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HEALTH TECHNOLOGY ASSESMENT FOR THE U.S. HEALTHCARE SYSTEM BACKGROUND PAPER

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The University of Southern California Schaeffer Center for Health Policy & Economics and the Aspen Institute have together established an advisory panel to consider how the U.S. can better link the price of health technologies to value while ensuring a sustainable healthcare ecosystem that also supports innovation. Experts on value assessment are convening for meetings in October 2019 and April 2020 to develop policy recommendations that support this ecosystem. While the U.S. can learn from other countries' implementation of health technology assessment the panel's aim is to make practical recommendations that are tailored to the unique U.S. healthcare system, and that can garner broad support from patients and other stakeholders.

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LIST OF ACRONYMS, GENERAL

| | |
|-----------|---|
| ACE | Angiotensin-converting enzyme inhibitor |
| AE | Adverse event |
| BIM | Budget impact model |
| CE | Cost-effectiveness |
| CEA | Cost-effectiveness analysis |
| CED | Coverage with evidence development |
| CI | Confidence interval |
| COI | Conflict of interest |
| HTA | Health technology assessment |
| ISPOR | International Society for Pharmacoeconomics and Outcomes Research |
| ISPOR STF | ISPOR Special Task Force |
| MCDA | Multi-criteria decision analysis |
| OOP | Out-of-pocket |
| QALY | Quality-adjusted life year |
| R&D | Research and development |
| VAT | Value-added tax |

LIST OF ACRONYMS, UNITED STATES

| | |
|---------|---|
| ACA | Affordable Care Act |
| ACIP | Advisory Committee on Immunization Practices |
| AHCPR | Agency for Health Care Policy and Research |
| AHRQ | Agency for Healthcare Research and Quality |
| CDC | Centers for Disease Control and Prevention |
| CEPAC | Comparative Effectiveness Advisory Council |
| CER | Comparative effectiveness research |
| CMS | Centers from Medicare and Medicaid |
| CTAF | California Technology Assessment Forum |
| DERP | Drug Effectiveness Review Project |
| EPC | Evidence-based Practice Center |
| ICER | Institute for Clinical and Economic Review |
| MedCAC | Medicare Evidence Development & Coverage Advisory Committee |
| OHTA | Office of Health Technology Assessment |
| OTA | Office of Technology Assessment |
| PBM | Pharmaceutical benefit managers |
| PCORI | Patient-Centered Outcomes Research Institute |
| PCORnet | National Patient-Centered Clinical Research Network |
| U.S. | United States |
| UCPSTF | U.S. Preventive Services Task Force |

LIST OF ACRONYMS, INTERNATIONAL

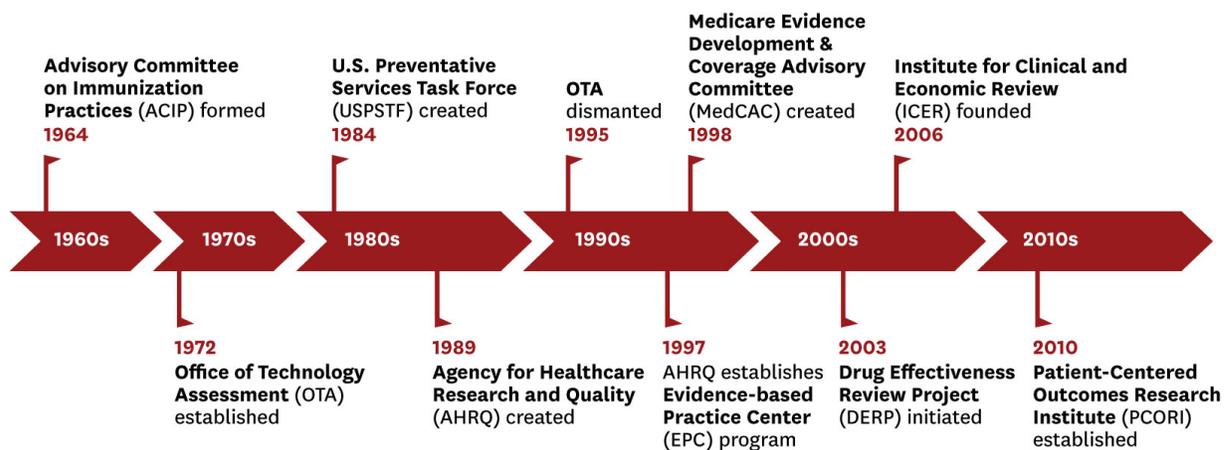
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|---------|--|
| ABPI | Association of the British Pharmaceutical Industry (U.K.) |
| ASMR | Improvement of Medical Benefit (France) |
| CADTH | Canadian Agency for Drugs and Technologies in Health (Canada) |
| CDEC | Canadian Drug Expert Committee (Canada) |
| CDIAC | Cancer Drug Implementation Advisory Committee (Canada) |
| CEESP | Commission Evaluation Economique et de Santé Publique (France) |
| CEPS | Le Comité économique des produits de santé (France) |
| CDR | Common Drug Review (Canada) |
| Chuikyo | Central Social Insurance Medical Council (Japan) |
| G-BA | Gemeinsamer Bundesausschuss (Germany) |
| HAS | Haute Autorité de santé (France) |
| HST | Highly specialized technology (U.K.) |
| IQWiG | Institute for Quality and Efficiency in Healthcare (Germany) |
| MSAC | Medical Services Advisory Committee (Australia) |
| MHLW | Ministry of Health, Labor and Welfare (Japan) |
| NHS | National Health Service (U.K.) |
| NICE | National Institute for Health and Care Excellence (U.K.) |
| NIPH | National Institute of Public Health (Japan) |
| PBAC | Pharmaceutical Benefits Advisory Committee (Australia) |
| PBPA | Pharmaceutical Benefits Pricing Authority (Australia) |
| PBS | Pharmacy Benefit Scheme (Australia) |
| pCODR | pan-Canadian Oncology Drug Review (Canada) |
| pCPA | pan-Canadian Pharmaceutical Alliance (Canada) |
| PMDA | Pharmaceutical and Medical Devices Agency (Japan) |
| PMPRB | Patented Medicine Prices Review Board (Canada) |
| SHI | National Association of Statutory Health Insurance (Germany) |
| SMR | Medical benefit (France) |
| UNCAM | Union Nationale des Caisses d'Assurance Maladie (France) |
| U.K. | United Kingdom |

This paper provided background information to facilitate discussion during the first advisory panel meeting in October 2019. Section 1 reviews the historical and political context for health technology assessment (HTA) in the United States (U.S.). Section 2 provides an overview of some methodological considerations for HTA in the U.S. Section 3 explores how HTA could be used to inform drug pricing decisions and presents options for how prices might be derived.

SECTION 1. HISTORICAL AND POLITICAL CONTEXT

The United States is one of the few developed countries without a national HTA program guiding coverage and pricing decisions, however, it has not always lacked such programs (see Figure 1). The first instance of an official U.S. HTA organization was the Office of Technology Assessment (OTA). Established in 1972,[1] the OTA was created to inform Congress of the impact of new technologies. OTA reports were publicly available, and usually described the potential impact of multiple policy options rather than making specific policy recommendations. A typical assessment took 18-24 months to complete and had a direct cost of approximately \$500K; at its peak, the OTA had approximately 140 permanent staffers.[2, 3]

Figure 1: Timeline of U.S. Organizations Related to HTA



The Health Program within the OTA assessed clinical and general healthcare technologies such as cancer screening, HIV vaccines, and bone marrow transplants. In addition, the OTA evaluated broader issues of health policy including patient cost-sharing and benefit design, pharmaceutical research and development (R&D), and medical malpractice. Critiques of the health-related arm of the OTA included concerns it would ration healthcare to contain cost, and fears that it would threaten innovation, organized medicine’s autonomy, and access to new technologies.[4]

Several factors led to the failure of the OTA. Although it was created in part to ensure the legislative branch’s scientific decision-making capabilities could keep pace with those of the executive branch, in its later years, Congressional members were concerned about OTA’s potential to attenuate their decision-making power. The OTA suffered criticism after its negative reviews of Reagan’s Strategic Defense Initiative (aka “Star Wars” missile defense) and thenceforth avoided controversial topics.[1] Congressional committee chairs increasingly wanted the agency to reflect their interests, rather than

to work as an independent resource. In addition to persistent concerns about Democrats misusing the OTA, incoming Republicans in 1995 lacked connections to the agency and did not perceive it as a valuable body.[1] Its final death knell came when the Republican Party identified the OTA as bureaucratic waste (despite representing \$20 million out of a \$2 billion budget), and a Republican-controlled legislature passed budget cuts eliminating its funding in 1995.

The health division of the OTA was not the only government agency that participated in the evaluation of health technologies. Research in 1970s and 1980s showing geographic variation in medical and surgical practice [5, 6] led to the creation of the Agency for Health Care Policy and Research (AHCPR, now known as the Agency for Healthcare Research and Quality (AHRQ)) in 1989. Within the AHCPR, the Medical Effectiveness Treatment Program was tasked with developing scientific information to improve the effectiveness and appropriateness of medical practice.[4] In addition, the AHCPR developed clinical guidelines based on systematic evidence reviews and established the Office of Health Technology Assessment (OHTA) to conduct formal assessments, usually at the request of the Centers for Medicare and Medicaid (CMS). OHTA reports did not include formal cost-effectiveness analyses (CEA), although they often included cost information.[7]

In 1997, AHRQ established its Evidence-based Practice Center (EPC) program.[8] EPCs were designed to provide high-quality evidence reports and technology assessments for clinical and healthcare organization and delivery, and to conduct technology assessments on behalf of OHTA.[9] EPC reports are available to a range of entities including state and federal agencies, private sector professional groups, health delivery systems, providers, and payers. While AHRQ stopped producing clinical guidelines in 1996, the agency still conducts technology assessments, both in-house and through EPCs. Current EPCs are located across the country at universities, research centers, and healthcare clinics. AHRQ encourages transparency in their assessments by inviting stakeholder and public comments, and all assessment materials and comments are available online.[10]

Most recently, the Patient-Centered Outcomes Research Institute (PCORI) was established in 2010, with the goal of focusing health research on patient and clinician concerns, while improving quality and relevance of evidence.[11] PCORI funds comparative effectiveness research (CER) and CER methods research and includes patients and healthcare stakeholders throughout the research processes.¹ Funding for PCORI comes from three sources: the general fund of the Treasury appropriations, CMS, and fees collected from private insurance and self-insured plans. PCORI has impacted policy and pricing through its accreditation standards, published evidence updates, and new academic initiatives. It has also created PCORnet, the National Patient-Centered Clinical Research Network to facilitate health research that is efficient, effective, and lower cost.

