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CURRENT OPINION

# From Vision to Reality: The EU's Pharmaceutical Reforms and the Path to Improved Access

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**Abstract**
Disparities in access to oncology medicines in European Union (EU) member states can impact patient outcomes profoundly, with availability and timely access varying significantly across and within member states. This paper discusses the intersection of the new European Health Technology Assessment Regulation (HTAR), the provisions of the proposed pharmaceutical legislation and their potential impacts on access to oncology medicines across EU member states. The HTAR, seeking to standardise the clinical evaluation of new medicines, has the potential to streamline the evaluation process but also risks oversimplifying diverse national healthcare needs. While the HTAR may accelerate access in countries with less-developed health technology assessment systems, it could potentially conflict with established practices in countries with advanced assessment systems, resulting in both joint and national clinical evaluations becoming necessary. The proposed pharmaceutical legislation reform, in both initial and updated forms, aims to incentivise an EU-wide launch of new medicines that challenges the feasibility for manufacturers, particularly in the context of diverse and complex national pricing and reimbursement systems. Both initiatives mark a significant shift towards more collaborative European healthcare policy yet faces the potential of unintended consequences owing to an apparent lack of pragmatism, such as delays in access because of increased administrative burdens and possible deterrents for innovation in Europe. The paper underscores the need for policy adaptation and multi-stakeholder collaboration to ensure the legislative changes achieve equitable and timely access to oncology treatments across the EU.

## 1 Introduction

Access to medicines encompasses three critical dimensions, notably the availability, affordability and timely introduction of new medicines [1, 2]. Several challenges and considerable disparities exist within the European Union (EU), particularly concerning access to new oncology medicines [3]. The 2022 WAIT indicator survey sheds light on these disparities. For instance, the average time from marketing authorisation (MA) to the availability of an oncology medicine varies significantly between countries, ranging from 102 days in Germany to 991 days in Romania [4]. Considering availability during 2018–2021, 98% of the 46 regulatory-approved oncology medicines were available in Germany compared with 2% in Malta, with an overall European average of 50% (Fig. 1) [4]. However, technical availability does not guarantee a medicine's uptake and diffusion within a market. Significant differences exist in that context; for example, 12 months after obtaining reimbursement status, the relative cumulative use of oncology products ranged from 22% in the Netherlands to 81% in France [5]. These differences underscore significant variations in access across member states, which can be attributed to country-specific factors such as varying economic strengths, different affordability thresholds, unique healthcare system characteristics and competing priorities for public funding [6]. Furthermore, disparities exist within nations owing to a lack of streamlining across multiple layers of decision-making and limited clinical guideline updates. These disparities have significant implications for patient outcomes; for example, delays in access to ipilimumab and abiraterone in Europe were calculated to result in the loss of more than 30,000 patient life-years [7, 8].

Oncology medicines increasingly obtain MA with early phase or immature evidence/conditional authorisation, often

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**Key Points for Decision Makers**

Under the HTA Regulation, it is essential to pragmatically develop population, intervention, comparator and outcome (PICO) parameters, improve the use of real-world evidence (RWE) in clinical benefit assessments, establish RWE monitoring mechanisms and overcome committee-based implementation hurdles.

The implementation of a new pharmaceutical legislation must coincide with streamlining administrative processes, refining pricing and value assessments at the EU level and utilising tools such as joint procurement to ensure access across EU-27.

Going forward, all stakeholders must work together towards the common goal of better access to medicines. To support this initiative, the European Commission should propose a strategy that details the required national-level reforms necessary for EU-wide access to medicines.

on the basis of surrogate endpoints or non-randomised trial designs, responding to the desire to address areas of significant unmet medical need [9]. This challenges HTA agencies, requiring robust evidence of added clinical benefit to prove value to health systems. These challenges are further exacerbated by variations in health system readiness, national HTA systems, their capacity levels, methods and processes in place and the criteria informing appraisals [10–12]. It also highlights the complexity of patient access to medicines, which involves several inter-connected stages such as MA, pricing decisions, assessment and reimbursement recommendations, negotiations and uptake and diffusion. Each stage presents its own set of challenges, acting as barriers to ensuring the availability, affordability and timely access to medicines (Fig. 2) [2].

