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Transformation of Market Access Strategies under the Influence of International Harmonization in Health Technology Assessment

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Abstract

By 2018, health technology assessment (HTA) had become a central determinant of reimbursement and patient access in most mature pharmaceutical markets, while differences in national assessment methods continued to create substantial evidence and planning burdens for manufacturers. At the same time, European cooperation was moving from voluntary methodological coordination toward a more institutionalized model: EUnetHTA had developed common assessment tools and joint relative-effectiveness work, and on 31 January 2018 the European Commission published proposal COM(2018) 51 for strengthened EU cooperation on HTA. This study examines how that emerging harmonization trajectory was likely to transform pharmaceutical market access strategy as it could reasonably be assessed at the end of March 2018. A structured comparative analysis was conducted for six HTA systems, namely NICE (United Kingdom), CADTH (Canada), G-BA/IQWiG (Germany), HAS (France), Zorginstituut Nederland (the Netherlands), and PBAC (Australia), together with a targeted analysis of EUnetHTA, EMA–EUnetHTA and European Commission documents published from 2014 through March 2018. The analysis identifies substantial convergence in the structure of clinical evidence assessment, especially around population, comparator, patient-relevant outcomes, systematic evidence synthesis and transparency, but persistent divergence in economic evaluation, comparator interpretation, decision rules, pricing mechanisms and the use of real-world evidence. The central strategic implication is that harmonization should not be treated as the creation of a single market-access dossier. Rather, it creates a transferable clinical evidence core that must be designed early and then connected to country-specific economic and reimbursement modules. To operationalize this approach, the paper proposes an Integrated Harmonized Market Access Strategy (IHMAS) framework linking evidence architecture, regulatory–HTA alignment, national economic adaptation, real-world evidence planning, early dialogue, budget impact, value communication and pricing scenarios.

Keywords: *Health Technology Assessment, Market Access, HTA Harmonization, EU HTA Regulation, Joint Clinical Assessment, Pharmacoeconomics, Cost-Effectiveness Analysis, Real-World Evidence, ICER, Reimbursement Strategy.*

INTRODUCTION

Market authorization and market access are related but distinct stages in the life cycle of a medicine. Regulatory authorization establishes whether a product has a favorable benefit–risk balance for a defined indication, whereas reimbursement bodies ask a different question: whether the technology offers sufficient clinical and, where relevant, economic value compared with alternatives already financed by the health system. Across Europe, evidence-based reimbursement and pricing processes have become increasingly institutionalized, but their organizational design and decision criteria remain heterogeneous [4, 5]. For manufacturers, this means that a successful development program must anticipate not only regulatory evidence requirements but also the comparative and economic questions that will be raised after authorization.

The period from 2014 to early 2018 was characterized by a gradual intensification of international HTA cooperation. EUnetHTA produced methodological guidelines for relative effectiveness assessment and health economic evaluation, released version 3.0 of the HTA Core Model®, and moved under Joint Action 3 toward a greater volume of jointly produced assessments [3, 7–9]. In parallel, the European Medicines Agency (EMA) and EUnetHTA strengthened

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mechanisms for parallel consultation so that developers could discuss regulatory and HTA evidence needs earlier in development [20]. These initiatives did not create a single European reimbursement authority; rather, they attempted to make scientific assessment more transferable while preserving national responsibility for pricing, reimbursement and context-sensitive decisions.

A major policy development occurred on 31 January 2018, when the European Commission issued a proposal for a Regulation on health technology assessment, COM(2018) 51 [1]. The proposal identified differences in national processes and methodologies, duplication of clinical assessments and the project-based nature of EU cooperation as structural problems. Its preferred architecture focused mandatory cooperation on clinical assessment, while leaving economic, organizational and ethical domains and final pricing and reimbursement decisions at Member State level [1, 2]. At the cut-off date of this study, this was a legislative proposal rather than an adopted or operational Regulation; therefore, any analysis of its effects must be prospective and scenario-based rather than presented as an observed post-implementation result.

This distinction is important for market access strategy. If a common clinical assessment becomes more influential, the manufacturer gains an opportunity to reduce duplication in evidence presentation, but simultaneously loses some freedom to reshape the clinical value narrative independently in every country. National systems can still differ in their preferred comparator, economic model, utility measurement, budget impact, eligible population and pricing logic. The strategic problem therefore shifts from producing many independent dossiers toward building a robust, reusable clinical evidence architecture with pre-planned national adaptation layers.

The objective of the present study is to analyze how international HTA harmonization, as it existed and was proposed by March 2018, changes the design of pharmaceutical market access strategy. The study addresses three questions: which HTA elements were already sufficiently standardized to support transferability; which elements remained structurally country-specific; and how should manufacturers reorganize evidence planning so that the same development program can support multiple HTA environments without assuming that harmonization eliminates national decision-making.