PCORI is unique for its focus on patient outcomes rather than CEA. Even given this distinction, it has faced criticism from Republicans that see it as a precursor for government rationing of care and controlling costs. Jon Kyl, (R-AZ) Senate minority whip from 2007 to 2013, opposed CER, citing concerns that it is a tool to deny care.[12] Although it failed to pass, Kyl offered an amendment to the Senate's budget resolution that would forbid Medicare and other federal health programs from using results of CER to deny coverage of any treatments.[13] His opposition is typical of prevailing negative attitudes toward CER, particularly among Republicans. Funding for PCORI was set to expire in September 2019; however, it received bipartisan support, and Congress renewed its funding through 2029.[14]

¹ PCORI engages patient and stakeholder partners in a variety of ways—serving on working groups or advisory committees, developing dissemination strategies, or engaging in study design and execution.

Efforts to create evidence to guide coverage are not limited to federal agencies. Motivated by increases in pharmaceutical costs, state Medicaid agencies initiated the Drug Effectiveness Review Project (DERP) in 2003 with the goal of creating comparative effectiveness reviews informing evidence-based decisions about drug coverage.[15] Although DERP is most closely associated with Oregon, 15 states currently participate in the collaboration and three EPCs serve as research partners. DERP seeks to have direct impact on policy and Medicaid decision-making, and several states use DERP reports as primary evidence to determine coverage.[16] DERP has faced criticism: pharmaceutical industry and some patient advocacy groups allege that it seeks to contain costs by restricting access.[17] Although the practical impact of DERP on coverage decisions is not well understood, one study found states that participated in DERP and used preferred drug lists had higher utilization of the three angiotensin-converting enzyme (ACE) inhibitors with the strongest evidence of mortality reductions in a DERP report.[18]

Despite reluctance to use HTA for making coverage decisions in the U.S., there are examples of influential “HTA-like” evidence-based recommending bodies. The Advisory Committee on Immunization Practices (ACIP) provides an example of successful implementation of an evidence-based recommendation process.[19] ACIP was formed in 1964 to provide regular advice on the most effective immunizing agents for controlling communicable diseases.[20] ACIP consists of 14 voting members with expertise in vaccinology, immunology, pediatrics, internal medicine, nursing, family medicine, virology, public health, infectious diseases, and/or preventive medicine, and one voting member who serves as a consumer representative. ACIP works closely with external stakeholder groups, including physicians; their meetings are open to the public and include open discussion and public comment. The committee primarily considers public health considerations such as disease epidemiology and vaccine safety when making recommendations, but economic analyses are often presented as well. ACIP recommendations are implemented at the discretion of the Director of the Centers for Disease Control and Prevention (CDC), and final recommendations are published in *Morbidity and Mortality Weekly Report*. ACIP is also responsible for determining which vaccines are covered under the Vaccines for Children program, which provides vaccines at no cost to low-income, uninsured, and underinsured children.

The U.S. Preventive Services Task Force (USPSTF) provides another example of effective implementation of an evidence-based recommendation process. Created in 1984, the USPSTF reviews effectiveness evidence and recommends clinical preventive services including screenings, behavioral counseling, and preventive medications. An independent volunteer panel of experts, the USPSTF makes recommendations that private insurance plans must cover without any patient cost-sharing under the Affordable Care Act (ACA). Prior to finalizing recommendations, materials are made available for scientific review and public comment. The recommendations are then published on their website [21] or in a peer-reviewed journal. The USPSTF assigns a letter grade to each recommendation based on the quality of evidence and the benefits or harms of a service, and not based on cost. Each year, the USPSTF provides a report to Congress on research gaps and recommends research priority areas.

More recently, national coverage determinations for Medicare are also made through an evidence-based process, although it does not consider cost-effectiveness in coverage recommendations. The Medicare Evidence Development & Coverage Advisory Committee (MedCAC) was created in 1998 to provide independent guidance and expert advice to aid CMS in making coverage decisions.² MedCAC consists of a maximum of 100 appointed members with expertise in clinical and

² Prior to the creation of MedCAC, coverage decisions were made through an internal process involving an informal committee of physicians, and occasionally used information from an HTA conducted by an external organization.

administrative medicine, biologic and physical sciences, public health administration, patient advocacy, healthcare data and information management and analysis, health economics, and medical ethics.[22] MedCAC's documents are posted online for public comment in advance of their meetings and deliberations, which are also open to the public.

A daunting obstacle facing coverage decisions today is the lack of high-quality comparative clinical effectiveness data, which is necessary to determine incremental benefit compared to other treatments. CMS's coverage with evidence development (CED) guidance represents an attempt to balance access to new treatments with paucity of data. CED allows Medicare to cover treatments contingent on the collection of additional data throughout coverage.[23] CED faces many challenges including a lack of resource infrastructure, limited time, and insufficient funding.[23] More generally, comparative clinical effectiveness data generation requires a significant investment of resources, but these data can be worth their high cost if they facilitate use of more effective technologies. PCORI represents an attempt to fill this gap, but in practice vague research objectives have impeded the collection of impactful comparative effectiveness data. Since comparative effectiveness meets the definition of a public good, there is arguably a role for the government in its development.[24]

As demonstrated by the organizations described above, using HTAs to inform coverage decisions is a process complicated by political resistance to HTAs, particularly those that consider cost or cost-effectiveness. Even organizations with a neutral objective can quickly fall prey to partisan politics, and the perception that an HTA body is aligned with a single political party has been a clear precursor to its failure. Lobbying efforts by powerful industries can also quickly derail and weaken the development and implementation of HTA. To win favorable public opinion, HTA processes and decisions should be transparent to avoid accusations of subjective decisions and government-sanctioned "death panels." Although cost must be considered in decision-making if resources are limited, effective communication and public relations to anticipate controversies around the consideration of cost are key to retaining support.

Obstacles faced by the ACA also highlight challenges to creating an official HTA organization in the U.S., including a polarized political environment, budget deficits and concerns about fiscal waste, public distrust of government interference in health care, and opposition from stakeholders and lobbyists. Many in Congress are eager for further healthcare system reform. Congressional Democrats³ and presidential candidates have proposed solutions ranging from Medicare-for-All to expanding the ACA exchanges to include a public option. However, many conservatives still maintain the views that stymied the ACA, with fewer than 40 percent of Republicans currently supporting a public option.[25] Concerns about government rationing of healthcare persist, as demonstrated by the Republican-led effort to abolish ACA's Independent Payment Advisory Board—an expert panel intended to provide Medicare savings recommendations.[26, 27] These attitudes signal difficulty and the necessity for bipartisan efforts to create a sustainable HTA environment in the U.S.

SECTION 2. METHODOLOGICAL CONSIDERATIONS FOR HTAs

The methodological scope of HTAs varies widely; while some consider clinical impact alone, others incorporate economic analyses and other factors as part of the assessment. Absent cost constraints, an HTA that focuses solely on clinical outcomes such as efficacy and safety will provide the necessary information to choose among alternative strategies. However, since resources are limited, the

³ For example, House Speaker Nancy Pelosi's (D-CA) office recently released a government price negotiation plan which would allow Medicare to negotiate the prices of 250 drugs annually.

economic value of health technologies has become an increasingly important factor in decision-making. Payers must balance access to effective interventions (including drugs) with the cost of providing them. HTAs would aid in determining which interventions provide value and which may be ineffective or overpriced; and while some organizations do conduct assessments (e.g., the Department of Veterans Affairs, CDC), the U.S. generally lacks government entities that conduct them on a broad scale.

CEA methods are well-developed and widely used, and provide a methodological framework for comparing the relative value of health interventions. Specifically, CEA estimates the ratio of an intervention's net cost to its effectiveness. Though it has its critics, the quality-adjusted life year (QALY), which incorporates both morbidity and mortality effects of health interventions, is the most accepted measure of health benefit (effectiveness) in CEA.[28] In 2016, the Second Panel on Cost-Effectiveness (henceforth "Second Panel") published recommendations on how to improve the quality and promote comparability of CEA.

The Second Panel's recommendations addressed 11 key areas: 1) perspectives for the reference case; 2) designing a CEA; 3) decision models in CEA; 4) identifying and quantifying the consequences of interventions; 5) valuing health outcomes; 6) estimating costs and valuations of non-health benefits in CEA; 7) evidence synthesis for informing CEA; 8) discounting in CEA; 9) reflecting uncertainty in CEA; 10) ethical and distributive considerations; and 11) reporting CEA.[29] One major update the Second Panel made to previous recommendations is for all analyses to report two reference cases—one from the healthcare sector perspective and another from the societal perspective. The societal perspective allows for an evaluation of broader effects of interventions beyond the health system perspective including time costs, productivity, and caregiver burden. Furthermore, the Second Panel recommended that all studies include an impact inventory that would allow analyses to be more transparent and explicit about the elements considered.

More recently, an ISPOR Special Task Force (STF) developed a set of recommendations for value frameworks. Although the ISPOR STF did not take the stance of the Second Panel with respect to two reference cases, they did recommend that frameworks be explicit in their decision context and perspective.[30] The ISPOR STF's recommendations affirmed the importance of CEA for making coverage decisions, and acknowledged that more research is needed to incorporate other elements of value that are not well-captured by traditional CEA methods. For example, severity of illness may be relevant for some decisions, and the ISPOR STF points out the best way to incorporate this element into CEA is yet to be determined. Deliberative processes provide a starting point for incorporating relevant criteria with CEA information, yet such processes risk opacity if they are not explicit. The ISPOR STF further recommended multi-criteria decision analysis (MCDA) or augmented CEA as explicit frameworks in deliberative processes.

ICER'S ROLE IN THE U.S.