The recent European efforts to improve equitable access to medicines have centred around two pivotal initiatives: the HTA Regulation (HTAR) and the reform of the pharmaceutical legislation (PL). The HTAR aims to build HTA capacity at the EU level, reduce duplication of effort, simplify the HTA process and provide technology suppliers with a single clinical assessment that all EU member states (MS) would uniformly embrace [13]. Although its specified aim is not to improve access, it is a potential outcome through circumventing the need for individual country-specific clinical evaluations. Comparatively, the reform of the PL aims to incentivise timely and equitable access to safe and effective medicines across all EU nations [14].

The effectiveness and suitability of these evolving pharmaceutical policies are the subjects of ongoing debate, with several questions about their ability to meet the needs they purport to address. This paper seeks to address three objectives: first, to discuss whether the EU HTAR and the proposed PL incentive structure may improve access to oncology medicines; second, to identify and reflect on potential obstacles and unintended consequences that may arise from these legislative changes, with a focus on oncology medicines; and third, to explore potential avenues to improve the probability of success of both initiatives going forward. While oncology is the focus of this paper owing to the unique challenges in access and evidence generation, these insights may have broader relevance to other therapeutic areas. As these topics are continuously evolving, our commentary excludes any information published after July 2024.

## 2 HTA Regulation, Pharmaceutical Legislation and Likely Impact on Access to Medicines

### 2.1 The EU HTAR

Building on the work of the European Network for Health Technology Assessment (EUnetHTA) [15], the HTAR seeks to standardise the clinical evaluation of health technologies across the EU through joint clinical assessment (JCA), joint scientific consultation (JSC) and horizon scanning (HS) (Fig. 3) [13]. The primary benefit foreseen is the harmonised assessment of health technologies, aiming to streamline disparate national HTA clinical evaluation processes and provide a standard methodology for all. This should, in principle, lead to a more transparent valuation of products. However, its subsequent uptake will depend on the robustness of the process, the criteria underpinning its implementation and the local HTA systems' ability to successfully adapt to its provisions [16].

Through a single submission process, the JCA aims to expedite time to access by circumventing the need for individual country-specific clinical evaluations (see Appendix for further details). However, it is important to note that countries still have autonomy over their reimbursement decisions and thus inclusion in national clinical guidelines. This means that while the JCA can inform clinical assessment, each member state still performs its own economic analyses and makes independent decisions on reimbursement and the integration of treatments into national guidelines based on local clinical practice standards and budgetary constraints. Regardless, it has been suggested that harmonised methodologies, clear evidentiary requirements and procedures, such as horizon scanning and early scientific advice, across HTA bodies at the supranational