The scientific novelty of the work is the proposed Integrated Harmonized Market Access Strategy (IHMAS) framework. In the 2018 version developed here, IHMAS is not a model of a future EU procedure and does not assume that the Commission proposal will be adopted without amendment. It is a strategic planning architecture that separates a transferable evidence core from national economic and reimbursement modules and connects both to early regulatory–HTA dialogue, real-world evidence generation and lifecycle reassessment.

The study hypothesis is that international HTA harmonization reduces duplication in the scientific assessment of transferable clinical evidence but does not eliminate the methodological differences that drive national reimbursement decisions and may instead make those differences more visible. Consequently, the value of harmonization for manufacturers depends on earlier evidence planning, explicit mapping of national decision rules and the ability to adapt economic and access arguments without reconstructing the clinical evidence base from the beginning.

The practical relevance of the study extends to pharmaceutical and biotechnology companies, health economists, HTA specialists, payer-facing teams and public decision-makers. The analysis is also relevant outside the European Union because the same strategic tension is visible in Canada and Australia: common principles of comparative evidence and economic evaluation coexist with jurisdiction-specific processes, thresholds or deliberative criteria [11, 14]. Methodological limitations should be stated clearly. The study is based on public documents and peer-reviewed literature, excludes confidential negotiations, and applies a strict evidence cut-off of 31 March 2018. Because the Commission proposal had not yet completed the legislative process, conclusions about future EU cooperation are framed as strategic implications rather than empirical effects.

MATERIALS AND METHODS

This study uses a structured comparative document analysis and narrative synthesis. The analytical period is restricted to materials published from 1 January 2014 through 31 March 2018 so that the conclusions are consistent with an April 2018 publication date. Sources published after the cut-off are not used to establish facts, outcomes or policy developments. Earlier institutional history is mentioned only when it is described within sources that fall inside the permitted publication window.

Six HTA systems were selected for comparison: NICE in the United Kingdom, CADTH in Canada, G-BA/IQWiG in Germany, HAS in France, Zorginstituut Nederland (ZIN) in the Netherlands and PBAC in Australia. They were chosen because they represent distinct decision logics, including cost-utility appraisal, comparative clinical benefit assessment, deliberative economic evaluation and different links between HTA and price negotiation. All six are important reference markets for international pharmaceutical development. The principal dimensions were: definition of the decision problem; comparator selection; clinical endpoint expectations; role of cost-utility analysis; existence or absence of an explicit cost-effectiveness threshold; use of real-world data; and the relationship between assessment output and reimbursement or price setting [4, 11–15, 23].

The harmonization component of the analysis draws on the European Commission proposal COM(2018) 51 and its accompanying impact-assessment materials [1, 2], the

EUnetHTA HTA Core Model® and methodological guidelines [3, 7–9], evidence on national adaptation of EUnetHTA outputs [21, 22], and the EMA–EUnetHTA work plan on parallel consultation and evidence alignment [20]. These sources were used to distinguish domains that are potentially transferable across jurisdictions from domains that depend strongly on local health-system context.

Real-world evidence (RWE) was analyzed as a cross-cutting component because by 2016–2017 it had become a prominent issue in regulatory and HTA methodology. RWE is used here in the broad sense of evidence generated from data collected during routine care, such as electronic health records, claims, registries and observational cohorts. The analysis follows contemporary distinctions between randomized efficacy evidence and observational evidence on effectiveness, utilization and longer-term outcomes [6, 16, 17]. It does not assume that RWE has a uniform evidentiary status across agencies.

The IHMAS framework was developed by synthesizing the recurring strategic requirements identified in the comparison. Each module was retained only if it addressed a problem observable in the 2014–March 2018 evidence base: transferability of clinical assessment, divergence in national economics, early dialogue, uncertainty management, RWE planning, budget impact, stakeholder communication or price/access scenarios. The framework is therefore an analytical synthesis rather than a validated prediction of the final form of future EU legislation.

RESULTS AND DISCUSSION

By 2018, the most important transformation in HTA harmonization was not the creation of a centralized reimbursement system but the gradual separation of assessment components according to how transferable they are. The EUnetHTA HTA Core Model® provides a common structure for multidimensional assessment and was designed specifically to support production and sharing of HTA information [3, 7]. Experience with national adaptation showed that common reports can be reused, but that additional local evidence and health economic analysis may still be required before national advice is issued [21, 22]. This finding is central to market access strategy: reuse is possible, but reuse is not equivalent to automatic adoption.

The January 2018 Commission proposal formalized the same distinction. It argued that clinical domains, particularly relative clinical effectiveness and safety, are based largely on evidence that can be shared across countries, whereas economic, organizational and ethical domains are more sensitive to national context [1]. The proposal therefore envisaged stronger EU-level cooperation on joint clinical assessments and joint scientific consultations, while explicitly leaving pricing and reimbursement decisions to Member States [1, 2]. At the time of writing, the direction of travel was clear, but the legal design and implementation timetable were not yet settled.

