Beyond pricing:
The HTA and public healthcare payers' vision for an innovative, stable and predictable pharmaceutical market in Europe

European Social Insurance Platform (ESIP)
Medicine Evaluation Committee (MEDEV)

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Executive Summary

Amid rising geopolitical tensions, supporting meaningful pharmaceutical innovation in Europe is crucial. At the same time, sustainable and robust healthcare systems must be preserved. It is essential to strike the right balance between incentives for innovation and measures to guarantee affordable patient access, to ensure that medicinal products align with broader societal goals and effectively reach patients.

European healthcare payers, pricing and reimbursement (P&R) and health technology assessment (HTA) authorities have the responsibility to provide the highest-quality care to the broadest possible patient population. Fulfilling this responsibility requires a robust, evidence-based understanding of the treatment expected value. Over the past decade, European authorities have made significant efforts to improve the assessment of innovation and adapt to new scientific methods by streamlining processes, reducing review times and strengthening access to data and the expertise needed to apply up-to-date statistical evaluation methods, thereby strengthening predictability for public healthcare systems and pharmaceutical companies alike. Some of these efforts are described in this paper.

As implementation moves forward, the EU HTA Regulation[1] can further enhance this predictability, streamline efforts and reward pharmaceutical innovation that delivers tangible benefits for patients and is aligned with public health goals.

In parallel, collaboration across countries and regions is essential to continue strengthening the capacity and negotiating position of healthcare systems. Along European HTA, horizon scanning, voluntary joint negotiations and procurement arrangements are increasingly being explored as ways to pool expertise and resources and support access to innovative medicines.

At the same time, the recommendations of the Draghi report[2] combined with an unstable geopolitical context, have shifted the focus predominantly on industrial and economic policies and objectives. While pursuing Europe's competitiveness agenda, any incentives or regulatory simplification should be systematically assessed together with their impact on healthcare budgets. This balance should underpin all European initiatives in the field of pharmaceuticals, medical devices and other health technologies, so that healthcare priorities, long-term sustainability and affordable access are preserved while pursuing market goals.

Above all, and in light of the growing budgetary pressure on healthcare systems to absorb high medicine prices,[3] competition among pharmaceutical companies should remain the most effective lever to reduce high price and ensure the widest, best possible access to patients. Equally important, the pharmaceutical ecosystem should remain demand rather

[1] Regulation (EU) 2021/2282 of the European Parliament and of the Council of 15 December 2021 on health technology assessment and amending Directive 2011/24/EU

[2] The Future of European Competitiveness. A competitiveness strategy for Europe. September 2024.

[3] ESIP-MEDEV report on trends in pharmaceutical expenditure. October 2024. https://esip.eu/news/rising-pharmaceutical-expenditure-a-call-for-sustainable-solutions

than supply-driven, focusing on unmet medical and societal needs. In this context, the concept of innovation should be understood in relation to products that demonstrably improve patient outcomes, especially in areas of unmet need.

A more strategic approach should drive investment and incentives towards therapies that provide meaningful benefits to patients and healthcare systems at large, with rigorous data proving the clinical efficacy, safety, as well as clinical- and cost-effectiveness of new products. Early dialogues could serve in this respect as an important tool to clarify the requirements of decision-makers across the product lifespan. Conversely, treatments with limited evidence, often coupled with high prices, introduce clinical and financial uncertainty into healthcare systems, with a significant risk of diverting resources from well-documented treatments.

However, complete evidence may not always be available at the time of market launch. Examples of valuable tools to facilitate timely access to promising therapies, yet without complete evidence, are early access schemes and managed entry agreements. Such mechanisms must be designed to safeguard progressive, robust and satisfactory evidence generation, with clear obligations and timelines for collecting the necessary data and reducing residual uncertainty in the post-marketing phase. Equally important are clear exit provisions to ensure that products with unresolved efficacy or safety concerns do not remain on the market indefinitely.

Real-world data (RWD) has in this regard the potential to reduce uncertainties, although it cannot substitute robust pre-market clinical evidence. While regulators have long been using RWD, its relevance for HTA and payer decision-making is growing, especially in light of the frequent lack of mature data at the time of approval. At the same time, it must be acknowledged that meaningful RWD on a newly launched pharmaceutical takes time to accumulate, therefore strong pre-market clinical studies remain essential.

In summary, HTA bodies and payers are committed to fostering an environment in which pharmaceutical innovation delivers tangible and sustainable benefits for patients and society. Thanks to predictable regulatory frameworks and reliable standards, Europe offers on the one hand healthcare systems that rank among the best in the world, and on the other a high-volume market for pharmaceutical companies, with nearly 450 million citizens. Maintaining this competitive edge requires a continued commitment to evidence-based decision-making and a shared determination to pursue goals that serve patients' interests, the long-term sustainability of healthcare systems and a healthy, competitive climate for pharmaceutical companies.

Chapter 1 – Defining innovation: Evidentiary requirements for HTA bodies, P&R authorities and public payers

The ESIP-MEDEV report on pharmaceutical expenditure revealed increasing prices of new pharmaceuticals. The related rise in spending does not necessarily correspond to an increase in added therapeutic value: not all new pharmaceuticals are innovative.

This chapter examines what actions are needed to make innovation meet the clinical and cost-effectiveness requirements set by HTA bodies, pricing and reimbursement authorities and healthcare payers. It provides recommendations for addressing situations where evidence is insufficient or unsatisfactory, and how decision-making can be facilitated throughout the product life cycle.

Particularly, the chapter explores key evidence requirements at all stages of developments: pre-launch, particularly comparative trials; post-launch, exploring conditional reimbursement pathways; and real-world data.

Clinical trials for new medicines are usually designed to meet the requirements for marketing authorisation and not for pricing and reimbursement decisions. Regulators should prove that a medicine's benefits outweigh its risks, and this does not necessarily require the medicine to be tested against current treatment options. However, HTA bodies and payers need to understand how well a new medicine performs compared to current standards of care, in order to assess its added benefit and cost-effectiveness. Eventually, new medicines may receive market approval based on evidence that is not sufficient to support reimbursement decisions, ultimately delaying or hampering patient access to new treatments.

Randomised controlled trials (RCT) remain the gold standard for generating unbiased causal evidence on interventions. However, because of their perceived complexity and resource-intensive nature, rapid signal-detection approaches based on strong surrogate endpoint assumptions have become increasingly common.[4,5] Waiving the randomised comparator and using single-arm trials (SATs) to achieve regulatory approval is another concerning trend.[6] In such cases, indirect comparisons and modelling methods are used to estimate relative effectiveness, but these approaches are often associated with significant uncertainty as to their therapeutic value. Developers occasionally use outdated comparators,

[4] Considerations on surrogate outcomes are included in the Guidance on outcomes for joint clinical assessments, adopted on 10 June 2024 by the HTA Coordination Group, pursuant Article 3(7), point (d), of Regulation (EU) 2021/2282 on HTA.

[5] Olivier T, Haslam A, Ochoa D, Fernandez E, Prasad V. Bedside implications of the use of surrogate endpoints in solid and haematological cancers: implications for our reliance on PFS, DFS, ORR, MRD and more. BMJ Oncology. 2024;3:e000364. https://doi.org/10.1136/bmjonc-2024-000364

[6] Bomfim Ribeiro T., Bennett C.L., Colunga-Lozano L.E., Vieira Araujo A.P., Hozo I., Djulbegovic B. Increasing FDA-accelerated approval of single-arm trials in oncology (1992-2020). Journal of Clinical Epidemiology (JCE). 2023. Volume 159, P151-158. https://doi.org/10.1016/j.jclinepi.2023.04.001

increasing the chance of demonstrating superiority, and eventually achieving a favourable benefit-risk profile that facilitates regulatory approval. This strategy undermines the generalisability of the results and complicates HTA evaluations. The uncertainty permeates the entire healthcare system, hindering cost-effective financial and infrastructural resource allocation and allowing more drugs to reach the market without sufficiently established clinical benefit.

In pursuing timely and affordable access to effective and safe medicinal products, HTA bodies and payers are often required to make decisions under pressure for rapid access, despite considerable uncertainty about the limitations of the available evidence. This challenge is particularly acute in areas with few treatment options, such as rare or orphan diseases, where pharmaceutical companies frequently refer to the practical difficulties of conducting comparative studies in small and geographically dispersed patient populations. While this concern may be valid, recruitment challenges and patient heterogeneity also affect non-comparative trials. Forgoing comparative clinical trials on this basis can therefore lead to submissions that provide only limited evidence on the added benefit of new products. Instead, adapted evidence requirements could be defined and agreed in order to enable the generation of the best possible data. At the same time, the emergence of personalised medicine and highly targeted novel therapies is contributing to a clinical development pathway in which small sample sizes, single-arm designs, surrogate endpoints, and shorter follow-up periods are becoming more common.