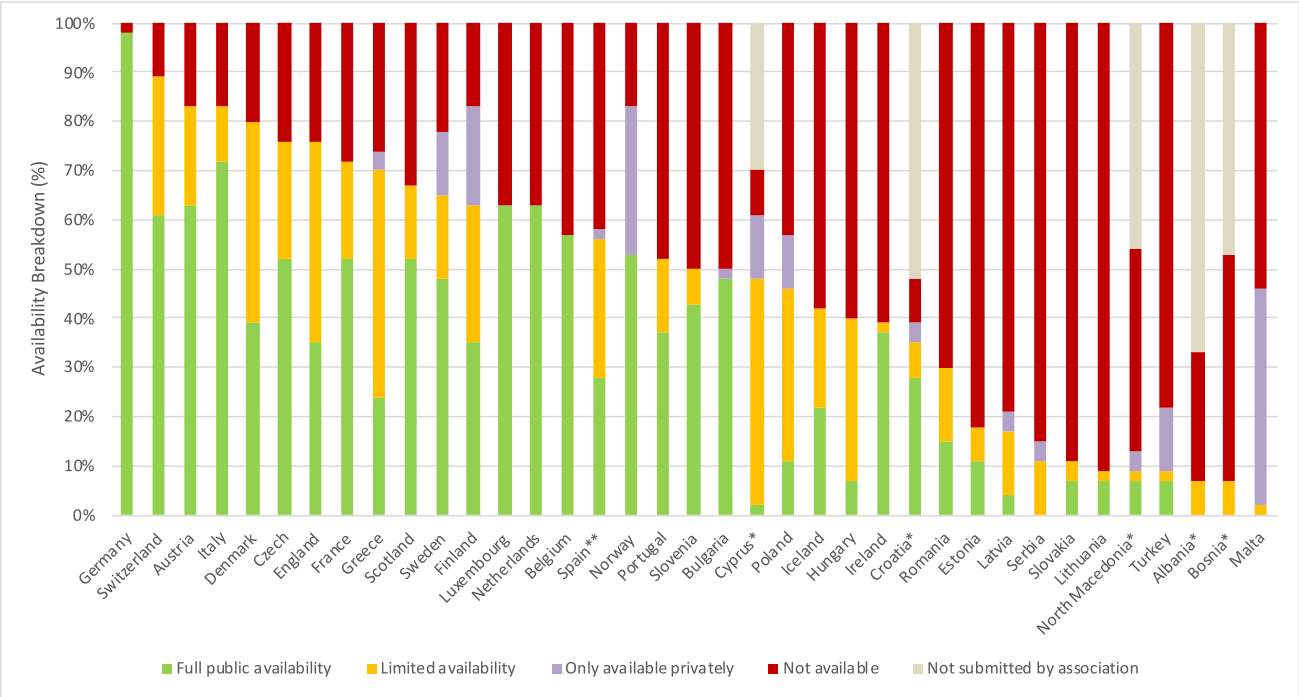


**Fig. 1** This figure displays a breakdown of oncology medicine availability in Europe (2018–2021) (%). The breakdown of availability refers to the compositions of medicines available to the public in European countries as of 5 January 2023. *Countries with asterisks did not complete a full dataset, and therefore, availability may be unrepresentative. **In Spain, the WAIT analysis does not identify those medicinal products that were accessible earlier in conformity with Spain's Royal Decree 1015/2009 relating to medicines in special situations. Source: EFPIA Patients WAIT Indicator 2022 Survey (IQVIA, 2023), p. 12

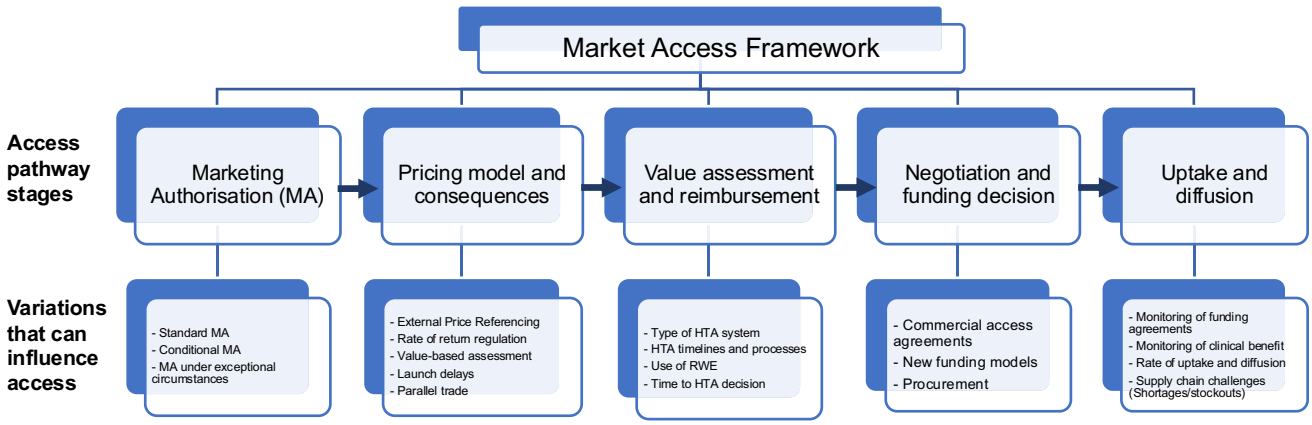


**Fig. 2** This figure displays the pathway of patient access to medicines. The figure is adapted from (Kamphuis et al., 2021). This framework highlights the key stages of the pharmaceutical market access pathway and identifies the key variations within each stage that can influence the time to access, affordability and availability of medicines

level will positively impact timely access to and availability of medicines [6]. While there are significant potential benefits, several questions remain about the Regulation's approach to achieving its goals, such as the development of PICO parameters, differing benefits to MS's, the role of real-world evidence (RWE) and the challenges associated with committee-based implementation.