This emerging model changes the optimal sequence of manufacturer activities. Under a predominantly country-by-country approach, evidence teams could begin with a common regulatory package and then construct each HTA submission relatively independently. Under stronger cooperation, weaknesses in the shared comparative evidence could be exposed simultaneously across several markets. Conversely, a well-designed common evidence core could reduce repeated systematic-review and clinical-effectiveness work. The value of early planning therefore increases because comparator choice, subgroup definitions, patient-relevant outcomes and indirect-comparison strategy become decisions with cross-market consequences.

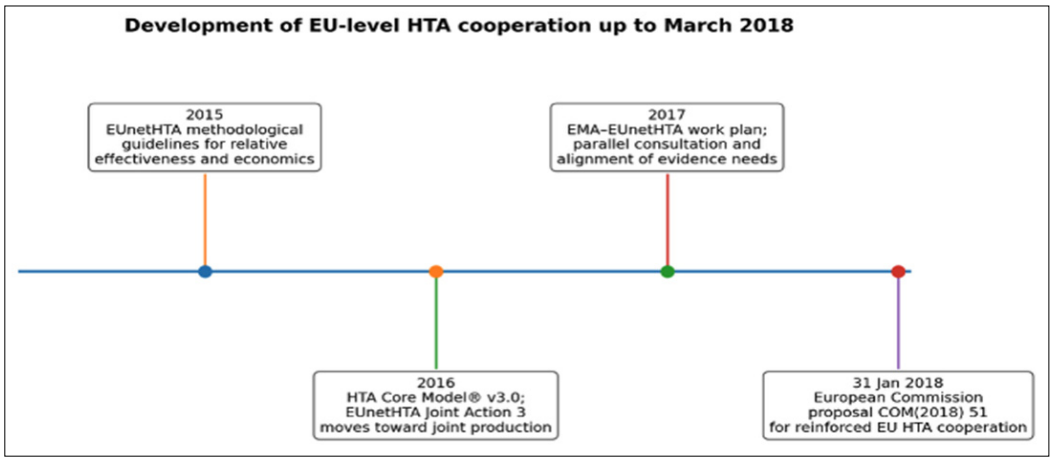


Figure 1. Development of EU-level HTA cooperation up to 2018 (compiled by the author based on [1–3, 7, 20]).

Despite convergence in the language of evidence-based assessment, the six reviewed systems differ fundamentally in decision logic. NICE uses clinical effectiveness together with cost-utility analysis and commonly interprets incremental cost-effectiveness ratios in relation to a range around £20,000–£30,000 per QALY, although decision-making remains deliberative and uncertainty matters [10]. CADTH's 2017 economic guidelines recommend cost-utility analysis as the reference form of economic evaluation, but the guideline does not establish a single formal willingness-to-pay threshold [11]. PBAC similarly requires comparative clinical and economic evidence but does not publish a single fixed threshold that mechanically determines listing [14].

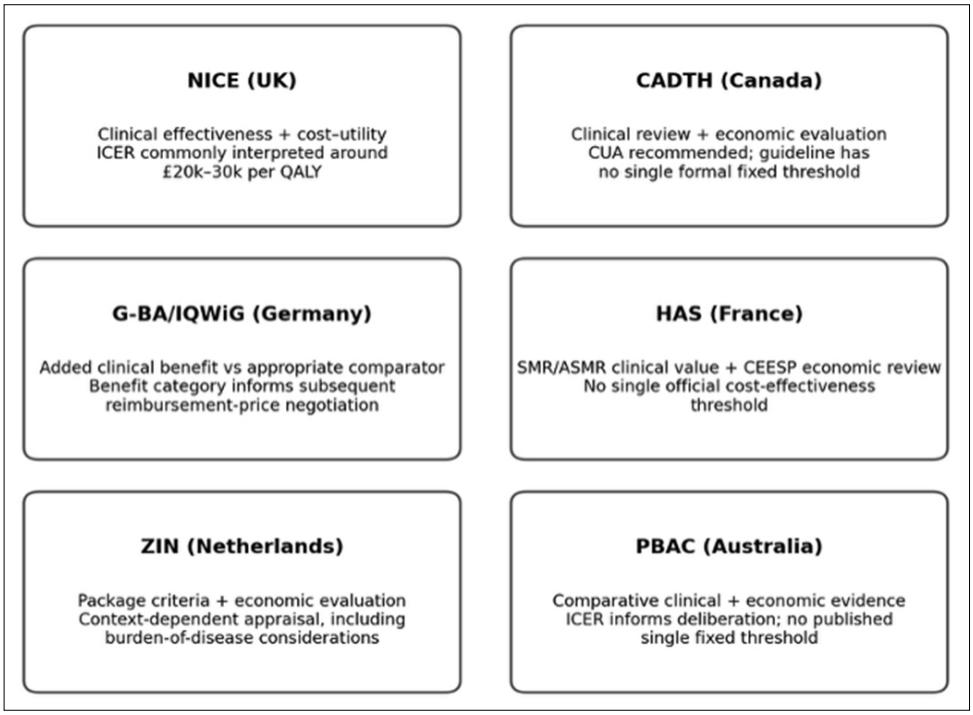


Figure 2. National HTA decision logic across six reviewed systems as of March 2018 (compiled by the author based on [4, 10–15, 23]).

