43 The examples in this table are alternative access schemes. Several of these countries also have tailored access pathways (e.g. flexible evidence requirements or alternative funding sources) that support reimbursement for specific types of medicine; these are not listed in this table.

reflected in measures of availability (or even access) as captured by the Patient W.A.I.T. Indicator and the European Access Hurdles Portal.

The rules governing alternative access schemes in smaller markets are changing, but it is likely these channels will remain significant in the future and an important pathway to provide patient access to innovative medicines. The most recent European Access Hurdles Portal data supports that alternative access schemes are of significant importance in smaller markets, particularly in Cyprus and Malta, where 27% and 15% of Portal products[44] respectively are available through alternative access schemes. However, given the heterogeneity in their design and degree of relevance to different types of medicine, collecting data on the use of these channels in a comparable manner is challenging. As a result, while the role of alternative access schemes is important, the utility of these channels for enabling access to different types of medicine is likely underestimated in the data generated through W.A.I.T. and the European Access Hurdles Portal.

5. Implications for policy solutions

The industry has developed policy proposals to improve availability across European markets,[45] and these remain relevant for smaller markets. Indeed, all five of the policy solutions have particular resonance in the smaller markets. (1) Improving the efficiency and quality of value assessment is likely to be particularly beneficial. The new EU HTA regulation and the phased implementation of joint clinical assessment (JCA) could address some of the complexity associated with diverging clinical evidence expectations and highly resource-constrained evaluation practices in different national HTA processes. This could be particularly useful in smaller markets that are still developing their approach to HTA (even if other barriers remain). (2) Smaller markets would benefit from the further development of Novel Payment Models to align price and value and manage affordability. Although some of the smaller markets use these types of agreements, they tend to focus on simple financial agreements that do not address the issue of affordability or allow for products with multiple indications. (3) Ensuring equity of access and solidarity across EU member states would benefit smaller markets. The consideration of Equity Based Tiered Pricing could address issues associated with transparency of prices and the impact of international reference pricing, which delays availability in markets with lower prices (so is likely to be particularly important for the smaller markets with the lowest ability to pay). (4) Improved transparency of information regarding placing centrally approved products on the market is particularly important for smaller markets. Indeed, this paper has substantially benefited from the data collected in the industry in the European Access Hurdles Portal (allowing us to identify the markets with the lowest filing rates). However, we should ensure that the Portal appropriately reflects the P&R process in smaller markets. For example, the collection of data on alternative access schemes can be improved substantially to reflect the access these provide. (5) Finally, all markets benefit from proposals to speed up the regulatory process to deliver safe and high-quality diagnostics, vaccines, and treatments to patients as fast as possible, but this is particularly important for smaller markets outside of

44 N=94 products that received marketing authorisation from the EMA between January 2021 and June 2024

45 EFPIA (2022) “Addressing patient access inequalities in Europe”. Available at: https://www.efpia.eu/media/677156/addressing-patient-access-inequalities-in-europe.pdf [accessed March 2025]

the EU, where resource constraints mean efficiency and international collaboration is even more important.

Turning to issues that are specific to smaller markets, we need to take into account that there are significant differences from country to country. The level of filing and availability in Slovenia and Croatia is significantly higher than in the other countries, so it is not surprising that they have different challenges. Each country is unique, but there are some shared challenges, especially when we consider country groupings:

- Croatia and Slovenia share similar budgetary constraints to the Baltic countries (after adjusting for income) but differ in that there is no formal HTA process in either country, and in Croatia a lack of transparency of what has driven reimbursement decisions can sometimes present an additional challenge. Croatia and Slovenia also have among the highest rates of availability of innovative medicines of the smaller markets included in this analysis, suggesting that there are aspects of these P&R systems that are working very effectively and may provide useful lessons for some other smaller markets.
- In the Baltics[46], although each country is distinct, there appears greater commonality in these markets, with health system funding and aligning price, value and evidence being the primary issues.
- In the smallest EU countries by population (Cyprus and Malta), there are intrinsic challenges related to the size of the patient populations in these markets and the implications this has for demand for a new medicine and feasibility of sourcing local data for required budget impact analyses. The structures of healthcare systems and P&R processes are also changing significantly, bringing about improvements but also challenges associated with the transition. For example, in Cyprus, the General Healthcare System, GeSY, introduced in 2019, has brought new agencies and processes, leading to some transitional challenges.
- In small countries outside of the EU (North Macedonia and Montenegro), there is the need to account for the delay between EU marketing authorisation and local marketing authorisation. However, this has been recognised as an issue, and there have been effective efforts to minimise the impact of this delay in both countries.

In terms of distinct solutions for smaller markets, a number of solutions should be considered.

One of the most pressing issues to be addressed in smaller markets is the low investment in the healthcare sector and the prioritisation of different disease areas within a limited budget. The level of government spending on healthcare as a percentage of GDP is fundamentally a policy choice. The average for the EU is 7.3%, and of the countries in scope, only Croatia (7.8%) and Slovenia (7.4%) spend above this. Spending in some of the smaller markets has increased significantly, but additional investment is warranted in Cyprus (6.1%), Estonia (6.5%), Latvia (5.3%), Lithuania (5.3%), Malta (5.1%), Montenegro

46 Baltics region refers to Estonia, Latvia, Lithuania

(6.9%), and North Macedonia (4.3%).[47] Although economic and global pressures may mean that raising the level of investment can only occur over time, it would be valuable to set out a pathway for increased investment and transparency regarding the areas that will be prioritised.