*Pragmatism in the Development of PICO Parameters*

The clinical assessment process by a central group or body raises questions regarding the determination of population, intervention, comparator and outcome (PICO) parameters. This composite challenge is amplified by the diversity of healthcare landscapes and variations in the 'standard of care' across MS, particularly when assessing oncology

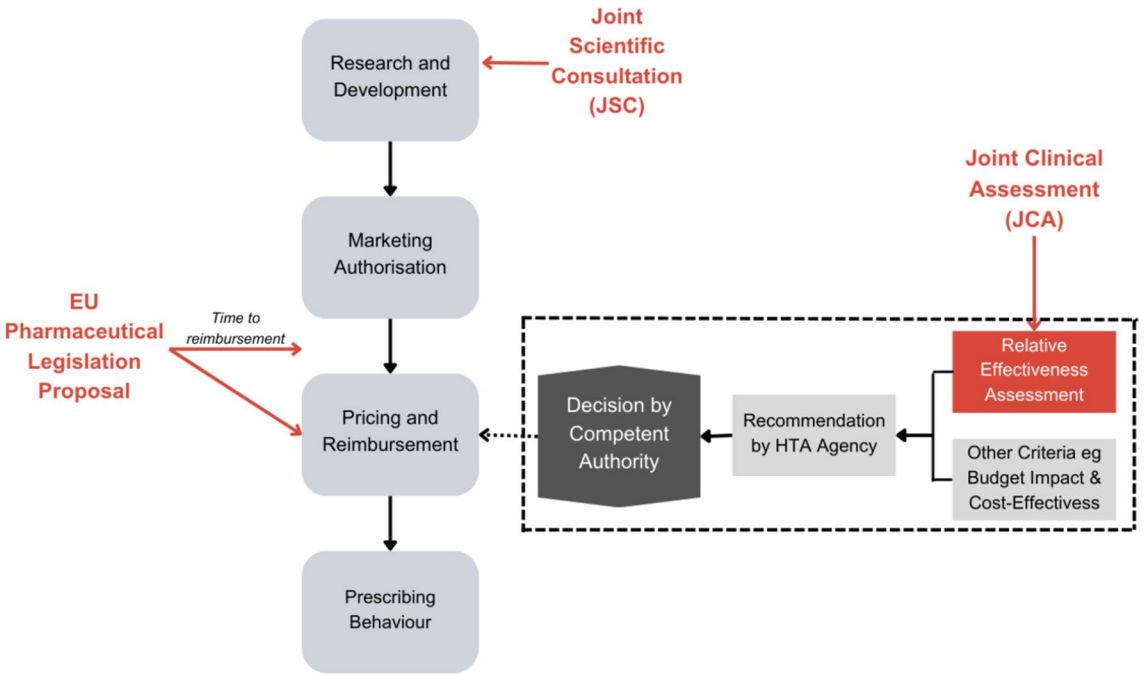


**Fig. 3** This figure displays the key aspects of pharmaceutical product market entry and use and where the EU HTA Regulation and proposed pharmaceutical legislation will fit into the process. Red indicates aspects covered by the EU HTA Regulation and proposed Pharmaceutical Legislation. The figure is adapted from ref. [17]

medicines [16]. 'EUnetHTA 21' proposed a policy-driven methodology to harmonise PICO parameters [18], aiming to utilise those that reflect the specific informational needs of MS over adhering to a set of 'best' PICOs based purely on empirical data. However, this approach generates concerns about the potential proliferation of PICOs within the JCA, imposing a significant burden on sponsors to conduct extensive analyses within the compressed dossier completion timeframe without the ability to consult with the assessors. This could hinder manufacturers from submitting high-quality dossiers, particularly with extensive PICOs requiring numerous comparisons. Such analyses complicate the task of assessors, particularly when dealing with indirect treatment comparisons (ITCs) involving small sample sizes, which can lead to conclusions with questionable validity. Moreover, many HTA authorities do not accept ITCs, raising questions about future cross-EU guidance and harmonisation.

To address the possible proliferation of PICOs, there have been proposals to 'weigh' PICOs on the basis of alignment with evidence-based principles and their clinical relevance to populations or subpopulations [19, 20]. However, this approach could lead to situations where MS may need to undertake their own assessments and request additional data if the JCA analyses do not meet their specific needs. Such a scenario could necessitate dual clinical evaluations—both joint and national—completed sequentially following the JCA, resulting in longer time to access and reduced efficiency owing to duplication of effort.

A further critical aspect of the PICO determination process is the need for MS to reach a consensus within their countries ahead of their PICO submission to the JCA. This can be challenging and time-consuming in decentralised health systems such as in Spain, where medicines are regionally managed across 17 regions. EUnetHTA's experience indicates that the initial 2-week period for MS to respond to the survey providing their PICO submissions is insufficient, underscoring the importance of allowing enough time for consensus development [20].