Germany represents a different logic. Under AMNOG, the core question for new medicines is whether an added benefit is demonstrated relative to the appropriate comparator, with the magnitude of that benefit informing subsequent reimbursement-price negotiation. Empirical analyses published before the cut-off show that the benefit rating is materially associated with negotiated price outcomes [23]. This framework places particular strategic weight on comparator alignment, patient-relevant endpoints and subgroup evidence; a conventional QALY model cannot substitute for failure to demonstrate comparative added benefit.

France also illustrates why a harmonized clinical evidence core cannot be equated with a harmonized reimbursement decision. HAS combines assessment of clinical value through SMR/ASMR with economic evaluation for products meeting relevant criteria, but France did not operate a single official cost-effectiveness threshold comparable with a mechanical decision rule [4, 13]. In the Netherlands, economic evaluation is embedded within a broader package-appraisal framework; the 2016 guideline standardizes analytic methods, while the final decision remains linked to contextual criteria and the characteristics of the health system [15].

The practical consequence is that the same clinical result can have different strategic implications. A statistically significant treatment effect may be clinically persuasive but insufficient if it is measured against a comparator that is not the locally relevant standard of care. An acceptable clinical comparison may still produce an unfavorable economic result if local resource costs, treatment pathways or utility values differ. Harmonization therefore increases the importance of distinguishing the evidence component that should be identical across countries from the assumptions that should deliberately vary.

Table 1. Comparative HTA decision architecture as of 2018 (compiled by the author based on [4, 6, 10–15, 23, 24]).

Dimension	NICE (UK)	CADTH (Canada)	G-BA/IQWiG (Germany)	HAS (France)	ZIN (Netherlands)	PBAC (Australia)
Primary decision logic	Clinical + cost effectiveness; CUA central	Clinical review + economic evaluation; CUA recommended	Added benefit vs appropriate comparator; price negotiation follows	SMR/ASMR clinical value; CEESP economic review for relevant products	Package criteria with clinical and economic evaluation	Comparative clinical evidence + economic evaluation
Cost-effectiveness threshold	Recognizable £20k–30k/QALY decision range; deliberative	No single formal fixed threshold specified in 2017 guideline	No QALY threshold for AMNOG added-benefit rating	No single official threshold	Context-dependent; no single universal decision rule	No published fixed threshold

Comparator emphasis	NHS-relevant alternatives	All relevant current and displaced interventions	G-BA appropriate comparator is pivotal	Relevant therapeutic alternatives	Dutch standard care / package context	Therapy most likely to be replaced
RWE position	Can inform uncertainty; managed access mechanisms exist	May inform effectiveness, resource use and model inputs when fit for purpose	Evidence hierarchy favors robust comparative evidence; non-randomized data require justification	Observational and post-registration evidence may complement assessment	RWD can support effectiveness and utilization questions subject to methods	Non-randomized evidence may be considered where appropriate, with uncertainty
Strategic implication	Plan utilities and economic model early	Build reference-case CUA and broad comparator set	Align pivotal evidence with appropriate comparator and patient-relevant outcomes	Separate clinical value rating from economic argument	Integrate economic evidence with package criteria	Link clinical comparison to economic evaluation and listing context
Dimension	**NICE (UK)**	**CADTH (Canada)**	**G-BA/IQWiG (Germany)**	**HAS (France)**	**ZIN (Netherlands)**	**PBAC (Australia)**

Comparator selection is one of the most important points of tension. EUnetHTA methodological guidance emphasizes explicit criteria for choosing the most appropriate comparator or comparators and for handling direct and indirect evidence [8]. However, national agencies may define the relevant standard of care differently because treatment patterns, reimbursement status and clinical pathways differ. For manufacturers, a development program built around a single regulatory comparator may therefore be insufficient for HTA purposes even when that comparator supports marketing authorization.

The same issue applies to endpoints. EUnetHTA guidance places emphasis on patient-relevant mortality, morbidity, safety and health-related quality of life outcomes, while national agencies differ in how they value surrogate endpoints, composite outcomes and utility measures. The strategic response is not to add every conceivable endpoint to a trial; it is to map the highest-risk national divergences early enough to incorporate feasible measures, predefined subgroups or indirect-comparison plans into the development program.

Economic evaluation is even less transferable than the clinical evidence base. Costs are inherently local; resource use may be transferable only after validation; discount rates, perspective, utility instruments and modelling conventions differ; and the price under evaluation is itself market-specific. EUnetHTA's 2015 health-economic guideline was designed to support methodological understanding across Europe, but it did not eliminate national reference cases [9]. A harmonized strategy therefore requires modular economic modelling: one disease model and evidence architecture, but separate parameterization and scenario layers for each jurisdiction.