Another issue to address is the complexity and bureaucracy of the current P&R processes relative to the size of the market and the administrative capacity of the agencies involved. This is exacerbated by the need to develop tailored channels for particular types of health technology. Efforts to modernise the P&R channels are underway, with governments working with payers and industry in many markets to improve the efficiency of the standard P&R process as well as to develop tailored pathways to enable patient access. In the analysis above we distinguish between tailored pathways (integrated into the P&R system) and alternative access schemes that are common in the smaller markets. For example:

a) There are **alternative access schemes** that attempt to address some of the acknowledged inefficiencies in the standard P&R process and provide patient access in parallel to efforts to modernise the standard pathway. An example of this is in Cyprus: in the five years since the introduction of GeSY (bringing improvements but also initial process-related challenges), a large proportion of medicines have been made available through an alternative route funded by the MoH. This has provided an effective stopgap for access to innovative medicines while the health system matures. This supports national governments' efforts to comply with the EU Transparency Directive in parallel to implementing more systematic improvements to their P&R systems.

b) There are also **tailored access pathways** that are integrated into the standard P&R system and provide a sustainable solution for enabling patient access to specific types of medicines that cannot otherwise get access through the standard P&R system. For example, in Croatia (where there is a relatively mature P&R system that works well for most types of medicine), drugs with a high budget impact are granted access to the list of "especially expensive drugs", enabling sustainable reimbursement via a separate national budget. Other such channels aim to address challenges with P&R decisions for specific types of medicine, such as orphan drugs.

To improve patient access, both of these types of channels are important in smaller markets. Where they are not being used effectively, it would be useful for smaller markets to learn from the different approaches being used by comparable countries. Irrespective of their specific design, these channels need to be transparent, efficient and based on clear procedures. This will reduce the uncertainty associated to the decision-making process – helping companies without an active presence in the market – while not creating additional workload and administrative burden for payers or companies (and thus contributing to delays in patient access as an unintended consequence). Both types of channels need to

47 EU average and EU country data sourced from Eurostat (indicator: General government total expenditure on health, 2023, % of GDP). Available at: https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Government_expenditure_on_health#Source_data_for_tables_and_graphs [Accessed May 2025]. Data for Montenegro and North Macedonia sourced from World Bank (indicator: Domestic general government health expenditure, 2022, % of GDP). Available at: https://data.worldbank.org/indicator/SH.XPD.GHED.GD.ZS [Accessed May 2025].

be included in assessments of unavailability and delay (and this will require ongoing adjustments to the European Access Hurdles Portal, for example).

Finally, the limited resources and size of administrative teams available is a significant issue in many of the smaller markets. There is also a role for collaborative approaches and dialogue between countries to address inefficiencies of P&R procedures in smaller markets and reduce the fixed cost of launch, particularly where there are small patient populations. Currently, smaller countries are developing similar approaches to larger markets, in terms of evidence and filing requirements, meaning the companies face the same cost but this will be recouped through a significantly lower level of sales, making the business case unsustainable. Collaborative efforts could reduce the cost of tailoring to each country's P&R requirements (assuming they face broadly similar needs), reduce the capacity issues in these markets, and overcome the challenge of small patient populations. Already, collaborative approaches can be observed in some smaller markets through the referencing of HTA decisions from larger countries when deciding on the inclusion of a new medicine into the national reimbursement list. This has the potential to reduce inefficiency and alleviate the HTA capacity issues in these smaller markets, but efforts must be taken to ensure this does not indirectly contribute to delays (due to the need to wait for published assessments in a certain set of countries before the P&R process can begin). Collaboration can take many forms but ultimately should be based on the principles of overcoming shared root causes of unavailability and reducing barriers to market entry, rather than adding additional steps to the P&R process and thus contributing to delays.

6. Conclusion

There is clearly a need for dialogue on how to improve availability and reduce delays. 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 over 800 days 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 proposals demonstrating how the industry can play a key role in addressing the issues of unavailability and delay, but this won't be enough unless there are changes in policy, particularly in smaller markets.

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 and 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 EU 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).

Abbreviations

CHMP	Committee for Medicinal Products for Human Use
EEA	European Economic Area
EMA	European Medicines Agency
ESMO	European Society for Medical Oncology
EU	European Union
GeSY	General Healthcare System (GHS) (Cyprus)
GFL	Government Formulary List (Malta)
HTA	Health technology assessment
ITC	Indirect treatment comparisons
MAH	Marketing authorisation holder
MEA	Managed entry agreement
MoH	Ministry of Health
NGS	Next generation sequencing
NHS	National Health Service (Latvia)
OECD	Organisation for Economic Co-operation and Development
P&R	Pricing and reimbursement
QALY	Quality-adjusted life year