While EUnetHTA's approach seeks to respect the nuances of each member state, it must be balanced against the operational feasibility of manufacturers and the capacity of JCA assessors. Manufacturers have lacked transparency on what will be required of them, with manufacturers beginning to prepare dossiers with significant uncertainty. Recommendations for improvement include the collaborative and pragmatic development of PICO parameters with manufacturers, alongside the release of clear guidelines well ahead of the implementation and stakeholder consultation for PICO assessment, ensuring that MS will still have their needs met.

*Balancing Member State Autonomy and Harmonisation in the HTAR* The implementation of HTAR is expected to

yield varying benefits across the EU, potentially improving evidence-based HTA processes in MS with less developed systems by sharing expertise and data. However, there is concern among MS with well-established HTA systems, such as France and Germany, that this approach could potentially lower the standards already set by their robust value assessment systems. It is possible that such countries may continue to complete their own analyses and request additional data or analyses from manufacturers to meet their own needs. Particularly, for countries such as Germany, where the median time to availability for oncology medicines is 37 days, any regulatory changes that slow down this process could be seen as a setback [4]. This divergence in timeliness and methodologies could increase the burden on health systems and potentially prolong the time to access, as national benefit assessments must await the JCA conclusions.

While the HTAR aims to harmonise clinical assessments across the EU, it does not address pricing disparities, which remain within the jurisdiction of the individual MS through their respective pricing and reimbursement frameworks. However, JCAs may expedite the process of national assessments and concomitant pricing and coverage decisions by national competent authorities and thus may call into question existing external reference pricing (ERP) practices. These practices often rely on delays to capitalise on the increasing numbers of low-price countries launching products to expand the pool of lower-price countries in national baskets, thereby impacting list prices downwards. Similarly, it may call into question frequent re-pricing practices, particularly as net price negotiations are concluded relatively quickly.

While HTAR is a stride toward more equitable healthcare with potential streamlined access for countries with less-established HTA systems and resources, its success hinges on its ability to provide value to all MS, even those with sophisticated systems already in place. As such, an approach that respects both regional variability and shared European goals is essential.

*The Crucial Role of Real-World Evidence in Assessing Clinical Benefit and Monitoring Mechanisms* The HTAR will be implemented progressively, starting with oncology and advanced therapy medicinal products (ATMPs) on 12 January 2025. In oncology, where clinical evidence is often early phase or immature, the assessment and integration of RWE becomes a critical factor for success [6]. Where the traditional model of double-blind, randomised controlled trials (RCTs) may be difficult or impossible to implement, and single-arm trials (SATs) are often used [21], recognition and standardisation of RWE may be a necessary way forward, with transparent methodologies in place.

Although some MS have shown flexibility towards evolving evidence standards, this is not uniform [16, 22]. The absence of harmonised standards for RWE—in terms of collection, interpretation and application—leads to inconsistencies in its adoption and acceptance and can adversely impact patient access [23, 24]. The drive towards more consistent use of RWE is also partly powered by advances in precision medicine, making RWE generation necessary.

Several European initiatives are already in place regarding this, such as the EMA's recent generation and implementation of the Data Analytics and Real-World Interrogation Network (DARWIN) [25], alongside EMA and EUnetHTA collaborations on registry methodologies and the establishment of the evidentiary value of RWE [26–28]. Individual jurisdictions follow similar paths, with the National Institute for Health and Care Excellence (NICE) in England developing a RWE framework and Haute Autorité de Santé (HAS) in France having a methodology guide for RWE studies utilised to assess medical technologies [29, 30]. According to an analysis of HTA reports across 83 global HTA bodies, the proportion of records incorporating RWE in submissions has risen from 6% in 2011 to 39% in 2021 [31]. Overall, establishing EU-wide RWE standards on the basis of clear and transparent methodology could enhance the HTAR by optimising its benefits and bridging the disparities in access to innovative oncology treatments [16].

Particularly for oncology medicines underpinned by a limited evidence base, it is crucial to consider how the HTAR can generate additional clinical data and establish monitoring mechanisms. Currently, the JCA is predominantly based on clinical evidence available at the time of submission, with options to either initiate a joint re-assessment or leave MS to complete their own re-assessment on the basis of additional data. As the generation of new data is time consuming, monitoring mechanisms need to be implemented to enable further assessments as more data is generated [22].