RWE can serve different purposes at different stages. Before launch, registry and database feasibility work can establish natural history, treatment patterns and external comparators. At submission, observational sources may inform epidemiology, resource use, utilities and external validity. After launch, prospectively planned studies may reduce uncertainty around durability of effect, safety or real-world utilization. The methodological credibility of such work depends on prespecification, transparent data provenance, appropriate control of confounding and reproducibility. These principles were emphasized by the ISPOR–ISPE task force in 2017 [17].

The EMA adaptive-pathways pilot reinforced the importance of lifecycle evidence generation and early interaction among regulators, HTA bodies and other stakeholders [18, 19]. Its relevance to market access strategy is not that all products should follow an adaptive pathway, but that evidence planning increasingly extends beyond a single pivotal-trial readout. Where uncertainty at authorization is expected to remain material for HTA, manufacturers should decide before launch which data source can realistically resolve the uncertainty, whether the relevant variables are captured, and whether the analysis can be completed within a useful decision horizon.

The combined evidence suggests a transition from independent country dossiers toward a 'common core plus national modules' architecture. The common core contains the elements with the highest potential transferability: disease definition, target population, intervention description, systematic clinical evidence, comparative effectiveness, safety and transparent methods for evidence synthesis. National modules contain the elements that depend on local context: treatment pathway, comparator weighting, prices, resource costs, utility preferences where jurisdiction-specific rules apply, budget impact, contracting arrangements and stakeholder priorities.

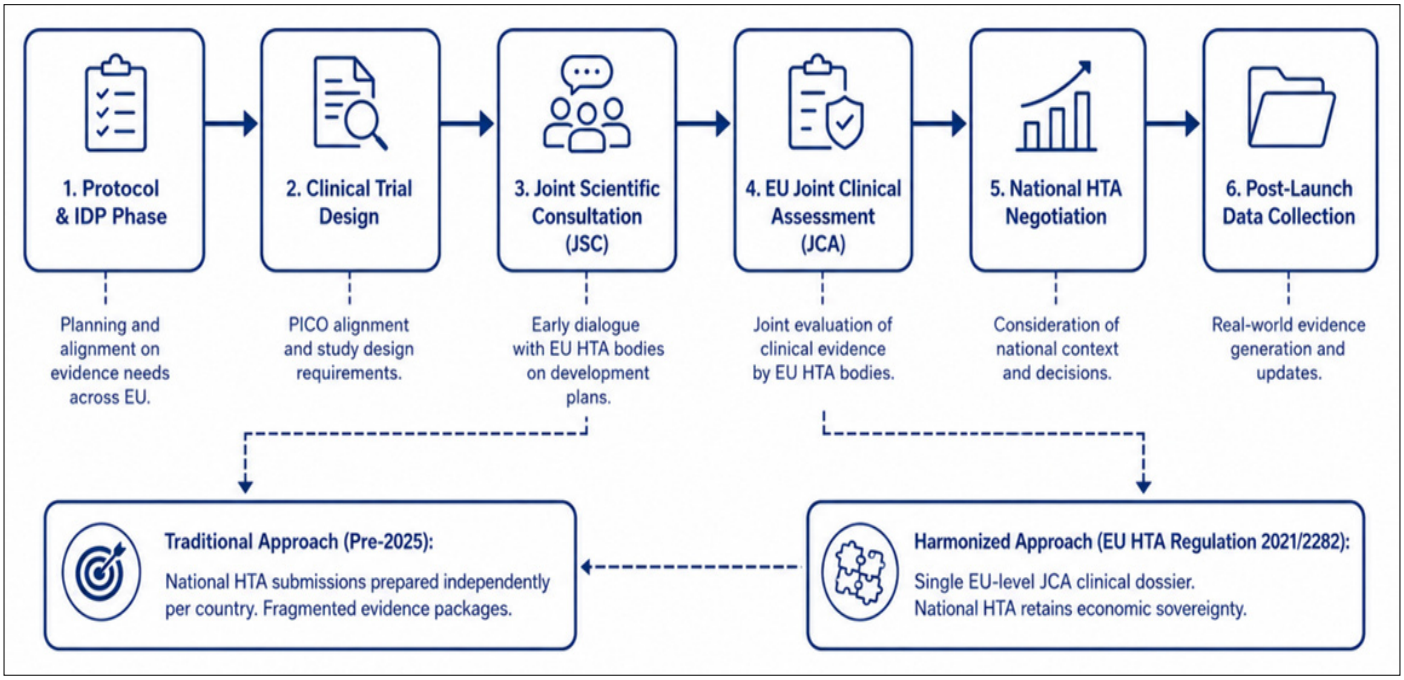


Figure 3. Transformation of Market Access Strategy Stages Under EU HTA Harmonization (compiled by the author based on [, 3, 8, 9, 21, 22]).