In addition, when limited evidence goes hand in hand with soaring prices, especially in the case of orphan and ultra-orphan medicinal products, it leaves payers with the choice to either provide or restrict access to products with unclear cost-effectiveness. This combination of high prices often coupled with the lowest level of evidence is highly challenging from a societal perspective. In these situations, where the inherent risk of post-launch evidence generation for the company due to potential loss of authorisation, reimbursement or sales, is higher than the potential gain, there is an incentive for developers to maintain uncertainty on the true value and added therapeutic benefit for as long as possible. When post-marketing studies are not performed or are delayed and not designed to produce the required data, HTA bodies and payers are left with highly uncertain information indefinitely, making it difficult to make or adjust the reimbursement decision.

To mitigate the financial risks associated with growing clinical uncertainty,[7] which can delay timely patient access, a suitable framework is needed to support the generation of robust evidence on clinical and cost-effectiveness across the life cycle of a technology, both before and after marketing authorisation, and reflecting the information needs of HTA bodies and payers. These needs should be considered throughout both the pre-approval and post-approval phases, including in horizon scanning, joint scientific consultations, clinical trial design, the selection of relevant endpoints, the acceptance of indirect comparisons where

[7] Shin G, Kwon HY, Bae S. For Whom the Price Escalates: High Price and Uncertain Value of Cancer Drugs. Int J Environ Res Public Health. 2022 Apr 1;19(7):4204. doi: 10.3390/ijerph19074204. PMID: 35409887; PMCID: PMC8998346.

appropriate, post-launch evidence generation planning, the appropriate and innovative use of RWD where applicable and managed entry agreements where needed.

At the same time, it is important to recognise that companies have long had to navigate a wide range of HTA guidelines and methodological requirements that differ across countries, often as a result of HTA systems evolving independently rather than because of well-justified substantive differences. A more prominent role for HTA bodies and payers in shaping evidence generation should be accompanied by stronger collaboration and greater alignment of methodological requirements across jurisdictions. The EU HTA Regulation is supporting progress in that direction.

Pre-approval

Horizon Scanning

Against the background of limited resources, Horizon Scanning activities, such as the International Horizon Scanning Initiative (IHSI),[8] are valuable tools to identify products with an expected high financial or clinical impact. Identifying these products early allows taking actions to promote early collaboration between regulatory authorities, developers, HTA bodies and payers; early planning of additional studies e.g. real-world data (RWD) and registry trials, during the evidence generation phase for approval; timely design of post launch studies and/or registries to address clinical uncertainties, such as long-term outcomes.

Joint Scientific Consultations (JSC)

A promising initiative to address challenges related to evidence quality for new medicines is the Joint Scientific Consultation (JSC) included in the EU HTA Regulation. Through the JSC, developers can request early advice from HTA bodies on evidence requirements for future clinical assessments. This can help ensure that clinical development plans take HTA needs into account from the outset. The JSC can take place in parallel with scientific advice from the European Medicines Agency (EMA), promoting alignment between regulatory and HTA requirements.

Furthermore, the revised EU pharmaceutical legislation provides for a consultation mechanism involving HTA bodies and pricing and reimbursement authorities specifically to support the design of clinical trials and the generation of evidence throughout the lifecycle of medicinal products. In particular, it promotes the development of comparative clinical evidence, including through the use of relevant evidence-based comparators and pre-authorisation scientific advice to support the design of comparative clinical trials. The acceptability and suitability of trial designs, endpoints and comparators can be addressed within these early exchanges.

To exploit the full potential of these early exchanges, HTA bodies and payers need sufficient assessor capacity as well as early industry engagement tools. Clarity on their evidentiary expectations – whether they align with those of regulators – is a prerequisite for companies

[8] https://ihsi-horizonscandb.ecri.org/

to generate the required evidence. Compliance by companies will need to be ensured through close scrutiny of non-compliant study designs. Companies, in turn, should break down internal silos and facilitate exchange between pre-marketing and post-marketing authorisation teams to support a comprehensive evidence-generation plan across the entire product lifecycle.

Advice in early stages is legally non-binding for both sides. Nevertheless, non-compliance with advice given may affect the later assessment and willingness to accept suboptimal evidence, when considered preventable.

Clinical trial design

Since HTA bodies and payers assess the added benefit of a new treatment in comparison to existing standard-of-care, the preferred study designs are randomised controlled trials (RCTs) with relevant comparators (instead of or in addition to placebo), with study populations which are generally similar to the actual patient population in clinical practice, and with sufficient follow-up time to capture the benefit, which should be measured by patient-relevant endpoints. The revised EU general pharmaceutical legislation offers an opportunity to reinforce expectations for comparative clinical evidence before launch. While the text does not provide for a formal validation by HTA bodies and payers of clinical study designs, it maintains that any alternative trial design must be justified. It also establishes a consultation mechanism involving HTA and P&R bodies on clinical trial design and evidence generation.

In settings where fully powered RCTs are not feasible, such as in rare diseases, even minimal randomisation is preferred over relying solely on a single-arm trial. A small, randomised control arm can then be augmented with an external control arm, constructed from high-quality RWD. In such a hybrid trial design, RWD-derived controls can be compared with the randomised controls in terms of prognosis, treatment patterns and outcomes. When discrepancies are identified, statistical calibration methods can be applied to adjust the RWD controls and improve their comparability.[9]

Endpoints

In order to obtain reimbursement, treatment effectiveness is ideally measured by patient-relevant outcomes which are "outcomes that directly measure mortality, morbidity and outcomes related to patients' feelings, beliefs, preferences, needs and functions (such as the ability to perform activities in daily life)".[10] In practice, however, clinical trials often measure indirect outcomes (surrogate endpoints), such as changes in blood tests or tumour size, which are assumed to predict real patient benefits. Yet these assumptions are often not well established, and the link between such measures and actual improvements for patients may be uncertain. To allow P&R decision-makers to assess the validity of surrogacy, additional

[9] Schneeweiss S. Enhancing External Control Arm Analyses through Data Calibration and Hybrid Designs. Clin Pharmacol Ther. 2024 Nov;116(5):1168-1173. doi: 10.1002/cpt.3364. Epub 2024 Jul 2. PMID: 38952236.
[10] HTA CG. Guidance on outcomes for joint clinical assessments. 2024 https://health.ec.europa.eu/document/download/a70a62c7-325c-401e-ba42-66174b656ab8_en?filename=hta_outcomes_jca_guidance_en.pdf

information is needed. This includes a systematic presentation of evidence on the association between the surrogate outcome and the final patient-relevant outcome, as well as information on whether and when results for the patient-relevant outcome are likely to become available. The inevitable increase in decision uncertainty created by the use of non-validated surrogate endpoints must be therefore acknowledged and handled either in the HTA process when estimating the added benefit, or at the level of price, or other mechanisms such as conditional reimbursement based on data collection either post-launch or by restricting access with conditional data collection only to patients that consent to and are informed on the existing uncertainties.

Indirect comparisons

When direct comparative (head-to-head) studies are not feasible, indirect evidence can inform decision-making, for instance through external control studies that provide individual patient data (IPD) and compare those to IPD of the single arm trial.[11] Population-adjusted indirect comparisons (propensity score, matching-adjusted indirect comparisons-MAIC) provide a method for attempting to generate more reliable results, such as differences in potential effect modifiers. While the acceptability of such methodologies may vary across HTA bodies, early dialogue can help clarify expectations and support more consistent use where appropriate. In this context, indirect treatment comparisons (ITCs) should be discussed at an early stage between HTA bodies, EMA and pharmaceutical developers.

Post-approval

Post launch evidence generation (PLEG)

For pharmaceuticals authorised based on less comprehensive data packages, strict criteria and timeframes for post-approval safety (PASS) and efficacy (PAESS) studies need to be defined a priori. Expanding collaboration on post-launch evidence generation (PLEG) among regulators, HTA bodies and payers would strengthen the EMA's current toolkit. Early exchanges between HTA bodies, payers and industry can support evidence generation for marketing authorisation and help anticipate post-authorisation information needs.

Overall, obligations for PASS and PAES could be improved, incorporating evidence needs of HTA bodies and payers and strengthening compliance with appropriate corrective measures. For example, when studies are not completed without justification within a pre-defined timeframe (e.g. 5 years), marketing authorisation should be revoked. This can only be done if the PLEG is done collaboratively with EMA.

Real World Data (RWD)

While the use of RWD in HTA varies considerably across countries, it is widely recognised that RWD can complement RCT data, helping close critical evidence gaps and supporting decision-making under uncertainty. Particularly, it can inform trial design, define comparators, and

[11] Hogervorst M.A., Soman K.V., Gardarsdottir H., Goettsch W.G., Bloem L.T. Analytical Methods for Comparing Uncontrolled Trials With External Controls From Real-World Data: A Systematic Literature Review and Comparison With European Regulatory and Health Technology Assessment Practice. Value in Health. 2025. Volume 28, P161-174. https://doi.org/10.1016/j.jval.2024.08.002

guide post-launch reassessments of effectiveness and value. In this context, RWD provides an opportunity to evaluate effectiveness in routine clinical practice over time, beyond the controlled setting of clinical trials.