In the absence of a governmental HTA body in the U.S., the Institute for Clinical and Economic Review (ICER) has filled the gap in evaluating new therapies. Founded in 2006, ICER is an independent, nonprofit research organization that evaluates the clinical and economic value of prescription drugs, medical tests, and other healthcare delivery innovations.[31] ICER's profile was elevated in 2015 with their evaluation of hepatitis C drugs and the initiation of their Emerging Therapy Assessment and Pricing program, funded through a \$5.2 million grant from the Laura and John Arnold Foundation. ICER consists of three appraisal committees including the California Technology Assessment Forum (CTAF), Midwest Comparative Effectiveness Advisory Council (Midwest CEPAC), and the New

England CEPAC. Each committee, comprised of recruited members with HTA expertise, convenes 3 to 4 times annually at public meetings.

ICER's review process is similar to HTA processes in other countries.[32] Following topic selection, the evaluation is assigned to one of the three appraisal committees, and the assessment takes approximately 30 weeks to complete. After initial discussions with stakeholders, the review is scoped and the evaluation is performed. Following the release of their draft report, the assigned appraisal committee meets publicly to review the evidence and make recommendations.

ICER reviews consider three core elements: clinical, economic, and budget impact. In addition to the core elements, the current ICER framework (2017-2019 iteration) also considers other benefits and disadvantages as well as contextual issues (see Appendix A1). ICER does not use an explicit framework to combine all elements into their recommendations since they found MCDA "too complicated for reliable use." [33] ICER currently splits their evaluations into two parts, which they have labeled "long-term value for money" and "short-term affordability." The long-term value for money element consists of comparative clinical effectiveness, economic analysis (CEA), other benefits and disadvantages, and contextual considerations. The short-term affordability element considers the budget impact analysis.

Although ICER prefers evidence from randomized controlled trials, they also consider observational studies, patient-reported data, and registry data. More recently, ICER has conducted indirect treatment comparisons using network meta-analysis. ICER's CEA uses a health system perspective as its base case, and conditional on data availability, conducts a scenario analysis using a societal perspective.⁴ ICER uses QALYs as their measure of benefit, and judges incremental CE ratios against a threshold. Specifically, ICER's "long-term value for money" recommendation is determined by panel vote if the base case incremental CE ratio is between \$50K and \$175K; the voting panel determines whether a drug provides low, medium, or high value. If the incremental CE ratio is less than \$50K, the technology is deemed high value, and if the incremental CE ratio is greater than \$175K, the technology is deemed low value.

The budget impact section of ICER reviews has arguably been one of the largest sources of criticism. Prior to 2015, budget impact was presented using a hypothetical framework. ICER was spurred to reconsider how budget impact was presented following their evaluation of Sovaldi.[35] Although ICER estimated an incremental CE ratio of approximately \$73K for Sovaldi, the committee voted the drug "low value" because of its large budget impact. Such an outcome is counter to the ISPOR STF recommendations that budget impact should not be an integral part of value assessment. ICER's second framework (2015-2016) split CEA and budget impact into distinct elements, yet the updated budget impact analysis still raised concerns among many stakeholders.[36, 37] The new framework tied budget impact to expected growth in GDP and set a budget threshold for new drugs at \$904 million annually (see Appendix A2 for threshold derivation). ICER claimed their budget threshold was not meant to be interpreted as a cap on spending but was meant to indicate when policymakers would need to manage short-term affordability.[35] Although budget impact was calculated for a five year time horizon to allow for longer-term cost offsets to accrue, ICER has been criticized for relying on an unrealistic "unmanaged uptake" assumption.[33]

The most recent iteration of ICER's budget impact framework (2017-2019) has improved in important ways, despite keeping the budget threshold, which increased to \$915 million per year.[33] First, ICER reframed the budget impact as "short-term affordability," which is a more accurate characterization

⁴ ICER has a separate framework for orphan drugs (defined as a treatment with a patient population of fewer than 10,000 individuals). Assessments for orphan drugs present the societal perspective alongside the health system perspective.[34]

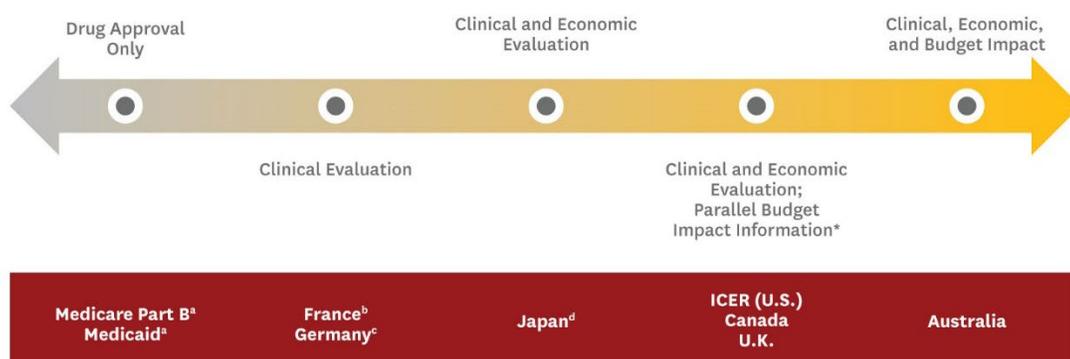
than their original label (“health system value”). Second, they no longer conduct the analysis using a single unmanaged uptake assumption. Instead, ICER calculates budget impact using a range of uptake rates and prices. Moreover, ICER now uses net prices to reflect rebates or discounts when possible. Most importantly, the budget impact no longer influences the “value-based” price.

Although ICER has received significant criticism, their process has become relatively transparent. All review documents are available online, and their meetings are open to the public and accessible online. ICER provides multiple opportunities for stakeholder and patient engagement, and allows manufacturers to submit data for consideration. Public comments are solicited several times over the course of their reviews, and stakeholders have an opportunity to comment during ICER’s meetings. The public comment period for ICER’s 2020 framework update is currently open;^[38] some proposed changes being considered include:

- Cross-referencing ICER’s clinical evidence ratings (see Appendix A3) against Germany’s categories for added clinical benefit
- Keeping CE thresholds, but extending the upper-bound of the range to \$200K
- Adding a “controversies and uncertainties” section to CEA that will focus on discussion of alternative model assumptions and structures
- Implementing a process through which to reassess whether new evidence has emerged that should be included in an update to reports one year following release.

We have included an overview of ICER’s process and methods because ICER currently represents a “de facto” HTA organization in the U.S. Other value frameworks have been developed and published (see Appendix Table A1), but are more narrow in scope compared with ICER. Since HTA implementation can vary to suit different objectives—the U.S. need not follow ICER’s model going forward. The remainder of this section presents different approaches to implementing an HTA that can inform drug coverage decisions (Figure 2). The outlined approaches range from no HTA process (i.e., a drug is reimbursed once it receives regulatory approval) to an HTA that incorporates all possible elements (clinical, economic, and budget impact). We provide examples of how other countries have implemented their chosen approach to HTA. Although we focus on drug HTAs, some countries use similar (or identical) processes to evaluate medical devices, procedures, and other health technologies.

Figure 2: Continuum of High-Level Approaches to an HTA Evaluation Framework



Notes: *In these cases, budget impact does not affect the HTA recommendation, but might affect whether health plans cover the drug or the pricing of the drug. ^aDrugs only undergo an economic evaluation if clinical benefits are significant (small minority of drugs). ^bOption to conduct economic evaluation (rarely applied in practice). ^cMost drugs do not undergo any HTA and only require drug approval for reimbursement; beginning in 2016, a small set of drugs underwent economic evaluation.

In addition to the elements enumerated in the approaches in Figure 2, HTAs might include other considerations that are not unique to any one approach. Specifically, contextual factors may be incorporated into recommendations, and exceptions might be made for certain drugs (e.g., cancer, orphan) or populations such as pediatric or end-of-life patients. Additionally, each HTA process should consider issues of transparency and stakeholder engagement.

FRANCE AND GERMANY: HTA WITH CLINICAL EVALUATION ONLY

In France, the technical assessment is conducted by la Haute Autorité de santé (HAS, an independent scientific body with financial autonomy) which houses the Commission d’Evaluation des Médicaments (also known as the Transparency Commission). Economic evaluations are conducted by a separate committee within HAS, the Commission Evaluation Economique et de Santé Publique (CEESP).

France’s HTA process relies on an evaluation of clinical benefit, although economic evaluations are conducted for drugs with the highest benefit level (which is generally rare). All drugs receive an evaluation of clinical benefit (“SMR”); drugs that are not first in class are also evaluated based on their added clinical benefit relative to an appropriate comparator (“ASMR”). The SMR recommendation determines reimbursement rates, and ASMR recommendations are used for price negotiations (Table 1).

Table 1. Summary of HTA Elements and Recommendation Categories (France)

| Element | Description | Considerations | Recommendations | Notes |
|---------------------------------------|--|---|---|---|
| Medical benefit (SMR) | Assess intrinsic value of drug | <ul style="list-style-type: none"> - Efficacy, safety - Position in therapeutic strategy - Disease severity - Type of treatment - Public health impact | <ul style="list-style-type: none"> - Major (SMR I) - Important - Moderate - Weak - Insufficient to justify reimbursement (SMR V) | No explicit weights for 5 areas considered |
| Improvement of medical benefit (ASMR) | Comparative assessment of new product with existing products in same treatment class | <ul style="list-style-type: none"> - Uses appropriate comparator(s) - Indirect comparisons acceptable under certain conditions | <ul style="list-style-type: none"> - Major innovation (ASMR I) - Important improvement - Significant improvement - Minor improvement - No improvement (ASMR V) | ASMR evaluated for all drugs that are not first in class |
| Economic evaluation | CE assessment, where QALY is the gold standard for effectiveness | No explicit incremental CE ratio thresholds; recommendations only reflect whether submission deviates from guidelines | <ul style="list-style-type: none"> - Minor methodological concern - Important methodological concern - Major methodological concern | Only considered if ASMR is level I-III; unclear how information is used in price negotiations |

Sources: [Pricing and reimbursement of drugs and HTA policies in France \(2014\)](#), Toumi et al (2017) [39]

Medical benefit can be deemed insufficient for reimbursement (SMR V) for several reasons, including a small effect without clinical significance and substantial adverse events (AE); mild disease or symptom; or an alternative therapy exists that has similar or better efficacy or less significant AEs. Drugs that receive an SMR V recommendation can still be listed in France, but patients pay 100 percent out-of-pocket for them. The highest ASMR levels (I-III) are difficult to achieve; ASMR I requires that a drug demonstrate an effect on mortality in a severe disease. Drugs that demonstrate non-inferiority will receive the lowest ASMR rating.