*Addressing the Challenges to Committee-Based Implementation* Introducing a committee-based approach to conduct technology assessment through JCAs raises some practical questions. One immediate concern is the allocation of resources for JCA assessors. The current approach appears to rely on assessors utilising their own resources, which has implications for countries with limited resources as it perpetuates the lack of ability of such MS to undertake clinical assessments rather than building their capacity. Unlike a specified institution, agency or body, a committee-based approach lacks a specialised workforce and dedicated budget, potentially complicating efforts to ensure seamless coordination and timely JCA outcomes [32]. Regardless, committee-based approaches can function well if they are adequately resourced, have supervisory capacity and are given sufficient flexibility to address differing needs.

## 2.2 Pharmaceutical Legislation and Incentive Structure

The initial EU PL proposal's key aspect was the transformative incentive structure directly relating to access (Fig. 4). However, the report filed by the Committee on the Environment, Public Health and Food Safety (ENVI) [33] led the European Parliament to adopt its position on 10 April 2024 [34]. This new position delinks the launch conditionality from the incentive framework and extends regulatory data protection (RDP) to 7.5 years (Fig. 4). The initial proposal reduced the baseline RDP by 2 years while offering additional regulatory protection to manufacturers that achieve a pan-European launch across all 27 MS within 2 years of MA (or 3 years for small and medium-sized enterprises (SMEs)) (further details in the Appendix) [14]. Comparatively, the new position requires filing for pricing and reimbursement upon request from MS within 1 year (or 2 years for SMEs), with no link to RDP [34]. Although the legislative process is ongoing and still subject to negotiations, there is an overall aim to focus on improving access to medicines across Europe. However, several concerns emerge regarding the proposals, including the feasibility of manufacturers adhering to its requirements and the possibility that it could result in reduced rather than improved access to medicines.

*Feasibility of Launch across the EU* The updated proposal represents a significant improvement from the initial requirement of simultaneous market launches, therefore considering operational realities and reducing the immediate burden on manufacturers. Nonetheless, navigating the diverse pricing and reimbursement policies of 27 MS is challenging for manufacturers within the proposed timeframe. There is also limited clarity on the consequences of non-compliance with the proposed timeframe. To date, no newly developed medicines have successfully launched in all 27 MS, let alone within a restricted timeframe, highlighting the need for practical and supportive policies that facilitate EU-wide access while considering operational challenges [35].

While the proposal has the potential to curb launch sequencing as an industry strategy, the widespread adoption of ERP mechanisms by EU MS continues to pose significant barriers for manufacturers seeking access across the EU [36, 37]. Delays often arise from low-priced countries awaiting positive HTA outcomes from other countries before engaging their own HTA processes. These policies significantly contribute to the access disparities across Europe.

While the updated proposal better aligns with current national policies, further harmonisation is needed. Moving forward, the European Commission (EC) needs to propose a collaborative strategy, outlining in detail the necessary reforms at national levels that would be a pre-condition to facilitate EU-wide access. Whilst the EC cannot impose changes on MS, they can identify roadblocks and support