Literature has helped clarify important differences between RWD analyses and RCTs, providing insights into the methodological and data-related issues that need to be addressed.[12,13] In parallel, experience with studies conducted in DARWIN-EU[14] have advances understanding of the practical considerations involved in generating and utilising RWD. With a better understanding of the limitations of data sources and identification of missing essential information, these sources can be improved to address more complex questions and address needs of different stakeholders. One way to improve credibility is through data calibration, where RWD is benchmarked against RCT data.

Furthermore, early-stage collaboration between regulatory authorities and HTA bodies helps identify potential evidence gaps. This would allow for an assessment of how additional RWD collection can be initiated pre-approval, thereby providing decision-makers with more comprehensive information. Such RWD should supplement - not replace - pre-approval data in well-justified cases. RWD can be used to construct external comparator arms using historical or prospectively collected registry data. RWD may also be used to validate these comparators and ensure their relevance to the local context. Furthermore, the adaptation of treatment effects to specific populations can be facilitated through transportability analyses.[15]

Advanced approaches like external control arms (ECA) combined with target trial emulation (TTE) allow RWD studies to mirror randomised trials, making their findings more interpretable for decision-makers. If HTA has to rely on external comparator evidence, it should do so only with stronger methods that improve transparency about assumptions and make residual bias more visible. To improve transparency and reliability in HTA, external comparator studies should be supported by methodological approaches such as TTE and quantitative bias

[12] Heyard R, Held L, Schneeweiss S, Wang SV. DESIGN DIFFERENCES EXPLAIN VARIATION IN RESULTS BETWEEN RANDOMIZED TRIALS AND THEIR NON-RANDOMIZED EMULATIONS. medRxiv [Preprint]. 2023 Jul 13:2023.07.13.23292601. doi: 10.1101/2023.07.13.23292601. Update in: BMJ Med. 2024 Feb 5;3(1):e000709. doi: 10.1136/bmjmed-2023-000709. PMID: 37502999; PMCID: PMC10370236.
https://pmc.ncbi.nlm.nih.gov/articles/PMC10370236/

[13] Wang SV, Schneeweiss S, RCT-DUPLICATE Initiative. Emulation of Randomized Clinical Trials With Nonrandomized Database Analyses: Results of 32 Clinical Trials. *JAMA.* 2023;329(16):1376–1385. doi:10.1001/jama.2023.4221
https://jamanetwork.com/journals/jama/fullarticle/2804067

[14] https://www.darwin-eu.org/

[15] Turner AJ, Sammon C, Latimer N, Adamson B, Beal B, Subbiah V, Abrams KR, Ray J. Transporting Comparative Effectiveness Evidence Between Countries: Considerations for Health Technology Assessments. Pharmacoeconomics. 2024 Feb;42(2):165-176. doi: 10.1007/s40273-023-01323-1. Epub 2023 Oct 27. PMID: 37891433; PMCID: PMC10811184.

analysis. Initiatives such as Q-BASEL,[16] which apply these approaches in practice, are therefore valuable. Innovation in artificial intelligence (AI) and machine learning (ML) is further improving how we use RWD. These methods can identify patterns in large, complex datasets, predict missing values, detect biases and generate better-matched comparator groups for ECAs. They also support automated quality checks and help optimise study design, improving the credibility and efficiency of RWD generation.

Moreover, RWD can also play a critical role in informing health economic models by supporting or adjusting treatment effect estimates, guiding decisions on long-term extrapolations, and assessing the applicability of transition probabilities to local patient populations and healthcare settings.

Case study: Benchmarking Observational Data Against a Clinical Trial

Matthews and colleagues (2022)[17] conducted a study to evaluate the extent to which RWD from the Swedish national heart disease registry, SWEDEHEART, could replicate findings from the TASTE RCT in patients diagnosed with ST-elevation myocardial infarction (STEMI). The aim of this benchmarking exercise was to determine whether treatment effects observed in the RCT could be reproduced using RWD via a target trial emulation. This initial calibration is a critical prerequisite for leveraging RWD to explore outcomes which were not addressed in the original trial, such as long-term effects or results within smaller patient subgroups.

The TASTE trial investigated one-year outcomes in STEMI patients undergoing percutaneous coronary intervention (PCI), comparing those treated with thrombus aspiration to those without. To emulate this trial, the researchers constructed a hypothetical target trial that closely followed the TASTE protocol and applied it to data from SWEDEHEART.

Using eligibility criteria aligned with the original RCT, the emulated trial included 18,222 patients - 3,462 of whom received thrombus aspiration, while 14,760 did not. Unlike the randomised nature of TASTE, treatment allocation in SWEDEHEART was based on routine clinical decisions. Consequently, the emulation relied on the assumption that treatment assignment was random within strata defined by confounding variables, accounted for in the statistical analysis. The researchers estimated the observational analogue of the per-protocol (PP) effect in SWEDEHEART, using standardised pooled logistic regression.

The one-year relative risks (RR) for death and myocardial infarction (MI) derived from the SWEDEHEART emulation were in line with those reported in the TASTE trial. Specifically,

[16] Gupta A, Hsu G, Kent S, Duffield SJ, Merinopoulou E, Lockhart A, Arora P, Ray J, Wilkinson S, Scheuer N, Ramagopalan SV, Groenwold RHH, Popat S, Hernán MA. Quantitative Bias Analysis for Single-Arm Trials With External Control Arms. JAMA Netw Open. 2025 Mar 3;8(3):e252152. doi: 10.1001/jamanetworkopen.2025.2152. PMID: 40136297; PMCID: PMC1194783

[17] Matthews AA, Dahabreh IJ, Fröbert O, Lindahl B, James S, Feychting M, Jernberg T, Berglund A, Hernán MA. Benchmarking Observational Analyses Before Using Them to Address Questions Trials Do Not Answer: An Application to Coronary Thrombus Aspiration. Am J Epidemiol. 2022 Aug 22;191(9):1652-1665. doi: 10.1093/aje/kwac098. PMID: 35641151; PMCID: PMC9437817.

TASTE reported an RR of 0.94 (95% CI: 0.78–1.15) for death and 0.97 (95% CI: 0.73–1.28) for MI, while the emulated trial yielded estimates of 1.09 (95% CI: 0.96–1.24) for death and 0.96 (95% CI: 0.79–1.17) for MI. Both sets of results indicated no significant difference between the treatment strategies.

Following this calibration, the analysis was extended to assess three-year outcomes using RWD. The treatment effects remained consistent over time, with a three-year RR of 1.07 for death and 0.97 for MI. Further stratified analyses were conducted based on age, sex, diabetes status, prior PCI, and previous MI.

Case study: Jaypirca Evaluation Using Real-World Data

Jaypirca (pirtobrutinib) was assessed in Sweden for adult patients with relapsed or refractory mantle cell lymphoma (R/R MCL) after at least two prior therapies, including a BTK inhibitor, and who are ineligible for CAR T-cell therapy. MCL is a rare and aggressive disease with limited treatment options post-BTK failure. Median overall survival (OS) in this population has been estimated at 9.7 months (SCHOLAR-2).

Efficacy data from the single-arm BRUIN 18001 trial (n=90) showed a 56.7% overall response rate and a median OS of 23.5 months. For indirect comparisons, the developer used external RWD from Concert AI (US EHR data, n=128) and SCHOLAR-2 (European observational study on CAR T ineligible patients, n=149). As individual-level patient data was available from Concert AI, various matching and weighting techniques were applied. An unanchored MAIC was implemented for the comparison with the SCHOLAR-2 patients. Jaypirca showed superior OS in both comparisons, though PFS was not significantly different.

The Swedish Dental and Pharmaceutical Benefits Agency (TLV) identified limitations in the external comparators, including concerns about their transportability from US to Swedish context and potential overestimation of long-term survival due to immature data. The Jaypirca cohort also included a higher proportion of healthier, CAR T-eligible patients. To address these concerns, TLV requested RWD from the Swedish National Lymphoma quality register. The resulting Kaplan-Meier OS curve (Figure 1) showed a median OS of 5.8 months - substantially lower than in the external datasets.

Based on this, TLV concluded that Jaypirca provides a better treatment effect than available alternatives. However, the health economic model was adjusted to reflect a more conservative effect size (due to uncertainties regarding healthier patients in the Jaypirca arm) and more realistic long-term survival estimates. Altogether, TLV could recommend Jaypirca to be included in the reimbursement program, justified by its clinical benefit.