Key points related to transparency and stakeholder engagement for the HTA process in France are provided in Table 2. Neither manufacturers nor payers have representation on the HTA committee,

but manufacturers can appeal the HTA decision, and both parties participate in price negotiations after the HTA process is completed.

Table 2. Summary of HTA Transparency and Stakeholder Engagement (France)

| Stakeholder engagement | HTA committee representation | Patient involvement | Appeals | Transparency |
|---|--|--|--|---|
| <ul style="list-style-type: none"> - Manufacturers submit dossier for assessment - Outside experts may brief HTA committee, but do not attend deliberations or voting - Outside experts cannot represent drug sponsor during adversarial phase | <p>Physicians, patients, and academics</p> <p>6 members from government agencies have an advisory role</p> | <ul style="list-style-type: none"> - Stakeholders or interested parties can be approached, including representatives of learned societies and associations of patients and users of the health system - HAS website informs patient and user associations of the purpose and scope of the drug evaluations | <ul style="list-style-type: none"> - Manufacturer has 10 days following draft notice to comment or ask to be heard by the board; if notice is not given, HAS opinion becomes final - Written observations and hearings give rise to debate in committee; arguments presented are likely to lead to a modification of the opinion | <ul style="list-style-type: none"> - Final reports are published online, (e.g. May 2019 report) - HTA high-level methods are published, but the basis of actual deliberations is opaque - HTA committee members publish conflict of interest (COI) |

Source: [Transparency Committee Doctrine \(2019\)](#)

In Germany, benefit assessments are conducted by the Institute for Quality and Efficiency in Healthcare (IQWiG). The Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA) issues benefit classifications based on recommendations by IQWiG. Although IQWiG conducts assessments, the G-BA regulates the methodological requirements for benefit assessment. As in France, the German HTA process relies on an evaluation of clinical benefit, but drugs can undergo an economic evaluation if price negotiations and arbitration fail. This, however, is very rare.

Table 3. Summary of HTA Elements and Recommendation Categories (Germany)

| Element | Description | Considerations | Recommendations | Notes |
|----------------------|--|---|--|---|
| Benefit | Assessment of benefit size (absolute and relative), relevant population subgroups, and certainty of evidence | <ul style="list-style-type: none"> - Appropriate comparator (driven by label and medical guidelines) - Patient- relevant endpoints - Subgroup analyses | <ul style="list-style-type: none"> - Major additional benefit - Considerable additional benefit - Minor additional benefit - Additional benefit not quantifiable - No additional benefit - Benefit smaller than comparator | G-BA does not have explicit thresholds for benefit categories |
| Economic evaluation* | Considers whether justifiable relation between costs and benefit exists | <ul style="list-style-type: none"> - Methodology and modeling - Benefit - Costs - Epidemiological data - CE (presented in form of efficiency frontier) - Uncertainty (sensitivity analyses) - Budget impact analysis | <ul style="list-style-type: none"> - Price is either appropriate or inappropriate based on position of CE ratio relative to efficiency frontier | Occurs only if price negotiations and arbitration fail (extremely rare) |

Note: *IQWiG provides full guidelines for economic evaluation in their [General Methods](#) paper. Costs and benefits depend on chosen perspective. The perspectives that might be considered include statutory health insurance (SHI), community of SHI insurants (includes costs borne by insurants), social insurance, or societal.

IQWiG developed specific criteria for added benefit categories, based on 3 patient-relevant outcomes. To qualify for a benefit category, the upper limit of the 95% confidence interval (CI) for the relevant outcome, which is presented using relative risk, must be below a certain threshold as shown in the following table.

| | | Patient outcome category | | |
|-----------------|----------------------------|--------------------------|--|--------------------------------------|
| | | All-cause mortality | Severe symptoms, side effects, and HRQoL | Non-severe symptoms and side effects |
| Extent category | Major added benefit | 0.85 | 0.75 and risk $\geq 5\%$ * | N/A |
| | Considerable added benefit | 0.95 | 0.90 | 0.80 |
| | Minor added benefit | 1.00 | 1.00 | 0.90 |

Note: *Percent of undesirable outcome is $\geq 5\%$ in at least one of the two groups compared. Cutoff values reference the required values for relative measures comparing two drugs such as relative risk or odds ratios. If we compare the effect of drug A relative to drug B on mortality, a value of 1.00 implies that drug A and drug B have the same effect on mortality. A value less than 1 implies that patients who receive drug A have a lower mortality risk compared with drug B. Further, if the upper limit of the 95% CI for that value falls below the given threshold (0.95 or 0.85), then drug A will be deemed to have either considerable added benefit or major added benefit, respectively.

Source: [General Methods, 5.0](#)

Similar to France, manufacturers are not represented on the HTA body in Germany, but they do participate in price negotiations following the HTA.

Table 4. Summary of HTA Transparency and Stakeholder Engagement (Germany)

| Stakeholder Engagement | HTA Committee* Representation | Patient Involvement | Appeals | Transparency |
|---|---|---|---|---|
| <ul style="list-style-type: none"> - Manufacturers submit dossier for assessment; medical experts and patients are regularly consulted for the assessment - In all important phases of report preparation, the law obliges IQWiG to provide opportunity for stakeholder comment - External experts are awarded research commissions or advise IQWiG on medical or other topic-related research questions | <p>Main committee: 2 Hospital Federation reps 5 Statutory Health Insurance (SHI) reps 2 SHI physicians 1 SHI dentists 2 impartial members</p> <p>Non-voting participants include patient reps, government reps, and reps from the German Medical Association, German Nurses Association, and Private Health Insurance Providers Federation</p> | <p>Patients or patient reps are asked to review certain text drafts as part of quality assurance</p> <p>Patients are allowed to comment on all feature articles, fact sheets, and research summary drafts</p> | <p>G-BA appeals are part of the price negotiation process (see Section 3)</p> <p>No IQWiG appeals process has been identified, (noted HERE)</p> | <ul style="list-style-type: none"> - IQWiG results and supplementary information available on their website - Stakeholder comments are published - Data submitted that cannot be published cannot be considered in assessments - All experts must disclose COI - IQWiG produces information for a variety of audiences |

Note: *The HTA committee we refer to is the G-BA, which makes the final recommendations; evaluations are conducted on behalf of G-BA by IQWiG staff.

Sources: [IQWiG Dossier Assessments](#); [General Methods](#); [G-BA Structure](#); Leverkus and Chuang-Stein (2016) [40]

JAPAN: HTA WITH CLINICAL AND ECONOMIC EVALUATION

In Japan, the Central Social Insurance Medical Council (Chuikyo) sets reimbursement prices based on clinical and “cost” information. Official HTAs (with CEA) were piloted in 2016 for a small set of drugs and devices (submission of economic evidence was previously recommended but not required). Japan does not have an official HTA agency, but assessments are coordinated by the National Institute of Public Health (NIPH). Discussions are held between the Ministry of Health, Labor and Welfare (MHLW), NIPH, and manufacturers. The expert committee on cost-effectiveness (within MHLW) reviews the economic data.

All drugs that receive regulatory approval are reimbursed at one rate irrespective of inpatient or outpatient setting. The reimbursement rate is determined by a clinical evaluation for drugs with comparators or a “cost” calculation method for drugs without a comparator.

Table 5. Summary of HTA Elements and Recommendation Categories (Japan)

| Element | Description | Considerations | Recommendations | Notes |
|---------------------|------------------------------------|--|--|--|
| Clinical (option 1) | Similar efficacy comparison method | <ul style="list-style-type: none"> - Efficacy and pharmacological properties relative to similar drugs - Degree of innovation (mechanism of action; higher efficacy/safety; improvement of treatment; beneficial drug formulation) | <ul style="list-style-type: none"> - Price set same as relevant comparator - Drug is deemed innovative and receives a price premium | |
| Clinical (option 2) | Cost calculation method | <ul style="list-style-type: none"> - Cost of manufacturing - Cost of administration - Marketing costs - Profit (adjusted to account for innovation) - Value-added tax (VAT) | <ul style="list-style-type: none"> - Price calculated based on set formula that combines each cost element | Only used if no appropriate comparator exists |
| Economic | Assessment of incremental CE ratio | <ul style="list-style-type: none"> - CEA, with incremental CE ratio as primary outcome | <ul style="list-style-type: none"> - A set formula is used to adjust the price and price premiums from the clinical evaluation according to the incremental CE values | Piloted in 2016 and used to adjust prices set by clinical information; only applies to small subset of drugs/devices |

Notes: Products that underwent economic evaluation were selected on the basis of innovation (i.e., likely to have a high price premium under clinical evaluation) and market size. Five of the seven drugs selected for evaluation were hepatitis C drugs; the remaining drugs were anti-cancer agents.

Source: Shiroiwa et al (2017) [41]

The economic evaluation process is relatively new in Japan, and although several publications provide details for the process, in practice stakeholder engagement and transparency are lacking. Of all the countries we reviewed, Japan is the only one that does not have patient involvement. HIV and hemophilia drugs as well as drugs used exclusively in pediatric populations are excluded from CEA in Japan. However, if annual sales from any of these drugs exceeds 35 billion yen, they may undergo CEA at the discretion of Chuikyo.

Table 6. Summary of HTA Transparency and Stakeholder Engagement (Japan)

| Stakeholder engagement | HTA committee representation | Patient involvement | Appeals | Transparency |
|---|--|---------------------|---|--------------|
| Manufacturers submit data at start of appraisal process; otherwise unclear how stakeholders are engaged but said to be "insufficient"[42] | <p>Organization includes 6 insurer reps, 6 provider reps, and 4 public interest reps</p> <p>Non-voting members include 4 manufacturer reps and 3 health economists</p> | None | Manufacturers can appeal if they disagree with price, but unclear how appeals have been implemented in practice | None |

CANADA AND U.K.: HTA WITH CLINICAL AND ECONOMIC EVALUATION WITH PARALLEL BUDGET IMPACT

In Canada, The Canadian Agency for Drugs and Technologies in Health (CADTH) conducts HTAs for all new drugs through the Common Drug Review (CDR) process and all new oncology drugs through the pan-Canadian Oncology Drug Review (pCODR). Note that Quebec has its own separate HTA body.