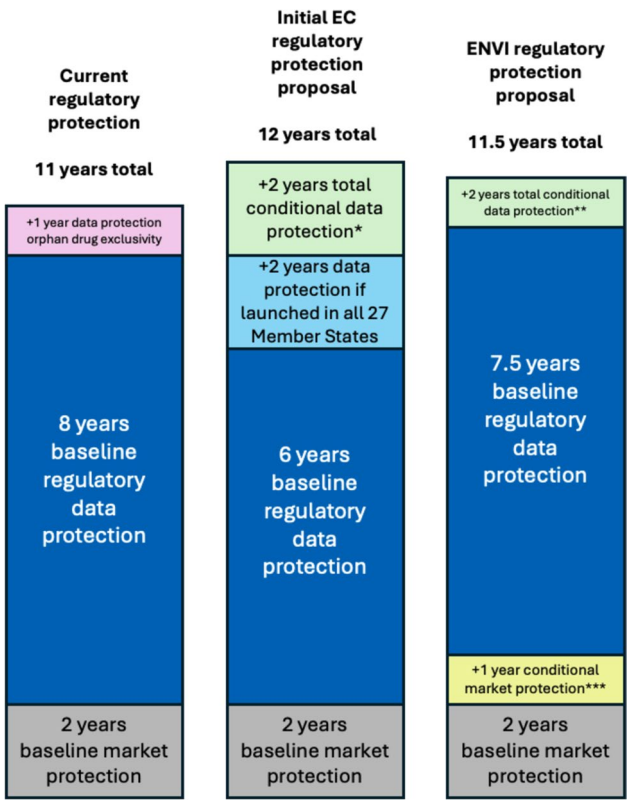


**Fig. 4** This figure displayes the proposed Pharmaceutical Legislation incentive structures compared with the existing regulatory protection structure. *Additional periods of protection can be obtained if the companies launch the medicine in all member states (+2 years), if the medicine addresses an unmet medical need (+6 months) or if comparative clinical trials are conducted (+6 months). A further year of data protection can be granted if the medicine can treat other disease(s) too [14]. **Additional periods of data protection can be obtained if the drug meets an unmet medical need (+1 year), if the drug was approved with comparative clinical trials (+6 months), if 'significant development, including clinical and preclinical' was carried out in the EU in collaboration with a public EU entity (university hospitals, centers of excellence or bioclusters (+6 months) [34]. ***Market protection can be extended for 1 year, if the marketing authorisation holder obtains authorisation during the RDP period for an additional therapeutic indication with significant clinical benefit in comparison with existing therapies. The extension can only be granted once [34]

MS in reducing or altogether eliminating their impact. Such proactive support may offer a practical way forward.

*Impact on Innovation in the EU* Although there are significant updates to the initial proposal, with the launch de-linked from RDP, there is still a baseline reduction in RDP compared with the current legislation. The potential of reduced market protection may impact incentives for EU launches, given the associated costs and effort required. Significant effort is required to launch in the EU, through harmonising with diverse national health systems, scaling production capabilities and the possibility of generating additional evidence to meet specific MS needs. This

disincentive is concerning given the significant decline in Europe's share of clinical trials based on company headquarter location—down from 38% in 2013 to 23% in 2023—signalling a decline in the region's appeal [38]. It is possible that the legislation could further decrease the attractiveness of Europe to undertake innovation-related activities.

*Greater Use of Joint Procurement* Joint procurement could play a pivotal role in the proposed legislation's success by streamlining negotiations and creating a united front of purchasers, particularly in ensuring equitable access to innovative medicines across the EU. Although joint procurement has primarily been used for immediate health threats and stockpiling [39], its broader application into oncology could help reduce disparities to access. Joint procurement approaches could mirror collaborations such as Beneluxa [40] or the Nordic Pharmaceutical Forum, leveraging collective bargaining power to secure better prices and improved access, particularly advantageous for small-volume oncology indications [39, 41].

As per the PL proposal, such initiatives will be supported by the European Commission [34]. Establishing such consortia could mitigate the time and resource investment needed from manufacturers, enhancing the feasibility of launching within all requested MS within the required timeframe. However, for a consortium to succeed, participating members would need to achieve consensus on HTA decisions, negotiating processes and outcomes, as well as making resources available for purchasing medicines, requiring consensus from members on affordability thresholds and health priorities.

## 3 Conclusions

The overarching objectives of HTAR and the PL proposal, aimed at expanding access to medicines and standardising assessment processes, are undeniably in line with all stakeholders' aspirations. However, a closer look at their implementation has highlighted several challenges that require careful consideration and adjustments. Without changes, there is a danger that both reforms may make Europe less attractive as a market for manufacturers and hinder innovation, especially in areas such as oncology, where timely access to innovative treatments is critical. As the EU moves forward with these reforms, a commitment to continuous evaluation, stakeholder engagement and adaptation is critical. In the context of HTAR, a number of refinements are necessary, including pragmatism in developing PICO parameters, improving the use of RWE and indirect treatment comparisons in clinical benefit assessments, and establishing monitoring mechanisms for RWE generation. Regarding the PL, although the latest development and adoption of the ENVI proposal represents a pragmatic improvement over the initial draft, MS and manufacturers still have significant challenges in its practical implementation. Ahead of its implementation, it is suggested that the EC works with MS to propose a collaborative strategy, outlining in detail the necessary reforms at the national level that would be a pre-condition to facilitate EU-wide access. There is a window of opportunity to ensure that the final legislation meets the needs of key stakeholders involved, achieves its aim of improved access to medicines and is viable in practice. The proposals made aim to steer these transformative initiatives towards their objective of improving the availability and timely access to safe and effective oncology medicines for all Europeans.

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## Declarations

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