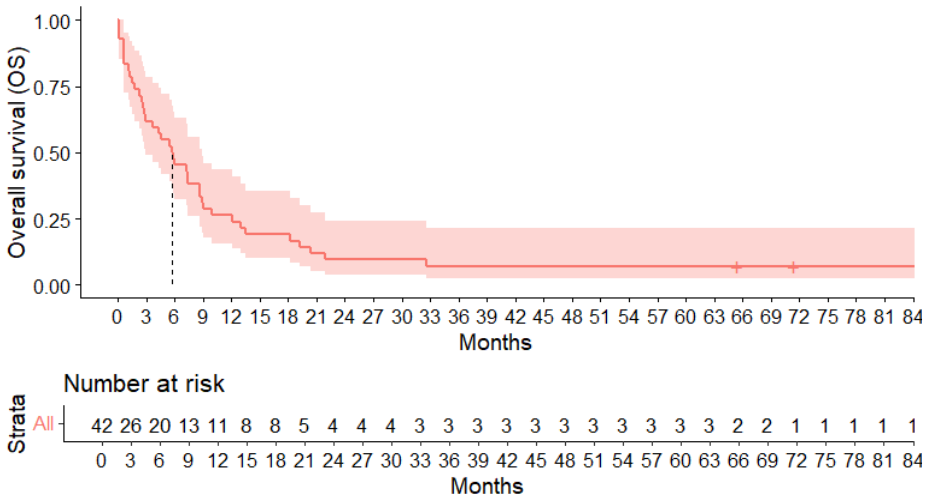

Figure 1

However, even the best methodologies cannot fully overcome the limitations of RWD. Missing information, inconsistent definitions and unmeasured confounding are common, and assumptions made in analyses may not always hold. This is why transparency is crucial: HTA bodies and regulatory agencies need clear reporting on data sources, analytic methods and remaining uncertainties to make well-informed decisions. European initiatives like DARWIN EU are promising, linking registries across countries and enabling pragmatic studies in routine care. But evidence gaps will remain, so early planning of post-launch studies, investment in high-quality data infrastructure and open communication of limitations are key to building trust and supporting evidence-based decisions.

Managed Entry Agreements (MEA)

Managed Entry Agreements (MEAs) are used to reduce the financial risk of introducing new medicines when there is uncertainty about their clinical benefit, cost-effectiveness or budget impact. In practice, most MEAs are simple agreements such as price-volume deals or spending caps. Another group of agreements, the outcome-based agreements, link payment to clinical outcomes, and are considered a way of reducing the financial risk and in some instances, simultaneously closing evidence gaps through data collection, to reduce clinical uncertainty. However, outcome-based agreements are often complex, difficult and costly to manage. The experience of many payers with outcome-based agreements is generally that they rarely involve real risk-sharing and that companies are often hesitant to enter them. For healthcare systems, it is also a challenge to plan for clear exit strategies in case the medicine does not deliver the expected results.

Treatment optimisation

An additional application of pragmatic clinical trials are treatment optimisation studies which intend to elicit optimal treatment duration, dosing and sequence of therapies. Findings from these studies allow to optimise treatment algorithms, reduce adverse events due to optimal dosing and duration of therapies and can provide relative effectiveness evidence against

relevant comparators. They therefore offer the opportunity to improve patient care while simultaneously accruing cost savings for health care systems. In order to facilitate conduct of such studies and in the absence of incentives for industry to fund such trials, the introduction of post-authorisation treatment optimisation studies in revised EU general pharma legislation is highly welcomed.

In conclusion, it is not only the responsibility of HTA bodies and payer organisations, but of the whole society, to make sure that the clinical benefit is properly established as early as possible. When the evidentiary bar is lowered to promote faster access, patients might be exposed to treatments with no or very limited benefit. Thus, data requirements of different decision-makers across the product life cycle – from regulatory to HTA bodies and payers need to be considered from the early stages.

Policy box: One-year since the HTAR implementation. A preliminary assessment

The EU HTA Regulation strengthens cooperation and harmonisation among Member States and aims to support timely patient access to innovative health technologies, while introducing new considerations for evidence generation and early-stage assessment of emerging technologies.

Its adoption represents a major step forward in fostering evidence-based, transparent and coordinated decision-making across the EU. By introducing Joint Clinical Assessments (JCAs), Joint Scientific Consultations (JSCs), and common methodological frameworks, the EU HTA Regulation seeks to streamline HTA processes, reduce duplication of effort and promote a shared understanding of clinical value among Member States. Furthermore, it introduces a systematic and uniform assessment process for developers, offering a transparent and highly predictable path when approaching the European market. It thus marks a strategic shift in EU health policy, from fragmented national evaluations to a more coordinated, innovation-supportive framework.

The JSC mechanism enables early dialogue between developers, HTA bodies and regulatory authorities. Through these consultations, developers can obtain coordinated advice on clinical evidence generation requirements well before P&R submission. This process promotes methodological consistency, reduces uncertainty and guides innovators toward producing data that meets both regulatory and HTA expectations, supporting more efficient and targeted innovation.

To effectively support this evolving landscape, it is essential to strengthen mechanisms for post-launch evidence generation, data sharing and adaptive reassessment. Overall, enhanced cooperation among the European Commission, EMA, national HTA bodies and industry stakeholders will be crucial to ensure that assessments remain robust, flexible and responsive to emerging technologies. Building shared evidence infrastructures and promoting the international exchange of best practices will reinforce Europe's capacity to deliver high-value, evidence-based healthcare.

Key considerations

- HTA bodies and payers should use horizon scanning activities to identify relevant products requiring early collaboration between regulators, HTA bodies and payers.
- Developers should focus on early planning of evidence generation with both regulators, HTA bodies and payers, to ensure evidence addresses the needs of decision-makers across the entire product lifecycle.
- Joint Scientific Consultations (JSCs) provide a safe environment for an early exchange between regulators, HTA bodies, payers and developers. All parties should prioritise this, to ensure better evidence.
- Randomised controlled trials (RCTs) using relevant comparators remain the gold standard for evidence for regulators, HTA bodies and payers. Other study design could be accepted where companies can credibly demonstrate that RCTs are unfeasible, or where the benefit of rapid availability of a medicinal product outweighs the limitations arising from the lack of comparative and controlled data. In such cases, real-world data (RWD) may serve as supplementary evidence but should not generally replace robust comparative evidence where this can be generated. The use of less rigorous trial designs should be discussed with all relevant stakeholders, including HTA bodies and payers.
- Alternative study designs such as pragmatic or registry-based trials as well as RWD allow HTA bodies to address questions under real life conditions but pose methodological challenges.
- To promote trust, credibility, reproducibility, and transparency in RWD studies, particularly in cases where the justification for not conducting a RCT is considered valid, involvement of HTA bodies and payers in designing such studies is key.
- Managed entry agreements (MEAs) place high administrative and financial burdens on payers but offer a possibility to allow patient access for selected products with high uncertainties.
- Premium prices only for premium evidence.

Chapter 2 – Rethinking incentives for areas of highest societal needs

This chapter explores measures to strengthen a demand-driven pharmaceutical ecosystem. By combining push and pull incentives and aligning fiscal, intellectual property and production policies, Europe can position itself as a strategic, reliable, and attractive partner for the pharmaceutical industry. Coordinated action across this ecosystem demonstrates Europe's commitment to supporting sustainable innovation and delivering science-based, high-value healthcare. To ensure a meaningful public return on investment, incentives must be linked to accountability frameworks and responsible pricing.

In times of fiscal constraint, all public sectors - including healthcare - compete for limited resources. Every investment entail opportunity costs and allocating funds to one area often means sacrificing potential benefits elsewhere. When it comes delivering healthcare for the entire insured community, payers must make difficult choices weighing prevention versus therapy, fostering primary care or investing in hospitals.

Healthcare in Europe is largely financed through publicly funded social insurance systems, based on the principle of solidarity. Consequently, spending decisions must be carefully justified, based on general criteria, to ensure clinical and cost-effectiveness of new treatment options. Payers are set between the legal obligation of providing high quality healthcare and the pressure to enable access to promising new treatments. This challenge is intensified through the rising costs of medicinal products, often accompanied by limited evidence of added clinical value.

A new approach for incentives

A balanced combination of both types of incentives is needed to efficiently steer research.[18]

Push mechanisms, including research and development (R&D) tax credits, public grants and collaborative public-private funding, reduce early-stage risk and costs and catalyses investment in research. Pull incentives, such as intellectual property (IP) protections and regulatory incentives, generate sustainable income, primarily intend to ensure future revenues that help finance R&D.

In practice, these incentives have primarily driven investment toward areas with high financial returns and a high willingness to pay,[19] such as oncology. At the same time, other fields with

[18] Suleman et al., New business models for research and development with affordability requirements are needed to achieve fair pricing of medicines, 13.01.2020, https://pubmed.ncbi.nlm.nih.gov/31932324/

[19] SiRM, L.E.K. Consulting & RAND Europe, The financial ecosystem of pharmaceutical R&D: An evidence base to inform further dialogue, 2022. https://www.lek.com/sites/default/files/PDFs/financial-ecosystem-rd.pdf

equally pressing public health needs, but little or no R&D activity, [20] remain underserved, as is the case with antimicrobials.

For this reason, the current system of incentives should be reconsidered so that it more effectively directs investment towards areas with the greatest unmet medical and societal needs, and thus where public value and willingness to pay is highest. The revised EU general pharmaceutical legislation offers the opportunity to target incentives towards urgently needed medicinal products, for example, through tiered regulatory data protection (RDP) for products addressing unmet medical needs.