Table 7. Summary of HTA Elements and Recommendation Categories (Canada)

| Element | Description | Considerations | Recommendations | Notes |
|----------------------|---|---|---|---|
| Clinical | Assesses clinical benefit of drug | <ul style="list-style-type: none"> - Efficacy - Effectiveness - Safety | <ul style="list-style-type: none"> - Reimburse: comparable or added clinical benefit and acceptable cost/CE relative to appropriate comparator(s) within the defined patient population - Reimburse with conditions* - Do not reimburse: drug does not demonstrate comparable clinical benefit relative to comparator(s) OR drug demonstrates inferior clinical outcomes or significant clinical harms relative to comparator(s) | No explicit weights across elements exist |
| Economic | Assesses economic impact of drug | <ul style="list-style-type: none"> - Cost utility analysis - Economic model - Parameter derivations | | |
| Epidemiological | Assesses potential patient population | <ul style="list-style-type: none"> - Disease prevalence, incidence - Number of patients accessing new drug | | |
| Other considerations | Supporting information that is considered when developing recommendations | <ul style="list-style-type: none"> - Unmet need - Patient and caregiver input - Input from clinical experts - Submitted price of drug under review and prices of comparators - Applicant's requested reimbursement conditions - Implementation considerations | | |

Notes: *Reimbursement conditions include initiation criteria (e.g., condition severity, subtype), renewal criteria, discontinuation criteria, prescribing criteria, and pricing conditions. Drugs that only show benefit or are cost-effective for a subgroup of patients will have reimbursement limited to that subgroup; drugs with comparable benefit relative to a comparator will have a reimbursement similar to that comparator; drugs with clinical benefit but unacceptable cost-effectiveness will be listed at a reduced price.

Source: [Procedure and Submission Guidelines for the CADTH Common Drug Review \(2019\)](#)

Canada uses a publicly funded payer perspective for their base case, and a discount rate of 1.5 percent. Although the HTA does not explicitly consider budget impact when making recommendations, manufacturers are required to submit budget impact models (BIM) as part of the HTA process. Separate BIMs are developed for each province/territory since plans are administered at that level; BIMs allow individual health plans to understand the potential economic impact of new drugs.

Table 8. Summary of HTA Transparency and Stakeholder Engagement (Canada)

| Stakeholder engagement | HTA committee representation | Patient involvement | Appeals | Transparency |
|---|--|---|---|---|
| <ul style="list-style-type: none"> - All interested parties can provide feedback (manufacturers, physicians, associations, etc.) - CADTH review team has at least one clinical expert - Drug plans identify issues that may preclude implementation of recommendations | <ul style="list-style-type: none"> - Appointed by and reports to CADTH President and CEO - Chair plus 14 members (2 public “lay”); members do not represent a specific constituency - Non-member experts may be invited to participate as needed - 66% required for quorum and all members get one vote (chair is tiebreaker); abstention is not allowed | <ul style="list-style-type: none"> - Call for patient input occurs 20 business days before CDR filing and remains open for 35 business days - Available on CADTH website, e-alert, or Twitter | <ul style="list-style-type: none"> - Manufacturer can request reconsideration of CDEC decision if 1) recommendation is not supported by evidence submitted or evidence identified in report; 2) CADTH and CDEC failed to act fairly and in accordance with its procedures - No new information can be considered during appeal - Existing recommendations may be revisited as a result of therapeutic review | <ul style="list-style-type: none"> - Details for HTA process available online - All stakeholders (including patients) must provide COI - Calls for feedback are posted online - All final recommendations are posted online |

Notes: Patient input ([CDR](#); [pCODR](#)); CDR process [CADTH Common Drug Review Procedures and Guidelines](#)

In the U.K., HTAs are conducted by The National Institute for Health and Care Excellence (NICE). A technical team prepares the technical report, and the appraisal committee produces recommendations based on the report. As of April 2017, the U.K. has incorporated budget impact into the HTA process, but like Canada, budget impact does not affect the HTA recommendations. Specifically, the National Health Service (NHS) has the option to initiate commercial discussions with manufacturers for drugs expected to exceed net budget impact of £20 million in the first three years of use. These discussions occur in parallel with the NICE appraisal, and if NICE recommendations are updated following their draft, budget impact will be revised accordingly.

Table 9. Summary of HTA Elements and Recommendation Categories (U.K.)

| Element | Description | Considerations | Recommendations | Notes |
|--------------------|---|--|---|--|
| Comparators | Determination of appropriateness and relevance of comparators | <ul style="list-style-type: none"> - Established NHS practice - Natural history of disease - Existing NICE guidance - Cost-effectiveness - Licensing status of comparator | <ul style="list-style-type: none"> - Comparator is valid - Comparator is not valid | |
| Clinical | Assessment of clinical benefit relative to comparators | <ul style="list-style-type: none"> - Nature and quality of evidence - Uncertainty in evidence - Efficacy and safety - Subgroup analysis - Position of treatment in care pathway | <ul style="list-style-type: none"> - Recommended for routine commissioning - Not recommended for routine commissioning - Not recommended for routine commissioning, but recommended for inclusion in Cancer Drugs Fund (or some other managed arrangement) - Not recommended for routine commissioning, invites company to submit proposal for inclusion in Cancer Drugs Fund | No precise ICER threshold for recommendations (although drugs are more likely to be recommended if ICER <£20K) |
| Economic | Cost effectiveness | <ul style="list-style-type: none"> - Strength of supporting clinical evidence - Economic model, inputs, assumptions - Range and plausibility of ICERs | | |
| Non-health factors | | <ul style="list-style-type: none"> - Broader social considerations - Whether substantial portion of cost (savings) or benefits are incurred outside of NHS or are associated with non-health benefits | | |

NICE has a “highly specialized technology” (HST) appraisal process for drugs for very rare conditions. Drugs must meet seven criteria to qualify for the HST appraisal pathway, including small target treatment population, clinically distinct target patient group, condition is chronic and severely disabling, technology is expected to be used exclusively in a highly specialized context, expected to have very high acquisition cost, potential for lifelong use, and need for national commissioning is significant.[43] Although the incremental CE thresholds are higher for the HST pathway (£100K to £300K), a recent report found that none of the non-cancer orphan drugs evaluated under the HST between 2013 and 2017 received their full marketing authorization.[44]

Table 10. Summary of HTA Transparency and Stakeholder Engagement (U.K.)

| Stakeholder Engagement* | HTA Committee Representation | Patient Involvement | Appeals | Transparency |
|--|---|--|---|--|
| <p>Consultees can submit evidence during the appraisal, comment on the appraisal documents, and nominate patient experts and clinical specialists</p> <p>Commentators are invited by NICE to take part in the appraisal process and comment on the various documents produced during the process</p> | <p>Manufacturers NHS (payers) Physicians Patients (as lay members) Academics Lay backgrounds</p> <p>Committee members are appointed for a three-year term, and are drawn from NHS, patient and carer organizations, academia, pharmaceutical and medical devices industries</p> | <p>-The Public Involvement Programme (PIP) at NICE supports and develops public involvement</p> <p>- A PIP adviser is assigned to each appraisal and supports patient and carer organizations, their representatives, and individual patients or carers throughout the appraisal</p> | <p>-All consultees have the opportunity to appeal recommendations, or report any factual errors, in the final appraisal document</p> <p>-Commentators cannot appeal the final appraisal determination</p> <p>-More about grounds for appeal</p> | <p>- Evidence on which the appraisal committee's decisions are based is made available to stakeholders and is publicly available</p> <p>- In some cases, unpublished evidence is accepted under agreement of confidentiality</p> <p>- Appraisal committee meetings are usually open to members of the public and press</p> |

Notes: *Manufacturers are not allowed to participate in the nomination process. Consultees include patient and carer groups, health professionals, manufacturers, government and health organizations. Commentators include manufacturers of comparators, clinical guidelines groups, NHS agencies, other governmental and health agencies.

Sources: [NICE Technology Appraisal Committee](#); [NICE Guide to the Processes of Technology Appraisal](#); [NICE Technology Appraisal and Highly Specialized Technologies Appeals](#)

AUSTRALIA: HTA WITH CLINICAL, ECONOMIC, AND BUDGET IMPACT EVALUATION

In Australia, drugs and devices/procedures are covered by two separate insurance plans, so each plan has a separate HTA body and process. Drug assessments are conducted by the Pharmaceutical Benefits Advisory Committee (PBAC), while assessments for devices or procedures are conducted by the Medical Services Advisory Committee (MSAC). We focus on PBAC.

Unlike the U.K. and Canada, Australia explicitly considers budget impact as part of their HTA. We do not know how often budget impact is used as the rationale for negative listing since we did not conduct a comprehensive review of all PBAC recommendations. We checked recommendations for Sovaldi and Harvoni since they had potential for high budget impact. Both were given positive listing on Pharmacy Benefit Scheme (PBS), although Sovaldi was rejected for consideration for streamlined (i.e., faster) listing based on budget impact. Some examples of reasons for recommendations against listing include uncertain clinical benefit, no clinical benefit, uncertain economic analysis, high and uncertain incremental CE ratio, and indirect treatment comparison did not support non-inferiority claim.

Table 11. Summary of HTA Elements and Recommendation Categories (Australia)

| Element | Description | Considerations | Recommendations | Notes |
|------------------------|---|--|---|---|
| Clinical | Assesses clinical benefit of drug | <ul style="list-style-type: none"> - Effectiveness - Adverse events - Subgroup analyses - Assessment of difference between trial population and Australian setting | <ul style="list-style-type: none"> - Medicine should be listed on PBS - Medicine listing should be changed (for medicines that are already listed) - Medicine should not be listed on PBS - Decision deferred pending provision of specific additional information that would be relevant and important to decision | No explicit weights across elements exist |
| Economic | Assesses economic impact of drug | <ul style="list-style-type: none"> - CEA preferred, but cost-minimization allowed - Uncertainty in model or analysis must be defined, justified, and examined via sensitivity scenarios | | |
| Budget impact | Use of medicine in practice | <ul style="list-style-type: none"> - Disease incidence, prevalence | | |
| Additional information | Other important factors not captured in clinical or economic elements | <ul style="list-style-type: none"> - Equity or access considerations - Relevant non-health patient outcomes or patient inputs - Development of antimicrobial resistance (if relevant) - Rule of rescue | | |

Notes: Each recommendation is published online and includes a reason for the recommendation. PBAC can also recommend maximum quantities or other restrictions for the listing.