This structure also clarifies what harmonization cannot accomplish. A joint or transferable clinical assessment can reduce repetition, but it cannot determine a single European price because willingness to pay, health-system budgets and negotiating institutions remain national. Nor can it guarantee identical reimbursement populations, because the relevant comparator and place in therapy may differ. The appropriate strategic aim is therefore consistency of scientific evidence combined with planned flexibility of economic and access assumptions.

Table 2 operationalizes this distinction. It shows that the closer an assessment element is to the internal validity of the clinical evidence, the greater its potential for common production; the closer it is to opportunity cost, service organization or price negotiation, the greater the need for local adaptation. This is also consistent with experience adapting EUnetHTA rapid reviews, where local decision-making still required contextual information and economic analysis [21].

Table 2. Transferable and country-specific elements of HTA under emerging harmonization (author's synthesis based on [1, 3, 8, 9, 21, 22]).

Assessment element	Potential common / transferable core	Country-specific adaptation	Market-access implication
Population	Disease definition; trial eligibility; key subgroups	Reimbursed population; epidemiology; place in pathway	Predefine subgroups that may matter across priority markets
Intervention	Dose, administration, treatment effect, safety	Local service delivery and implementation costs	Keep clinical description common; adapt delivery consequences
Comparator	Evidence network and direct/indirect comparisons	Local standard of care and reimbursed alternatives	Map comparator divergence before pivotal-trial lock
Outcomes	Patient-relevant clinical endpoints and safety	Local preferences for utility measurement or decision weighting	Collect outcomes that can support both clinical and economic use
Evidence synthesis	Systematic review, meta-analysis, indirect comparison methods	Local supplementation only when required	Maintain one traceable evidence repository
Economic model	Disease model structure where transferable	Perspective, costs, utilities, discounting, price, treatment mix	Use modular model architecture rather than unrelated country models

Drawing on these findings, the Integrated Harmonized Market Access Strategy (IHMAS) framework is proposed as a planning tool for the 2018 policy environment. Its purpose is to organize market access work around the distinction between transferable and non-transferable evidence while preserving a single cross-functional decision process. The framework consists of eight modules coordinated through a core decision node. It does not replace regulatory, HTA or payer procedures; it defines what a developer should prepare before entering them.

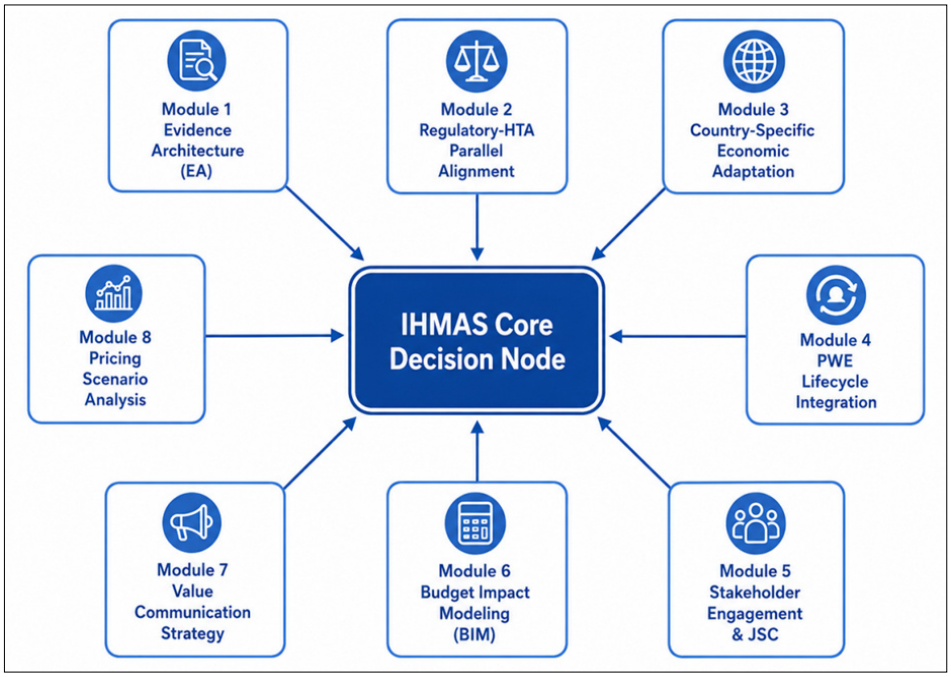


Figure 4. Integrated Harmonized Market Access Strategy (IHMAS), 2018 version (author's framework based on the comparative analysis in this study).

Module 1, Evidence Architecture, defines the reusable clinical evidence core. It begins with an explicit multi-jurisdictional decision-problem map covering populations, comparators, outcomes, key subgroups and likely indirect comparisons. The output is a development evidence matrix that identifies which requirements can be met by the pivotal program and which require complementary analyses. The objective is to avoid the late discovery that a trial is clinically persuasive for regulators but misaligned with the comparator or endpoint logic of a priority HTA market.