Pull incentives beyond regulatory protection and intellectual property (IP) may include market entry rewards, milestone prizes, tax breaks, and guaranteed revenue schemes that delink profits from sales volume. Their potential impact on R&D investment and healthcare budgets should be further explored. On the push side, tax reductions could encourage product development especially for rare diseases, alongside direct investment, subsidies and public-private partnerships between universities and industry.

R&D costs for developers can also be reduced by pooling mechanisms based on information and data sharing, eventually lowering the cost of innovation. One example for this method is the use of a common trial infrastructure and common comparator arms in platform trials. In this regard, the Regulation (EU) 2025/327 on the European Health Data Space (EHDS) will be a useful tool.

In general, any (new) incentive should be accompanied by clear conditions on accessibility and affordability, [21] in order to ensure strong pricing and access criteria in funding agreements and better enforcement of existing provisions. Given the substantial contribution of the public sector, returns on investment should be considered not only in terms of company revenues, but also in terms of broader societal benefit.

Furthermore, to fulfil the goal of a demand-driven pharmaceutical ecosystem, public healthcare payers should contribute to defining neglected disease areas, in close collaboration with HTA and regulatory bodies and patients, as provided by the consultation mechanisms established in the revised pharmaceutical legislation. In parallel, progress was made on identifying areas of greater unmet need in order to support a more targeted allocation of resources. The NEED project was launched to help identify and assess areas of greater unmet need, with a view to informing more needs-driven priority-setting and policymaking.[22]

Where payers can clearly identify priority areas, the corresponding medicinal products may be incentivised through national subsidies and faster access pathways, ensuring that

[20] Gandjour et al., A new prize system for drug innovation, 02.07.2011, https://www.sciencedirect.com/science/article/abs/pii/S0168851011001114

[21] See Suleman et al., New business models for research and development with affordability requirements are needed to achieve fair pricing of medicines, 13.01.2020, https://pubmed.ncbi.nlm.nih.gov/31932324/

[22] https://health-needs.eu/index.php/en/

pharmaceutical companies receive fair return on investment while fulfilling their corporate social responsibility. In this context, greater transparency is needed regarding companies' actual spending on R&D and their profits, with a clear delineation between genuine research investment and expenditure on advertising, marketing, litigation and other non-research activities. This would contribute to a more predictable framework for pricing negotiations.

In conclusion, it must be acknowledged that there is no 'silver bullet', rather a combination of different measures on the push as well as on the pull side to facilitate R&D in areas of public interest. Given the complexity of aligning these tools effectively, a carefully calibrated interaction between national and European incentive frameworks is essential, with all such measures linked to conditions on accessibility and affordability.

Policy box: The EU Biotech Act

The EU regulatory framework is constantly evolving to respond to scientific and economic developments. The recently published EU Biotech Act[23] is part of a wider EU strategy to strengthen the biotech sector including initiatives like the Life Sciences Strategy and the Bioeconomy Strategy.

Biotechnology is the leading contributor to innovation at the early stages of development, particularly in areas such as cell and gene therapies, mRNA platforms, rare diseases, oncology and AI-driven drug discovery. Over the past two decades, large pharmaceutical companies have increasingly shifted from in-house R&D to acquiring or partnering with biotech companies for innovative drug development.

The Biotech Act seeks to improve access to finance through both public and private channels, simplify the legislative environment for biotechnology and strengthen the EU's capacity to scale up production, in line with broader objectives on competitiveness and strategic autonomy. Particularly, it aims to streamline clinical trial processes in the EU and to foster biotech R&D through extended IP.

From the ESIP and MEDEV perspective, accelerating market entry for biotech products may be beneficial, but it must not come at the expense of robust evidence. This concern applies equally to cutting-edge products developed through regulatory sandboxes, which should be approached with caution because of their potential implications for the integrity of regulatory processes. While such alternative pathways may be justified for certain products, they remain untested in the context of healthcare provision and treatment, and their consequences are therefore still uncertain. The scope of application of regulatory sandboxes should be clearly defined, and any unjustified shift in risk from the pre-authorisation to the post-authorisation stage should be avoided.

[23] Proposal for a REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on establishing a framework of measures for strengthening Union's biotechnology and biomanufacturing sectors particularly in the area of health and amending Regulations (EC) No 178/2002, (EC) No 1394/2007, (EU) No 536/2014, (EU) 2019/6, (EU) 2024/795 and (EU) 2024/1938 (European Biotech Act)

The HTA and payer community supports the EU's ambition to strengthen Europe's biotechnology ecosystem. At the same time, there are concerns that new IP-related provisions in the forthcoming Biotech Act could further delay competition. Given that EU patent and supplementary protection certificate (SPC) protection is already among the most generous globally, additional extensions could create significant and difficult-to-predict pressure on health insurance budgets, which are already under strain, without clear evidence that such measures would attract greater R&D investment in Europe.[24] Such approach could delay biosimilar entry, challenging affordability and the resilience of healthcare systems. New exclusivity extensions should be avoided and coherence with the broader pharmaceutical framework should be ensured, including support for timely competition after IP expiry and earlier market entry of biosimilar and other competing products.

In general, the various legislative initiatives in the pharmaceutical field reflect the EU's determination to adapt its regulatory framework to new realities. Its success, however, will ultimately depend on their coherent and integrated development. Innovation, clinical research, manufacturing, access and sustainability cannot be addressed in isolation. Only through alignment across legislation, timelines and policy objectives can Europe make full use of this evolving framework, remain an attractive and predictable strategic partner for the pharmaceutical industry and deliver tangible benefits for patients and healthcare systems.

Key considerations

- Target incentives for innovation to areas of unmet medical and societal needs.
- Explore alternative push and pull incentives while better streamlining European and national efforts.
- Introduce binding requirements as a condition of all public R&D funding to promote affordability and access.

[24] Medicines for Europe. Biotech Act – Factsheet on the Proposed 12-month Extension of the Supplementary Patent Protection (SPC). https://www.medicinesforeurope.com/wp-content/uploads/2026/03/SPC-Biotech-Act-factsheet.pdf

Chapter 3 – Future-proof decision-making: how do HTA bodies, P&R authorities and public payers innovate?

This chapter examines how HTA bodies and payers are adapting to the evolving pharmaceutical innovation landscape. It highlights the strategies adopted by Member States to improve their negotiating capacity within the pharmaceutical ecosystem, with focus on non-traditional access pathways as well as multi-country collaborations. The chapter will provide a critical analysis of how these collaborations work and how they could potentially be improved in the future.

Willingness and capacity to pay

It is an overarching and fundamental principal of statutory health insurance systems that are financed by social contributions or tax money to ensure access to state-of-the-art evidence-based medical care and medicinal products. Unfortunately, trends in development of innovative medicinal products constantly challenge affordability of novel treatment options mostly for already high-cost therapeutic areas. As these high prices are often accompanied by significant uncertainty regarding the effectiveness of new medicinal products, patients may face additional risks, while healthcare systems struggle to allocate limited financial resources efficiently.

As the available financial and infrastructural resources of healthcare systems in the EU are limited and need to be thoughtfully used, new medicines must demonstrate a clear or potential benefit through robust and high-quality evidence in order to receive appropriate reimbursement. Investment in a certain therapeutic area cannot be spent elsewhere and could be compensated by savings from other healthcare areas or reimbursement restrictions to keep within tight budgets. Therefore, strict evidence requirements are important for identifying medicines that do not provide an added benefit or are even less effective compared to a comparator drug. In this way, healthcare systems are protected from spending on less effective medicines through the standards set for evidence. Without these requirements, the already high expenditures for medicines would likely increase even further.

One consequence of rapidly rising expenditures is the increasing financial burden on contributors. They are the foundation of any healthcare system. An additional burden on contributors must be prevented through evidence-based resource allocation.

Case study: The experience with orphan medicinal products in Sweden

The Swedish Dental and Pharmaceutical benefits Agency (TLV) has analysed whether there is a rationale for accepting a higher cost per Quality Adjusted Life Year (QALY) for medicines for rare diseases. The conclusion is that there is, but only for the most rare and severe conditions.

The orphan drug legislation[25] was created to incentivise the development of medicines for rare diseases, addressing the reluctance of pharmaceutical companies to invest in treatments for small patient populations. The main hurdle from an industry perspective was a high risk of not achieving profitability, as the target patient populations may be too small to generate sufficient revenue to cover the high R&D costs.

In most industries, economies of scale reduce average production costs as output increases. However, the pharmaceutical industry, particularly in R&D, experiences a greater degree of economies of scale. This is due to high fixed costs, such as R&D and production setup, which dominate total costs, with relatively low marginal costs for producing additional units.

It is worth highlighting that R&D costs are often lower for orphan drugs than for other drugs because clinical studies are run in smaller populations, and less evidence may be required for a regulatory approval than for other medicines. However, in general the lower R&D cost does not compensate for the higher average R&D cost per patient for these medicines.

A prerequisite for a drug to be granted orphan drug designation under EU law is that the target patient population does not exceed 5 out of 10 000 people in the EU, which corresponds to a prevalence of approximately 5 000 patients in Sweden (225 000 in the EU). However, whether a medicine is used by 5 or 5 000 patients makes a big difference to companies' ability to cover R&D costs.