Source: [PBAC guidelines, Version 5.0](#)

Although Australia does not have special considerations for subsets of drugs or specific populations, all drugs receive consideration for the “rule of rescue.” This rule is very rarely applied, and only for medicines for life-threatening conditions for which there is no other treatment available in Australia.

Table 12. Summary of HTA Transparency and Stakeholder Engagement (Australia)

| Stakeholder engagement | HTA committee representation | Patient involvement | Appeals | Transparency |
|--|---|--|---|---|
| <ul style="list-style-type: none"> - Manufacturers have two opportunities for input: pre-subcommittee response and pre-PBAC response - Manufacturers can present comments to PBAC in form of a hearing - Stakeholder meetings may be held if PBAC issues a negative recommendation but the drug treats a serious, disabling, or life-threatening condition with no other treatment option | <p>Members include doctors, health professionals, health economists, and consumer reps appointed by the Australian government</p> | <p>HTA consumer consultant committee has several key roles:</p> <ul style="list-style-type: none"> - Assist Department of Health to work more closely with consumers in HTA decision-making - Bring consumer evidence into HTA processes - Inform policy on consumer and patient matters in HTA - Create opportunities for better public understanding of HTA - Enhance methods for formal patient inputs | <ul style="list-style-type: none"> - No appeals - Manufacturers can request independent review (very rare) - No new information is allowed in review, which is conducted by single expert reviewer - Manufacturers can resubmit with new evidence or change to indication or restrictions | <ul style="list-style-type: none"> - PBAC decisions and summary documents published online - Committee agenda, minutes, and deliberations posted online - HTA committee members must disclose COI annually |

Source: [PBAC website](#)

DISCUSSION

Absent other HTA organizations in the U.S., ICER's visibility and influence will likely continue to increase. Whether the U.S. would be better off developing an official governmental HTA organization with agreed upon principles, methods, and processes or continuing the status quo model where ICER serves as the de facto HTA organization is worth discussing. While ICER has generally been open to public input on their assessment process, important questions of accountability exist. As a private organization, ICER may not adequately consider issues most relevant to the general public (i.e., patients, family members, and caregivers). Because ICER is not a government-sanctioned body and has no official bearing on coverage and reimbursement decisions, ICER should, in theory, provide impartial information to decision makers. However, certain elements of ICER reviews, such as choosing incremental CE thresholds and specific budget caps, have resulted in ICER taking a more subjective role in their assessments.

Each of the countries we reviewed conducts HTAs following regulatory approval of a drug if the manufacturer plans to obtain marketing approval for inclusion on the (usually government-run) insurance plan. If the U.S. were to create an official HTA body, topic selection may need to be narrower depending on the budget and resources of the organization. Japan provides an example of a pilot approach that selected a small subset of drugs for evaluation that had relatively high reimbursement prices or were considered highly innovative. Using their selection criteria, Japan's initial HTA evaluated five hepatitis C drugs, nivolumab (for non-small cell lung cancer), and trastuzumab emtansine (for breast cancer). The U.S. may use different selection criteria for an initial set of drugs to undergo HTA than Japan's, but an incremental HTA roll-out would also allow for the process to be adjusted based on input from a handful of pilot evaluations.

The United States must also consider which elements should be included in an official HTA process. An HTA approach that includes CEA may face excessive opposition in the U.S. (CE is currently prohibited from being considered in Medicare coverage decisions), therefore an approach that only considers clinical benefit may be a useful first step. However, an HTA process that excludes CEA does not provide guidance for whether drug prices reflect value. If CEA is included in the HTA process, methodological details such as base case perspective, what to include in costs, and how to incorporate other factors will need to be agreed on. While these will be important details, this panel's aim is to focus on higher level decisions as a first step. Finally, the fact that ICER receives significant criticism for their budget impact framework should not be interpreted as a preference against budget impact analysis in the U.S., but rather a reaction to ICER's implementation of budget impact thresholds. Despite lingering critiques of ICER's framework, it is important to note that budget impact no longer influences their value-based price. Additionally, a single budget impact estimate is not particularly useful given the mix of private and public payers in the U.S. ICER's latest framework attempts to address this by estimating budget impact for a range of uptake and prices. If the U.S. coverage system remains as it is, and budget impact is to be considered in some form in a U.S. HTA process, adopting an approach similar to Canada's might be the most informative for individual payers.

Finally, adequately addressing issues of transparency and stakeholder engagement will be equally important for ensuring the success of any official HTA body in the U.S. An official HTA body would likely need to be at least as transparent as ICER. Additional improvements could be made with respect to transparency, such as posting the CEA model or source code and parameters online. While all stakeholders should have some degree of engagement during the HTA process, examples from other countries indicate that it is not universally agreed that all stakeholders should have a vote on the HTA recommending bodies. Manufacturers are consistently excluded from voting, but they receive representation during the price negotiations phase. Most countries have increased patient involvement in the HTA process, but very few give patients voting rights. The ultimate degree of stakeholder involvement in the U.S. should reflect the goals and principles of the HTA organization.

SECTION 3. USING HTA TO INFORM DRUG PRICING DECISIONS

Drug pricing plays a key role in financing pharmaceutical innovation. What we pay for drugs today affects the pipeline of drugs discovered in the future.[45] While lower drug prices today benefit patients in the short run, this could slow innovation and deprive future generations of greater access to new treatments. A dynamic balancing of short-term objectives and long-term promotion of investment in R&D results in progressively more efficient innovation.

Various stakeholders agree that drug pricing should reflect the value treatments bring to patients and society. If drug prices are set too low relative to value, manufacturers may be reluctant to invest in R&D, thereby stifling future innovation. On the other hand, prices set too high relative to value stimulate inefficient levels and sometimes types of innovation, and may limit access. Yet prices for medical technology in the U.S. seem decoupled from value,[46] which is largely a reflection of the current U.S. drug marketplace.

Current drug provision and pricing in the U.S. comprises a mix of private and government plans. Pricing decisions are decentralized as each plan negotiates individually and privately. Moreover, drug prices are influenced by multiple entities in the supply chain, including insurers, manufacturers, wholesalers, pharmacies, and pharmaceutical benefit managers (PBMs). Drug markets involve multiple prices for the same product—pharmacists acquire drugs from manufacturers or wholesalers. Insured consumers rarely face the full price of a drug, but are responsible for a co-pay or coinsurance. PBMs pay the difference between the pharmacy price and the co-pay, plus a dispensing fee, and may receive manufacturer rebates, often volume driven, which may be passed to insurers. The presence of middlemen implies manufacturers do not necessarily face declines in consumer demand when prices rise. Prices ultimately depend on the relative bargaining position of buyers (insurers/PBMs) and sellers (manufacturers) and tend to be linked to volume.[47] In theory, the seller's bargaining position improves when underlying consumer demand for the product is stronger, but a variety of market failures might interfere with this ideal outcome. For example, buyers might focus on satisfying employers, rather than the underlying employees they insure. Employees might overspend on drugs and healthcare due to tax breaks for the purchase of private health insurance. Finally, incomplete information might prevent consumers and employees from making good decisions, even if all other parts of the market were functioning perfectly.

One or more of these reasons might explain why U.S. drug pricing does not consistently reflect value. It also helps explain the momentum behind calls for value-based pricing and decision making in healthcare. Currently, insurers in the U.S. do not follow formal guidelines on how to use value assessment or CEA in coverage decisions or drug price negotiations; Medicare cannot use CEA in coverage decisions.[48-51] However, even if no explicit link between CEA and prices exists, payers are likely using CEA results in some implicit way. Further, rising drug prices in the U.S. have prompted calls for government intervention to regulate them. The question then arises, would drug prices set by the government be more closely tied to value?

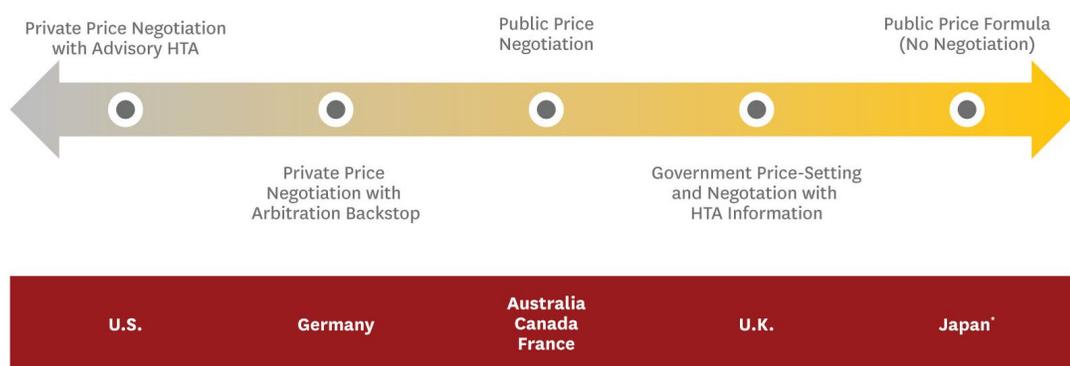
Several aspects of government-led drug pricing provide opportunities for improvement in the current pharmaceutical market. Specifically, the role of existing middlemen in drug pricing would be removed and the government would have a relatively strong negotiating position. Traditionally we would be concerned with crowd-out when the government becomes involved in the provision of healthcare and insurance. The situation in this case, however, is unique. For example, if we believe that prices set through a deliberative value assessment process are a better reflection of value, patients who currently have insurance with inefficient prices will be better off switching to a public option tied to value assessment. Despite these potential benefits, government pricing may still be inefficient, particularly if the strong bargaining position results in artificially low prices or the government eschews

value in the price setting process. Given the size of the U.S. market—the largest national market for pharmaceuticals and a key player in global pharmaceutical innovation [45, 52]—it is worth considering whether manufacturers would choose to exit the U.S. market if prices were set too low.⁵

Even if the U.S. decides drug pricing should become less decentralized and the government could play a role, we will need a discussion on how to effectively set prices which reflect value. Elements for consideration include how value is reflected in pricing and whether prices are negotiated or set based on a formula. If prices are determined through negotiations, we must also decide which parties participate, whether negotiations are bilateral or multilateral, and what happens if a price agreement cannot be reached.