Module 2, Regulatory–HTA Alignment, links regulatory scientific advice with HTA early dialogue or parallel consultation where available. The EMA–EUnetHTA work plan published in 2017 specifically aimed to align data requirements and implement a common European procedure for parallel consultation [20]. The strategic value of this module lies in identifying divergent questions while protocol changes are still possible. It should be used selectively for high-impact uncertainties rather than as a substitute for internal evidence planning.

Module 3, Country-Specific Economic Adaptation, creates a modular economic platform rather than unrelated national models. The clinical natural-history structure and treatment-effect evidence are shared where scientifically justified, but perspective, resource use, unit costs, discounting, utilities, comparator mixes and price scenarios are parameterized according to national reference cases [9, 11, 13–15]. This approach improves consistency while making local assumptions transparent instead of hiding them inside independently constructed models.

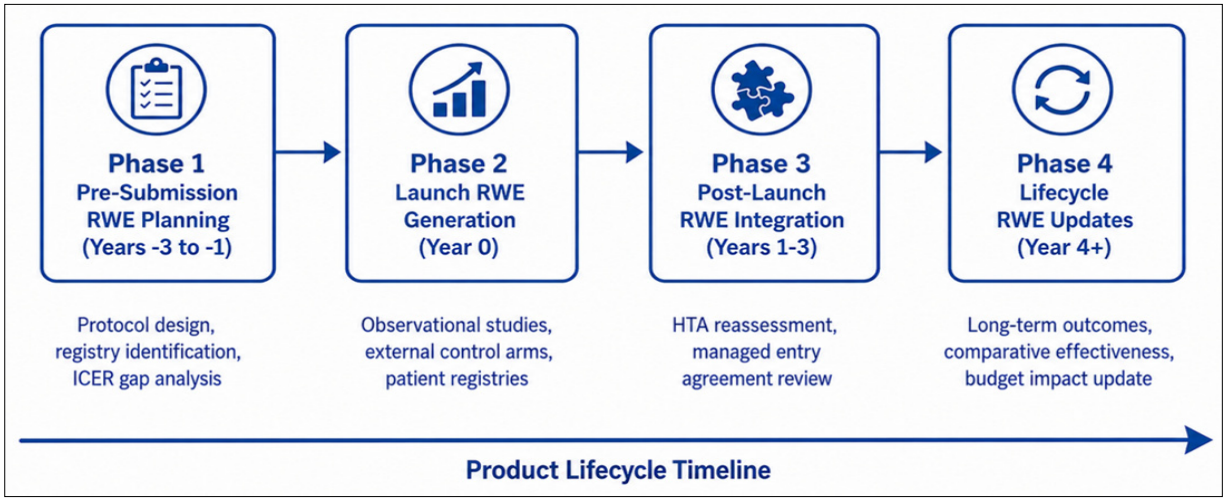


Figure 5. Phased real-world evidence integration model for HTA dossier preparation (author's synthesis based on [6, 16, 17, 19]).

Module 4, RWE Lifecycle Integration, specifies which post-randomization uncertainties may require observational evidence and links each uncertainty to a feasible data source, protocol and decision point. The module requires a clear statement of causal question, target population, exposure, comparator, outcome, follow-up and planned analytical controls. Where RWE is used to support reassessment or managed access, data collection should be designed before launch rather than improvised after reimbursement conditions are imposed [6, 17].

Module 5, Early Dialogue and Stakeholder Engagement, covers interactions with HTA bodies, clinicians, patients and payers that affect the relevance of the decision problem. Harmonization increases rather than eliminates the importance of these interactions because a common clinical question must still reflect real treatment pathways. Module 6, Budget Impact Modeling, translates the value proposition into affordability under national uptake, population and displacement assumptions. Cost-effectiveness and affordability are analytically distinct; a technology may be cost-effective yet create a budget impact that changes implementation or contracting strategy.

Module 7, Value Communication, converts the evidence architecture into audience-specific narratives without changing the underlying facts. Scientific assessors require transparent comparative evidence and uncertainty; payers require consequences for health-system resources and alternatives; clinicians and patients require clinically meaningful outcomes and implementation context. Module 8, Pricing and Access Scenarios, links national decision logic to feasible launch-price, discount, managed-access and sequencing options. The output is a scenario matrix showing which evidence uncertainties threaten price, reimbursement breadth or time to access in each market.

The central decision node integrates the eight modules and prevents local optimization from damaging the overall strategy. For example, a subgroup that improves an economic model but is not prespecified or clinically credible should not be treated as a sustainable access solution. Likewise, an aggressive launch price in one country may alter external reference-pricing consequences elsewhere. The framework therefore treats market access as a portfolio of linked evidence and pricing decisions rather than a sequence of isolated HTA submissions.

Table 3. IHMAS modules and operational outputs for market access planning as of March 2018.