TLV has made calculations to understand the validity of the argument that medicines targeting rare conditions must be allowed to cost more, in order to provide sufficient incentives to develop them. The first step in the calculation was to make credible assumptions on what the R&D and production costs are for an average drug for a rare condition, taking into account that companies' investments not only need to cover costs but also generate a profit. The second step was to calculate what proportion of this cost Sweden should cover, given our share of OECD GDP. The third step was to calculate the annual revenue per patient the company needs to be able to cover these costs, and to see how that varies depending on the rarity of the condition. In the last step, TLV calculated how high the incremental cost-effectiveness ratio (ICER) threshold (cost per QALY) needs to be in order for the company to obtain the revenue needed to cover costs. The conclusion from TLV's calculation is that a higher ICER threshold is justifiable on these grounds for very rare conditions. If the number of patients is less than 50-100 patients in Sweden (corresponding to 1 out of 100 000) a higher

[25] Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products.

ICER threshold may be called for. That is, a much lower patient number than the criteria for the EU orphan drug designation of 5 out of 10 000 people.

Moreover, the calculation demonstrated that while the required cost per QALY rises steeply as patient numbers decrease, the slope becomes much flatter as the number of patients increases. This indicates a significant difference in the required cost per QALY between 5 and 10 patients, but a much smaller difference between 55 and 60 patients. Therefore, TLV concluded that economic arguments support accepting higher cost per QALY for the rarest conditions (significantly rarer than the criteria for regulatory orphan status), though this should be adjusted based on patient population size.

This approach also applies to high-volume, blockbuster drugs, for which prices may need to be reduced to align with the economic reality of R&D and production costs.

Case study: Direct acting antivirals to treat hepatitis C: A reflection

Interferon-free therapeutic regimes with highly effective direct-anting antivirals have revolutionised the treatment of patients with hepatitis C. The first substance, sofosbuvir, received marketing authorization by EMA on 16 January 2014 as Sovaldi®. It immediately triggered criticism because of the initial price in the US: one thousand dollars per tablet, meaning that a course of treatment for a single patient cost US$ 84 000. The price in Europe was somewhat lower.

The high price and the large number of patients eligible for treatment limited affordability, and many payers originally restricted treatment to patients with advanced liver disease – even though more patients could have benefited.[26]

Other, similarly effective alternatives were soon also approved, so competition helped bring the prices down. A course of treatment with a modern combination in Europe is now estimated to cost less than 25 000 (prices are often subject to confidential discounts). As prices dropped, or could be re-negotiated, restrictions were eased, so that more patients could be treated.

Attempts to justify this price often included pharmacoeconomic evaluations, which showed that even at such high prices, direct acting antivirals could be cost-effective, at least compared to prior, less effective and more onerous interventions. One of the factors that were included

[26] Marshall, Alison D., et al. "Restrictions for reimbursement of interferon-free direct-acting antiviral drugs for HCV infection in Europe." The lancet Gastroenterology & hepatology 3.2 (2018): 125-133, Simão, Margarida, and Cristina Gonçalves. "Hepatitis C Virus Infection in Europe." Pathogens 13.10 (2024): 841

in the pharmacoeconomic evaluations was the reduced need for liver transplantations in patients with liver cirrhosis or cancer caused by hepatitis C.[27,28]

Indeed, hepatitis C-related liver transplantations have decreased in Europe and the US.[29] However, this has not led to a reduction of liver transplants, because the number of patients needing liver transplantation far exceeds the number of available organs; indeed the number of liver transplants has increased, due to advances in technique and technology. But the proportion of patients needing a liver transplant due to hepatitis C-related disease has decreased, freeing up capacity for other patients. So, while money spent on liver transplants was not reduced, there is a considerable benefit for patients who are now able to get a liver transplant.

In conclusion, eliminating hepatitis C is biologically feasible. High prices of current antiviral therapies are one of the major obstacles to achieving the WHO goal of eliminating hepatitis C as a major health threat - others being limited awareness, testing and social support. Currently in Europe, competition among pharmaceutical companies is the most effective lever to reduce high prices in absence of an EU-wide joint negotiating strategy. European Member States should make every effort to prevent the need for restricting access to beneficial medicines due to unaffordable prices. This includes exploring reimbursement models that de-link prices from compensation to pharmaceutical companies.

Regional collaborations

In an increasingly complex pharmaceutical landscape with rising medicine prices, countries across Europe are exploring new ways to ensure timely, equitable, and sustainable access to medicines. Regional collaboration has emerged as a powerful tool to strengthen national efforts by allowing countries to pool expertise, share resources and increase their negotiating power.

By working together on the assessment, negotiation and decision-making processes, countries can reduce duplication, streamline procedures and develop more transparent frameworks for evaluating new treatments. Such collaboration not only benefits healthcare systems by improving efficiency but also serves the broader goal of ensuring that patients across borders have access to the medicines they need.

[27]Institute for Clinical and Economic Review (ICER). The comparative clinical effectiveness and value of novel combination therapies for the treatment of patients with genotype 1 chronic hepatitis C infection. A technology assessment. 20 January 2015.
https://icer.org/wp-content/uploads/2020/10/CTAF_HCV2_Final_Report_013015.pdf,

[28] National Institute for Health and Care Excellence (NICE). Single Technology Appraisal. Sofosbuvir-velpatasvir-voxilaprevir for treating chronic hepatitis C.
https://www.nice.org.uk/guidance/ta507/documents/committee-papers

[29] Symeou, Solonas, et al. "Global transplantation: Lessons from organ transplantation organizations worldwide." *World Journal of Transplantation* 15.1 (2025): 99683. Müller, Philip C., et al. "Current status of liver transplantation in Europe." *International Journal of Surgery* 82 (2020): 22-29

Initiatives such as the Nordic collaborations and the Beneluxa Initiative provide concrete examples of how regional partnerships are driving innovation in how new pharmaceuticals are assessed and accessed. While each initiative reflects the specific priorities and structures of its members, they all share a commitment to collaboration to achieve more sustainable and patient-centered pharmaceutical policies.

The Nordic collaboration

The Nordic collaboration on pharmaceuticals is a strategic effort to strengthen public decision-making by pooling expertise, aligning processes and building critical mass in the face of a growing number of new and often high-cost medicines with uncertain long-term value. Through cross-country collaboration, Nordic public institutions aim to safeguard timely, equitable and evidence-based access to medicines across the region.

Rather than duplicating efforts, the Nordic countries are increasingly coordinating their work in HTA, procurement and policymaking. This collaboration enables more coherent responses to shared challenges and increases the ability to influence developments in the pharmaceutical landscape.

A cornerstone of the collaboration is the Joint Nordic HTA Bodies (JNHB) framework, which allows for joint assessments of new medicines. The collaboration was established in 2018 by Finland, Norway and Sweden, and has since been joined by Denmark (2023) and Iceland (2024). The joint HTA process reduces duplication by enabling companies to submit a single dossier for clinical and economic evaluation across the Nordic countries. This results in a shared scientific report that supports national decision-making and contributes to more synchronised timelines. For patients, this means more aligned timing of decisions and decisions taken on a more harmonised basis. For countries, this means better use of limited HTA capacity. For companies, it offers a streamlined and predictable engagement across multiple markets.

However, the voluntary nature of the JNHB procedure poses a challenge. Participation depends on whether companies choose the joint route or prefer separate national procedures. While interest is growing, further progress hinges on stronger incentives, or even mandates, for companies to participate in joint procedures. Nordic HTA bodies have responded by increasing transparency, aligning evidence requirements, improving timelines, and proactively identifying candidates for joint assessments. Still, without a formal mandate, the potential of Nordic collaboration cannot be fully realised.

Beyond HTA, the Nordic Pharmaceutical Forum, established in 2015, facilitates strategic cooperation on procurement, horizon scanning, supply security and environmental aspects of pharmaceutical use. In parallel, Nordic decision-makers maintain informal dialogues to exchange experiences and address shared challenges.

As the EU HTA Regulation introduces new requirements for joint clinical assessments at the European level, the Nordic collaboration remains a valuable complement. The Nordic HTA

bodies are committed to building on EU assessments by jointly conducting health economic evaluations tailored to the Nordic context. In doing so, they preserve the ability to innovate and adapt shared processes to regional needs.

Ultimately, the Nordic collaboration demonstrates how smaller countries, by working together, can amplify their influence, strengthen the quality of their assessments and drive more efficient and equitable decisions in the pharmaceutical field. The gained efficiency of joint work can be exemplified by the substantially shortened assessment times for products assessed through JNHB, as the goal of finalising assessments within 90 working days has been reached. A goal that is beneficial for patients in the Nordic countries.

The Beneluxa Initiative

The Beneluxa Initiative is a pioneering example of cross-border collaboration aimed at strengthening national pharmaceutical policy through shared action. Established in 2015 by Belgium and the Netherlands, and later joined by Luxembourg, Austria, and Ireland, the initiative seeks to ensure sustainable access to high-cost medicines by combining resources and expertise.