The remainder of this section explores alternative approaches to linking HTA results to pricing decisions, as outlined in Figure 3. The options we outline range from the current situation in the U.S., where health plans negotiate prices independently and privately, to systems where HTA information is used in price setting by government payers similar to the approach taken by the U.K. Along the continuum of options, we draw on examples from price setting approaches in countries around the world. These are described in more detail below. We focus on outpatient drugs, but similar principles could be applied to inpatient drugs, medical devices, or other health technologies. Although this section does not address plan design, we provide information on cost-sharing and patient out-of-pocket (OOP) payments across countries in Appendix Table A2 as these arrangements relate to drug pricing.

Figure 3: Continuum of Options for Linking HTA to Pricing



Notes: We are unaware of countries that engage in public negotiations with arbitration or private negotiations without arbitration. *All drugs undergo public price formula process, but additional HTA information applied to the pricing formula is applicable only to a small set of selected drugs since April 2016.

⁵ Sovaldi provides an interesting thought experiment in this case, since it represents a drug that effectively provides a cure and has an incremental CE threshold below \$100K. The WAC price was originally set at \$84K for a 12 week course. If the US were able to negotiate a substantial discount, would the manufacturer forego the US market given approximately 2.4 million individuals have hepatitis C? While the full WAC price would generate approximately \$200 billion in revenues if all individuals diagnosed with hepatitis C received Sovaldi, a 75% discount would still generate \$50 billion in revenue. It is not obvious that a drug manufacturer would leave \$50 billion in revenues on the table because they deemed a 75% discount unreasonable.

ADVISORY ONLY OPTIONS

On the spectrum of options, without an official HTA body, the U.S. would remain on one extreme if the current approach to pricing decisions continues. Under the current system, pricing decisions are decentralized, and payers have access to HTA information to guide their price negotiations and coverage decisions. In the absence of an official HTA body in the U.S., ICER effectively fills the advisory role through its current assessment of health technologies. While ICER's recommendations do not play an official role in pricing decisions, they are beginning to gain traction. For example, Regeneron/Sanofi lowered PCSK9 inhibitor prices based on ICER recommendations, the Department of Veterans Affairs now uses ICER value assessments in their formulary development and price negotiations, and CVS Health allows its clients to exclude drugs whose cost per quality-adjusted life years (QALY) does not meet benchmarks set in ICER analyses.[53-55]

Although an advisory-only system is the most market-oriented approach on the continuum, the mechanisms to ensure prices reflect value are relatively weak. Moreover, an advisory-only HTA body will not overcome market inefficiencies that exist in the current pharmaceutical supply chain. Finally, if the U.S. opted to create an official (i.e., governmental) HTA body, opponents may question the need to publicly finance the efforts to generate CE information that are already undertaken in the private sector.

PRICE NEGOTIATION OPTIONS

Several options exist to incorporate HTA information into coverage decisions and price negotiations that go beyond an advisory-only system. The next step in the continuum involves less decentralized price negotiations that are based on HTA recommendations. In this option, the U.S. must consider whether private insurers will retain negotiation responsibilities, or whether the government will assume the role of negotiator. Even if the government assumes responsibility for price negotiations, drug coverage could still be administered through private insurers. Additionally, if prices are set through negotiations, we must additionally consider what happens if negotiations fail. Under a worst-case scenario, if an agreement cannot be reached, manufacturers may exit the market entirely or limit access to patients who pay with cash or have supplemental insurance. An arbitration backstop would prevent such a scenario from occurring.⁶

Germany: Private Price Negotiation with Arbitration Backstop

Among our example countries, the German approach is unique in that it couples private price negotiations with an arbitration backstop. Like the U.S., Germany relies on private health plans, known as sickness funds. Although many sickness funds provide coverage, they negotiate prices as a single entity through the head of the National Association of Statutory Health Insurance (SHI). Consolidation across private insurers during price negotiations would represent an incremental change to the current U.S. bargaining system, since it would simplify the negotiation process yet retain insurance choices for consumers.

In Germany, price negotiations occur following the assessment of added clinical benefit by the G-BA, which is conducted by IQWiG on G-BA's behalf.[40, 56] If the G-BA concludes the new product has no additional benefit (or negative benefit), it is assigned to a fixed reference price group; if a reference

⁶ Government-mandated (compulsory) marketing of a product following failed price negotiations is another mechanism for ensuring drug access, but this does not align with free market principles.

price group does not exist, then negotiations occur but the maximum reimbursement price is the comparator price.[40, 57] If the new product has additional benefit, then bilateral negotiations between the manufacturer and the head of SHI occur and must conclude within 6 months. Price negotiations must consider actual prices in other countries. The process of negotiating prices for new drugs in Germany is illustrated in Appendix Figure A1.

If no agreement is reached, either side can appeal to an arbitration board. The arbitration committee consists of 2 manufacturer representatives, 2 SHI representatives, and 3 independent members agreed upon by the manufacturer and SHI. If agreement on the independent members is not reached, selection is based on drawing lots. Each side is allowed to appeal the arbitration decision and request a formal CEA. The manufacturer also has the option to withdraw from the German market, but even in that case the new price would be available for cross-referencing and could impact price negotiations in other countries.

Australia, Canada, and France: Public Price Negotiation

Unlike the German system, where private payers retain negotiation responsibilities, Australia, Canada, and France provide examples of systems with public price negotiations. Moreover, these countries do not have an arbitration backstop or other mechanism to address failed price negotiations. These systems would represent a larger change from the current U.S. system since price negotiations would shift to the government from private payers even if individual payers retain authority over coverage decisions. The Canadian system linking HTA recommendations to pricing retains some degree of decentralization compared with Australia or France since coverage determinations are ultimately made at the provincial/territorial level. Similar to Germany's system, provinces and territories negotiate prices as a single entity through the pan-Canadian Pharmaceutical Alliance (pCPA).

In Canada, formulary placement and pricing occur following an assessment of clinical and economic benefit by CADTH as part of the Common Drug Review (CDR) or pan-Canadian Oncology Drug Review (pCODR). CADTH makes a recommendation for formulary inclusion for reimbursement; however, the recommendations concerning public coverage are only advisory.[58] Each province and territory (except Quebec, which has its own HTA process) makes its own determination for reimbursement, although most make the same recommendation as CADTH. Private insurance plans may or may not operate with a formulary; some adopt the public formulary that applies in the respective province or territory.

An overview of the reimbursement decision pathway for new medicines in Canada is provided in Appendix Figure A2. Prices are negotiated by pCPA and manufacturers, although for some drugs, the pCPA recommends each province/territory negotiate individually.[59] Negotiated price discounts or rebates, through product listing agreements, are paid directly to participating drug plans, in return for including the medicine on the formulary. Private drug plans do not generally negotiate drug prices with manufacturers; some use the local government's allowable limits for generics, while some agree to pay higher prices than government plans will allow.

Drug prices are also controlled through statutory regulations. For example, drug price ceilings are determined by the Patented Medicine Prices Review Board (PMPRB) through a mix of internal and external reference pricing. The maximum price of a newly patented medicine is set at the median price of the product across comparator countries, including the UK, France, Germany, Italy, Sweden, or at the equivalent maximum allowable price of comparators already on the Canadian market.

PMPRB can collect rebates from manufacturers who sell medicines at an average price above the maximum allowable level.

In Australia, price negotiations occur following clinical and economic assessment by PBAC. The economic assessment uses the manufacturer's proposed reimbursement price, and price negotiations only occur if PBAC recommends the new drug for listing on the PBS. Negotiations occur between the manufacturer and the Pharmaceutical Benefits Pricing Authority (PBPA),^[60] which is separate from the PBAC (Appendix Figure A3). The government and manufacturer must formally agree on price before listing on the PBS, and the government cannot compel manufacturers to list on the PBS. Drugs that are not recommended for listing on the PBS are available through private insurance and manufacturers can set prices without regulatory intervention.

In addition to price negotiations, PBS pricing is further regulated through position on the formulary (F1 or F2).^[60]⁷ Single-brand medicines without therapeutic substitutes (F1) are generally protected from price reduction, but prices may fall if a new and more effective drug enters the market. Medicines on F1 formulary are subject to statutory 5%, 10%, and 5% price cut on their 5th, 10th, and 15th birthday on the PBS, respectively. If another brand of the same drug enters the market, all medicines are moved to F2, and there is a one-off 25% price reduction. For medicines with substitutes on F2, manufacturers must disclose actual selling price plus all rebates and incentives paid to wholesalers/pharmacies; the PBS price is reduced to disclosed selling price if >10% price difference is observed.⁸

In France, price negotiations occur following assessment of clinical benefit by HAS—an independent scientific body with financial autonomy—which hosts a commission known as the Transparency Commission.^[61] Price fixing is done by Le Comité économique des produits de santé (CEPS) after negotiation with the manufacturer, and reimbursement rate fixing is conducted by Union Nationale des Caisses d'Assurance Maladie (UNCAM) (Appendix Figure A4).

Price negotiations consider multiple elements in addition to the HTA comparative benefit rating (ASMR, Table 13),^[62] including price of local comparators, price of product in other markets (primarily UK, Germany, Italy, and Spain), 3-year sales forecasts, conditions for use, and target population size. To our knowledge, no set formula exists to combine these elements into a single price. The amount consumers are reimbursed for drugs depends on the benefit level, and ranges 0–100%. Registration on the reimbursable list is valid for 5 years, at which time the Commission re-evaluates the benefit level and the price can be reviewed by CEPS.

⁷ F1 list contains single-brand (single-source) medicines that do not have therapeutic substitutes on the PBS; these are typically on-patent and the first medicine of its type on the PBS. F1 list does not contain those single brand drugs that are interchangeable on an individual patient basis with drugs that have multiple brands or single brand combination item. F2 list contains drugs with multiple brands (multi-source) and those single brand drugs that are interchangeable at the individual patient level with drugs that have multiple brands on the PBS; these are typically off-patent generic medicines subject to competitions.

⁸ PBS introduced price disclosure arrangements in 2007 to capture the benefits of competition for F2 medicines and adjust the PBS price according to market prices. Prior to this, PBS had been paying more than the market price for medicines, because manufacturers were selling medicines to pharmacists for less than the PBS price.