IHMAS module	Primary purpose	Core output	IHMAS module	Primary purpose
1. Evidence Architecture	Design a reusable comparative evidence core	Multi-jurisdiction PICO/ evidence matrix	1. Evidence Architecture	Design a reusable comparative evidence core
2. Regulatory–HTA Alignment	Identify divergent evidence needs while protocols can change	Integrated advice and risk log	2. Regulatory–HTA Alignment	Identify divergent evidence needs while protocols can change
3. Country-Specific Economic Adaptation	Translate shared clinical evidence into national reference cases	Modular economic model and country parameter sets	3. Country-Specific Economic Adaptation	Translate shared clinical evidence into national reference cases
4. RWE Lifecycle Integration	Plan observational evidence against named uncertainties	RWE protocol/data-source roadmap	4. RWE Lifecycle Integration	Plan observational evidence against named uncertainties
5. Early Dialogue & Stakeholder Engagement	Validate decision problems and implementation context	Engagement plan and issue tracker	5. Early Dialogue & Stakeholder Engagement	Validate decision problems and implementation context
6. Budget Impact Modeling	Assess affordability under local uptake and displacement	Country budget-impact scenarios	6. Budget Impact Modeling	Assess affordability under local uptake and displacement

Several practical recommendations follow from the IHMAS analysis. First, the international HTA decision map should be built no later than the point at which pivotal trial design is being finalized. The map should identify the regulatory comparator, the principal HTA comparators in priority markets, patient-relevant outcomes, expected utility requirements and high-risk subgroups. This is the stage at which additional endpoints or stratification can still be incorporated at reasonable cost.

Second, evidence that is likely to be transferable should be standardized internally. Systematic-review methods, definitions of outcomes, evidence tables, network-meta-analysis assumptions and traceability from source data to value claims should be maintained as common assets. Country teams should adapt context, not re-create the scientific record. This reduces contradictory claims across markets and makes it easier to respond if EU cooperation increases the reuse of joint assessments.

Third, economic models should be built as modular platforms. A common model structure should be used only when disease progression and treatment effects are sufficiently comparable, while local reference-case requirements remain

explicit. Sensitivity analysis should separate uncertainty in clinical effect from uncertainty caused by local prices, resource use and methodological rules. This distinction makes cross-country differences interpretable rather than presenting them as unexplained variation in the ICER.

Fourth, RWE should be planned against named uncertainties. The evidence plan should state whether the purpose is to estimate natural history, comparative effectiveness, long-term durability, utilization, quality of life or costs. Data-source selection should follow that purpose. Registration of protocols, transparency of analysis and reproducibility are particularly important when observational data are expected to influence coverage decisions [17].

Fifth, the January 2018 Commission proposal should be treated as a strategic scenario, not as settled law. Manufacturers should prepare for stronger reuse of clinical assessments and greater demand for comparable evidence, but they should not remove national HTA capabilities or assume a single European dossier will determine reimbursement. The prudent strategy as of March 2018 is dual readiness: a rigorous shared clinical evidence core and resilient national economic/access modules.

CONCLUSION

This study examined the transformation of pharmaceutical market access strategy under the international HTA harmonization trajectory observable by 31 March 2018. The evidence supports a clear conclusion: harmonization is most advanced and most plausible in the scientific organization of clinical assessment, while final economic valuation, affordability and reimbursement decisions remain strongly dependent on national institutions. The European Commission's proposal COM(2018) 51 represents an important policy shift toward permanent cooperation, but at the time of publication it remains a proposal rather than an implemented regulatory framework.

The comparative analysis of NICE, CADTH, G-BA/IQWiG, HAS, ZIN and PBAC demonstrates that shared principles do not imply a shared decision rule. Cost-utility analysis is central in some systems, comparative added benefit is decisive in Germany, and threshold use ranges from a recognizable reference range in NICE to the absence of a single formal published threshold in several other jurisdictions. Comparator selection, local treatment pathways, economic reference cases and price negotiation therefore remain core sources of strategic divergence.

The main strategic consequence is the need to separate evidence architecture into two layers. The first is a transferable clinical core built around transparent comparative evidence, patient-relevant outcomes and reproducible synthesis. The second is a set of national modules covering economics, budget impact, implementation and price/access strategy. Real-world evidence should connect these layers across the lifecycle when it addresses a clearly defined uncertainty and is generated with methods credible to decision-makers.

The IHMAS framework translates these findings into an operational model with eight modules: Evidence Architecture; Regulatory–HTA Alignment; Country-Specific Economic Adaptation; RWE Lifecycle Integration; Early Dialogue and Stakeholder Engagement; Budget Impact Modeling; Value Communication; and Pricing and Access Scenarios. Its purpose is not to predict the final design of European HTA legislation, but to provide a robust strategy under uncertainty and to prevent companies from confusing methodological harmonization with harmonization of reimbursement decisions.

Future research, after sufficient experience with reinforced EU cooperation becomes available, should test whether joint assessments reduce duplication in practice, how often national bodies require supplementary analyses, and whether earlier regulatory–HTA dialogue changes trial design. Those questions cannot be answered empirically within an April 2018 publication because the proposed EU framework had not yet been legislated or implemented. For the present period, the defensible conclusion is that market access strategy should become more integrated, earlier and more modular as HTA cooperation expands.

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