At its core, the Beneluxa Initiative is built around four strategic pillars: joint HTA, collaborative price negotiations, horizon scanning and policy exchange. These pillars reflect a shared commitment to addressing common challenges such as limited evidence for new medicines, rising costs and fragmented national decision-making. By creating a space for practical and flexible cooperation, the initiative has demonstrated how countries together can shape the pharmaceutical landscape more effectively than alone.

One of Beneluxa's strengths lies in its pragmatic approach. Joint HTA and collaborative negotiations are conducted on a voluntary, case-by-case basis, allowing for flexibility while building trust between countries. The initiative has also contributed to structural innovation, such as the development of the International Horizon Scanning Initiative (IHSI), which provides early intelligence on upcoming pharmaceuticals to support better preparedness and planning.

However, several challenges have also emerged. The absence of a formal Beneluxa procedure means that participation depends on the alignment of company submissions, national priorities and legal timelines, factors that can vary significantly. As a result, much of the HTA and pricing work still occurs at the national level. Moreover, the lack of legal integration limits the initiative's ability to fully harmonize processes among Member States or mandate participation from companies.[30]

[30] Claessens Z et al. Opportunities and challenges in cross-country collaboration: insights from the Beneluxa Initiative. Journal of Market Access and Health Policy 2024;12:144-157

In its first decade, Beneluxa has shown pragmatism by cross-country mutual learning.[31] Therefore, Beneluxa continues to serve as a valuable testing ground for deeper European cooperation. It offers a model for how countries can engage in strategic, flexible and scalable collaboration, driven by a shared goal of delivering value for money and timely access to medicines. From an industry perspective, three drawbacks of regional collaboration in Beneluxa were explicitly highlighted:[32] it presents procedural and timeline uncertainties, it is sometimes difficult for companies to understand how national legislation can operate in parallel, and there are challenges on the side of the industry with their internal organisation. Building on its experiences, Beneluxa is ready to progress towards more joint activities in pharmaceutical policy across borders.

Looking ahead, the full potential of the Beneluxa Initiative depends on its ability to further streamline its processes, improve coordination of timelines and incentivise joint engagement from industry. The introduction of joint clinical assessments under the EU HTA Regulation may offer new opportunities for alignment. As pricing and reimbursement remain national competences outside the HTA Regulation and situated after the EU HTA process, the Beneluxa Initiative seeks to strengthen its activities there as a new focus.

Key recommendations for strengthening regional collaboration

- Encourage early and aligned industry engagement:
  Companies should coordinate submissions and timelines across countries to support timely and efficient joint assessments and negotiations.
- Strengthen mandates and shared procedures:
  Countries should formalise collaboration through incentives or mandates, with political support and cross-country learning to maintain momentum.
- Invest in joint capacity and tools:
  Sustainable collaboration depends on both shared infrastructure and a sufficient volume of joint assessments to justify investment.
- Coordinate with EU-level processes:
  Regional efforts should complement EU HTA by building on joint assessments and adding value through aligned economic evaluations.

[31] Vreman RA et al. The Beneluxa Initiative domain task force health technology assessment: a comparison of member countries' past health technology assessments. International Journal of Technology Assessment in Health Care 2023;39,e44,1-7

[32] Claessens Z et al. Opportunities and challenges in cross-country collaboration: insights from the Beneluxa Initiative. Journal of Market Access and Health Policy 2024;12:144-157

Early access schemes

In the recent context of therapeutic innovations, particularly in the field of oncology and rare diseases, ensuring rapid access to treatment while preserving patient safety is a major challenge. Early access schemes (EAS) have been implemented at the national level as a derogatory procedure allowing patients to access medicinal products before they complete the standard P&R procedure, even before marketing authorisation, with an anticipated favourable benefit-risk profile. They respond to legitimate patient needs where traditional HTA and reimbursement processes can take years for these specific medicines.

While allowing early access to products with great potential can be a support for innovation, especially when funded by health systems, medicines granted early access before price and reimbursement are often costly medicines and challenge health systems sustainability and payers negotiation power. In France, expenditures of medicines with early access increased by 35% in 2023, reaching €640 million (net expenditures) and accounted for around 5% of total net drug expenditures in 2023.

Furthermore, once a treatment is available and used by a significant number of patients, often in high-need therapeutic areas, the option of denying reimbursement becomes politically and ethically very difficult. This dynamic can lead to higher prices and constrain payers' ability to ensure long-term sustainability and equitable resource allocation.

While EAS are designed as temporary derogations, in practice they can create path dependency: once early access is granted, withdrawal may be difficult, regardless of the eventual clinical assessment outcomes. Evidence from the French experience show that the "bet" on innovation is not always successful based on early and often limited evidence: 82% of medicines that were granted early access demonstrated an additional clinical benefit while 18% have been assessed with no clinical improvement.[33]

A potential solution for fostering true innovation within early access frameworks would be to link them systematically with RWD collection. Structured evidence generation during EAS use could help reduce uncertainty and enable more balanced negotiations. Such a model would transform EAS from an access tool into a learning system, aligning patient access with evidence-informed affordability decisions.

In conclusion, EASs are a policy innovation for timely access, but their design and implementation should evolve to avoid undermining financial sustainability and payer negotiating powers. Embedding robust, RWD generation could make them an innovation for both access and affordability, closing the current gap between early promise and long-term value.

[33] Haute Autorité de Santé (HAS). Accès précoce des médicaments: un bilan positif après deux ans de mise en place du dispositive. 12 Novembre 2025. https://www.has-sante.fr/jcms/p_3470178/fr/acces-precoce-des-medicaments-un-bilan-positif-apres-deux-ans-de-mise-en-place-du-dispositif

Early access overview in some European countries: insights from the European medicines access time monitor

Derogations within the framework of EAS are usually granted for products that address unmet medical needs. For promising innovative products, derogations are granted whether on a case-by-case basis (often as compassionate use) or on a wider scale (population-based, like in France and Italy). These programmes differ from fast-track procedures where medicines that undergo HTA can be approved for standard coverage under specific condition and through MEAs, for example in England through the Cancer Drugs Fund or the Innovative Medicines Fund, and in Italy through the Innovative Medicines Fund.

EAS are quite developed in France, Italy and Spain where coverage decisions (inclusion on a reimbursement list) follow clinical assessment and price negotiations.[34] Different frameworks regulate early access whether funded by public payers or by the pharmaceutical companies, cover all or specific therapeutic areas.

France has a long-established early access programme, progressively implemented since the 1990s in the context of the AIDS pandemic: compassionate use or early access for supposedly innovative medicines (that can be granted at the company's request) are fully funded by the national health system.[35] Since being reformed in 2021, about 140,000 patients have benefited from early access over four years, mainly in oncology (half of the indications) and more than doubled in the last couple years.[36] In Italy, funded programs include population-based "648 law" programme and the nominative-based "5% fund" for rare diseases, while the compassionate use programme is pharma-sponsored. In Spain, early access is only granted through a nominative-based programme and can be either funded or pharma-sponsored. Early access is more limited in Germany as medicines are covered shortly after marketing authorisation and before HTA, which may be considered as a 'generalised post-marketing early access', and in England, where medicines are available after HTA. In both countries EAS are not publicly funded at national level.

The scope of covered indications within EA authorisations also differ: according to the 2025 edition of the European Medicine Access Time Monitor[37] produced by the French National Health Insurance Fund (CNAM) and focusing on new medicines with medical added value (according to French HTA ratings: medicines with at least a minor added benefit), indications

[34] S. Delcroix-Lopes et al., Early access to medicines with added therapeutic value: Measuring and comparing time to medicines access in England, France, Germany, Italy and Spain, Health policy, April 2025

[35] French governement report on early access schemes : rapport évaluant l'impact de la refonte des modalités d'accès et de prise en charge des nouveaux médicaments innovants, nov. 2025.

[36] Haute Autorité de Santé (HAS). Accès précoce des médicaments: un bilan positif après deux ans de mise en place du dispositive. 12 Novembre 2025. https://www.has-sante.fr/jcms/p_3470178/fr/acces-precoce-des-medicaments-un-bilan-positif-apres-deux-ans-de-mise-en-place-du-dispositif

[37] Christophe Chaignot, Nadia Amer, Sophie Delcroix-Lopes. Assessing medicines access time: a cross-country comparison in Europe - insights from England, France, Germany, Italy and Spain. 2025 edition. Comparaisons internationales n° 7. September 2025.

allowed under early access are more often restricted than the marketing authorisation in France while all fully funded, whereas in Italy and in Spain they are mostly the same.

Regarding access times, as shown in the European medicine access times monitor, EAS enable rapid patient access. Early access cut access times in countries where the standard pricing and reimbursement pathways are longer : France and Spain record faster first access times thanks to early access (respectively median times 18 days and 35 days before marketing authorisation) while access through standard procedure (from marketing authorisation to the inclusion on positive list for reimbursement) are the longest : 549 days in France and 628 days in Spain (median values).

However, granting early access can also prolong standard procedures, as price negotiations become more complex once the medicine is already available and the company has greater leverage. In light of this, CNAM recommends in its latest annual report,[38] that negotiation timelines be limited for medicines granted early access.

Finally, early access is key when measuring access times for patients due to their impact on standard procedure. Measuring access times only within the standard pathway does not depict the full picture as in the widely shared pharma-sponsored access time "W.A.I.T" indicator. Other initiatives to measure access times have recently emerged as in Spain with the report on the financing of innovative medicines in Spain (2025)[39] and the ongoing EURIPID access times project following the OECD study on the feasibility or measuring access times.[40]

Key recommendations for improving early access schemes

- Link early access programmes to systematic real world data collection. Structured evidence generation could help reduce uncertainty and enable more balanced price negotiations. Such a model would transform these programmes from an access tool into a learning system, aligning patient access with evidence-informed affordability decisions.

Data collection through registries: The Italian and Spanish experience

The AIFA Monitoring Registries were established in 2005 by the Italian Medicines Agency (AIFA) as part of a broader initiative to promote the appropriate use of high-cost and innovative medicines within the National Health Service (NHS). A complex legal framework - which introduced the concept of conditional reimbursement linked to registry-based data collection - defines the system's purposes and objectives, notably to ensure the appropriate use of a drug for a specific therapeutic indication. Compliance with these criteria, including conditions for prescribing, is mandatory for reimbursement by the NHS. Since 2005, the

[38] CNAM. Rapport charges et produits pour 2026.
[39] Ministry of Health of Spain. 2025. Financiación de medicamentos innovadores en España
[40] OECD. 2023. Exploring the feasibility of monitoring access to novel medicines: A pilot study in EU Member States.

registries have become a central regulatory tool for post-marketing surveillance and RWD generation in Italy. The registries serve multiple purposes: they monitor compliance with therapeutic indications approved by the European Medicines Agency (EMA) or AIFA, support the implementation of MEAs - both financial- and outcome-based - and provide RWD on effectiveness, safety and patient access. Physicians are required to enter patient-specific clinical data at treatment initiation, during follow-up, and upon therapy completion, ensuring continuous oversight of prescribing behaviour and therapeutic outcomes.

As of December 2023, more than 250 active registries have been launched, covering approximately 150 pharmaceutical products. Oncology is the therapeutic area with the highest concentration of registries, accounting for around 40% of the total. Other major areas include haematology, neurology and infectious diseases. Collectively, the registries encompass hundreds of thousands of therapies, creating one of the most extensive national RWD repositories in Europe.

For several drugs, real-world outcomes collected through the registries have confirmed - or in some cases differed from - those observed in RCTs, thus informing future regulatory and pricing decisions. MEAs linked to registries have enabled the NHS to enhance prescribing appropriateness and reduce economic uncertainty through payback mechanisms when pre-specified outcomes were not achieved, although exact figures often remain confidential.

In Spain, there is a strong emphasis on data collection. The NHS set up Valtermed in 2019, a web-based information system to collect RWD from all the autonomous healthcare regions in the country and not restricted to certain therapeutic areas. Valtermed provides information for decisions about the therapeutic value of medicines with high clinical and economic impact. As of May 2026, 38 drugs across 29 indications have been included in Valtermed, most of which are orphan. All approved advanced therapeutic medicinal products are part of Valtermed, with oncology being the most common indication.

In Spain, the Ministry of Health discusses about the need for additional RWD. Once agreed, an administrative resolution will outline how RWD will be collected and how the evidence will be used in the P&R agreement. A pharmaco-clinical protocol is then designed by experts from the autonomous regions in Spain, professional societies and the health technology developer, a process which usually takes several months. Healthcare professionals from autonomous regions across Spain must enter the required data manually.

The Spanish Ministry of Health is trying to improve this process noting that the protocols, collecting a wide range of data can be quite extensive (10–28 pages) and resource-consuming to develop (taking 1–6 months). Further work is ongoing to better identify and prioritise products for which data collection may be feasible and valuable, through a decision tree to determine the benefit-risk of early access and the potential for Valtermed to collect sufficient data. Also, it has been recognised that engagement with health technology developers is needed prior to marketing authorisation to enable data collection to start earlier.

The Spanish Ministry of Health noted challenges arising from delays in contracts with vendors and of coordination across regions with different needs and capabilities. Furthermore, it was also noted that currently too many outcomes are collected. Therefore, action has been taken to better select outcomes with a checklist indicating relevant uncertainties (risk of bias, indirect evidence, imprecision, inconsistency and insufficient follow-up).

Reflections, challenges and recommendations

Reflections, challenges and recommendations for data collection through registries

- Registries are often perceived as administratively burdensome by clinicians.
- Automation can enhance data analytics capabilities and improve integration with other administrative databases.
- Data collection should be fit-for-purpose e.g. shifting from product specific to indication specific data collection in larger databases.
- Consider a multistakeholder approach: the inclusion of different expert roles within the design and analysis of these registries/repositories would add unique insights.

About the European Social Insurance Platform (ESIP)

The European Social Insurance Platform (ESIP) represents 46 national statutory social insurance organisations in 19 EU Member States and Switzerland, active in the field of health insurance, pensions, occupational disease and accident insurance, disability and rehabilitation, family benefits and unemployment insurance. The aims of ESIP and its members are to preserve high profile social security for Europe, to reinforce solidarity-based social insurance systems and to maintain European social protection quality. ESIP builds strategic alliances for developing common positions to influence the European debate and is a consultation forum for the European institutions and other multinational bodies active in the field of social security.

ESIP members support this position insofar as the subject matter lies within their field of competence.

About the Medicine Evaluation Committee (MEDEV)

The Medicine Evaluation Committee (MEDEV) was established in 1998 by representatives of the social health insurance organisations in Austria, Finland, Germany, Luxembourg, The Netherlands, and Switzerland to facilitate informed discussions and exchanges on pharmaceutical policy developments in the EU. MEDEV is a network of 25 national authorities from 20 Member States and Norway bringing together all the relevant institutions (national HTA agencies and social health insurers-payers) responsible for the assessment, pricing and reimbursement of medicines in Europe. The overarching mission of MEDEV is to further the sustainable provision of medicines to patients who are publicly insured. The European Social Insurance Platform (ESIP) in Brussels was commissioned with the role of coordinating the activities of the Committee.

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Annex - Glossary

Early access schemes
National legal framework to grant earlier patient access to new health technologies before a marketing authorisation and/or final pricing and reimbursement decision has successfully been issued.

Early dialogue
Exchange of health technology developers and national HTA bodies and healthcare payers to identify evidentiary requirements for decision making especially for pricing and reimbursement in early development stages.

Horizon scanning
The systematic identification of health technologies that are new, emerging or becoming obsolete and that have the potential to effect health, health services and/or society. An emerging health technology in this context is a health technology that has not yet been adopted within the healthcare system. Pharmaceuticals are in the Phase II or III clinical trial, or pre-launch stage; medical devices are in the pre-marketing stage. A new health technology is a health technology that is in the launch, early post-marketing or early diffusion stages. Horizon scanning systems (e.g. early awareness and alert (EAA) systems) aim to support decision-making and the adoption and use of innovative technologies to the benefit of patients and health services.[41]

Joint Scientific Consultation (JSC)
Framework to discuss clinical development programmes for health technologies by health technology developers with European and national regulators and HTA bodies to identify evidentiary needs for subsequent clinical assessments and marketing authorisation.

Managed Entry agreement (MEA)
An arrangement between a manufacturer and payer/provider that enables access to (coverage/reimbursement of) a health technology subject to specified conditions. These arrangements can use a variety of mechanisms and are usually classified into financial-based and performance-based MEA. The latter links price (reward for manufacturers) to health outcomes.

Examples of managed entry agreements:[42]
- Access with evidence development (AED)
- Conditional coverage
- Conditional treatment continuation (CTC)
- Coverage with evidence development (CED)
- Only in research (OIR)
- Only with research

[41] https://ppri.goeg.at/horizon_scanning
[42] https://ppri.goeg.at/MEA

- Outcome guarantees
- Patient access scheme (PAS)
- Pattern or process care
- Performance based agreement
- Performance based health outcome reimbursement schemes
- Performance-linked reimbursement
- Price volume agreements
- Risk sharing schemes

MEAs can be part of national early access schemes.

Post launch evidence generation (PLEG)
Evidence that is generated after launch of a health technology to fulfil evidentiary requirements of regulators and health systems. Mainly based on an obligation by EMA within an evidence generation plan for post-approval safety (PASS) and/or post-approval efficacy (PAES) studies.

Real world data (RWD)
Real-world data (RWD) refers to observational data obtained outside the context of randomised controlled trials (RCT) that is generated during routine clinical practice, such as from pharmacovigilance reports, electronic health records, registries, medical or reimbursement claims databases. RWD is addressed as additional evidence generation tool to fulfil requirements for authorisation of health technologies also post launch, requirements of national pricing and reimbursement as well as evaluating risks and benefits at later stages of a health technology's life cycle.[43]

[43] https://ppri.goeg.at/RWD