Table 13. Comparative Benefit Rating Implications for Pricing in France

| Comparative benefit rating | Implication for pricing |
|----------------------------|---|
| ASMR I–III | Price notification rather than negotiations; price will be consistent with reference countries; faster access |
| ASMR I–IV | Possibility of higher price relative to comparators |
| ASMR IV | Price depends on target population; if drug targets same population as comparator, parity price is best outcome; if drug targets new population relative to comparator drug, then price can be higher |
| ASMR V | Drug can be listed only if costs are less than comparators, resulting in cost savings for health insurance; discounted pricing is typical |

Notes: ASMR I = major improvement; reserved for a few drugs that demonstrate effect on mortality in severe disease; ASMR II = important improvement; ASMR III = moderate improvement; ASMR IV = minor improvement; ASMR V = no improvement.

PRICE SETTING OPTIONS

The remaining possibilities along the continuum for setting prices eliminate price negotiations entirely. In these cases, prices are directly tied to HTA results. Although price setting is potentially more restrictive than negotiations, it may provide a more well-defined and transparent process for linking HTA recommendations (and presumably value) to drug prices. Linking HTA results to pricing could be implemented in several ways. For example, the price could be adjusted using a formula based on the incremental CE or by combining CEA results with other elements from the HTA (e.g., clinical evaluation or contextual factors). Alternatively, coverage could be determined using an incremental CE threshold. Even if incremental CE thresholds are used, flexibility in coverage determinations and prices could be introduced through the use of variable thresholds and/or exceptions for certain disease areas or populations.

Japan: Public Price Formula

In Japan, if a drug is approved by the Pharmaceutical and Medical Devices Agency (PMDA), it will likely be reimbursed by MHLW. Chuikyō, within MHLW, determines official, uniform reimbursement prices.[41] Prices are set according to a detailed pricing rule, not price negotiation.

If an appropriate comparator exists, the similar efficacy comparison method is applied, and the new drug price is the same as the comparator price. If there is no comparator, the cost calculation method is applied, and the cost is calculated as the sum of manufacturing, administration, marketing, profit, and value-added tax costs. For innovative products, a price premium ranging 5–120 percent of the comparator daily price can be applied. The profit rate is set at negative 50 percent to 200 percent of the standard profit rate depending on the determined degree of innovation. The standard profit rate was 14.6 percent in 2016.

HTA in Japan is still relatively new and has only been applied to a small set of selected drugs and medical devices (henceforth, we use drugs for shorthand, but this refers to both drugs and medical devices). For drugs that undergo HTA, the results impact pricing, but not access (Appendix Figure A5). New incremental CE-based pricing for drugs that undergo HTA was first implemented in April 2016 and adjusts price premiums calculated during official price setting (Table 14).

Table 14. ICER-based Value Implications for Pricing in Japan

| ICER value | Premium adjustment | Operating profit adjustment |
|--------------------------------|--------------------|-----------------------------|
| <5 million yen (about US\$46K) | None | None |
| 5–7 million yen | 30% reduction | 17% reduction |
| 7.5–10 million yen | 60% reduction | 33% reduction |
| >10 million yen | 90% reduction | 50% reduction |

In practice, if the needed evidence for CEA is not available, the manufacturer is allowed to discontinue CEA, and Chuikyo sets a timeline for data generation. If the necessary data are not obtained, the product is assigned the worst cost-effectiveness profile (>10 million yen, Table 14) and the price is adjusted accordingly. If Chuikyo is able to conduct a CEA themselves, then their results are used. If the manufacturer disagrees with the price calculated by the MHLW, they can submit an opinion to Chuikyo once, although it is not clear how the appeals process has been implemented in practice.

UK: Government Price Setting & Negotiation with HTA Information

The UK approach provides an example of value assessment feeding into drug prices. Prices are set based on CEA by the National Institute for Health and Care Excellence (NICE), and the National Health Service (NHS) is legally obligated to fund and resource medicines recommended by NICE's technology appraisals.[63] Every 5 years, a Voluntary Scheme for branded medicines pricing and access is signed by the UK Government (Department of Health and Social Care) and the Association of the British Pharmaceutical Industry (ABPI).[64] The most recent Scheme (valid since January 2019) confirms a CE threshold used by NICE of £20,000–30,000 per QALY. If the manufacturer or supplier of a branded medicine who participates in the Scheme is unable to set an NHS list price that would be considered cost-effective, a simple confidential discount remains the preferred means of providing a cost-effective price to the NHS. Most manufacturers participate in the Scheme and are bound by its rules. In 2016, about 80 percent of the treatments appraised by NICE fell below the CE threshold. As of April 2017, if a new treatment is expected to cost the NHS over £20 million (about U.S. \$24.5 million) for the first 3 years of use, NICE invites the manufacturer to “undergo confidential discussions with the NHS to negotiate discounts.”[65]

TRADE-OFFS AND OTHER CONSIDERATIONS

Healthcare decision makers around the world face many trade-offs and challenges when choosing how value assessment will be used to inform drug price negotiations and reimbursement decisions. Any approach to drug pricing decisions must balance the priorities and budget constraints of the health system (and individual plans) and the preferences of different stakeholders, who may have different objectives with respect to drug access or price setting. Although the countries we reviewed have developed more streamlined approaches for drug pricing compared with the current U.S. system, trade-offs associated with their systems are instructive as we consider whether (and how) the drug pricing process in the U.S. might be modified.

HTA Timing vs. Access Delays

HTAs are time intensive and often do not occur until after a drug has received regulatory approval; as a result, one critique of HTAs is their potential to delay market access. Consequently, countries that use HTA in their coverage and drug pricing decisions must decide whether new drugs will be accessible while the HTA or price negotiations are ongoing. An HTA process need not delay access, as evidenced by Japan and Germany. In Japan, since price is set following regulatory approval, the HTA does not impact access even though it can result in a downstream price adjustment. Germany ensures new products are immediately available at a price set by the manufacturer while the HTA/pricing process is ongoing. In France, however, the product is not available while price negotiations are ongoing, except for the highest benefit levels (ASMR I-III, Table 13). In Australia, “parallel processing” allows manufacturers to apply for PBS listing while seeking regulatory approval; however, patients must still pay full price for approved medicines until PBS listing.[66] Similarly, CADTH accepts drug submissions to the CDR up to 6 months before an anticipated approval in Canada.[67, 68]

Tradeoffs Associated with Decentralization

Canada’s decision to conduct HTA at the national level has led to greater efficiency, consistency, and transparency, but their system also allows for coverage flexibility across provincial/territorial drug plans. This element of decentralization, however, has led to inequalities in access to certain technologies across the country. Similarly, if the U.S. were to implement a system that uses a national HTA body yet retains individual plan autonomy for coverage and pricing decisions, we would expect similar inequalities. For example, if plans were administered at the state level (analogous to Canadian territories) and were not required to adhere to a national HTA recommendation, drug access and pricing could ultimately reflect political preferences or state budget constraints rather than value.

Transparency vs. Flexibility in Price Setting

Even if the HTA process itself is fully transparent, the linkage between HTA elements and prices may not be, particularly in systems that employ negotiations to determine prices. For example, even though we know France uses HTA recommendations in price negotiations, they also consider five other factors. Even if the U.S. produced HTA recommendations to guide pricing, black box price negotiations would undermine stakeholder confidence that prices are being set appropriately based on value. By contrast, a predetermined (and transparent) link between HTA results and drug pricing, as used in Japan, may be overly rigid or still result in prices that do not reflect value if the linkage is not developed appropriately.

Comparator Choices and Regulatory vs. HTA Requirements

The comparator used for price decisions can result in suboptimal pricing. For example, regulatory approval might be gained using a comparator that does not reflect the current standard of care. If the same comparator is used for price setting, the price of the new drug may be too high. In contrast, German price negotiations are based on an *appropriate* comparator which may not have sufficient data available at the time negotiations begin. In general, poor alignment between requirements for regulatory approval and HTA/pricing process is observed in many countries.

Price Negotiation/Setting at the Drug- or Indication-level

This may ultimately depend on whether HTA evaluations are conducted at the drug- or indication-level. The benefit of indication-level pricing to payers has been a subject of debate.[69] In Germany, a drug with multiple indications will be compared against a relevant comparator for each indication (and further within subgroups if possible). The relative benefit and population size for each indication form the basis for a single price negotiation. Similarly, ASMR ratings are assigned separately for each therapeutic indication and a volume-weighted average price is negotiated in France.

The U.S. healthcare system is complex, comprised of public and private payers. Although many healthcare systems around the world rely on both public and private plans, most HTA and pricing processes apply to the public option in these countries. A formal implementation of HTA in drug pricing decisions in the U.S. would require a determination of which plans would be impacted by a new system. One possible option would be to offer tiered plans (such as gold, silver, bronze) that use different incremental CE thresholds for their coverage and pricing decisions. For example, a bronze plan might only cover drugs with incremental CE ratios below \$50K, while a gold plan would use a higher threshold of \$200K. Alternatively, various CE thresholds could be used to place drugs in cost-sharing tiers within each metal plan. Another possibility would involve creating a public option for drug coverage in the U.S. (“Medicare Part D for All”). This would still require a decision of whether “Medicare Part D for All” would determine prices through negotiations or some form of price setting. Irrespective of how the U.S. might implement a process that directly links HTA to pricing, if only a subset of plans (for example public options) use the process, the U.S. would need to consider potential spillover effects on other plans and how these changes will impact patients, the healthcare system, and society at large.

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71. Rice, T., et al., *Revisiting out-of-pocket requirements: trends in spending, financial access barriers, and policy in ten high-income countries*. *BMC Health Services Research*, 2018. 18(1): p. 371.

APPENDIX

APPENDIX A1. ICER'S OTHER BENEFITS, DISADVANTAGES, AND CONTEXTUAL CONSIDERATIONS

| When compared to the “comparator” used in the CEA, does this intervention offer one or more of the following “other benefits or disadvantages”? | | | Potential Other Benefits or Disadvantages: Compared to the “Comparator” |
|---|----|-----------|---|
| Yes | No | Uncertain | This intervention offers reduced complexity that will significantly improve patient outcomes. |
| Yes | No | Uncertain | This intervention will reduce important health disparities across racial, ethnic, gender, socio- economic, or regional categories. |
| Yes | No | Uncertain | This intervention will significantly reduce caregiver or broader family burden. |
| Yes | No | Uncertain | This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed. |
| Yes | No | Uncertain | This intervention will have a significant impact on improving return to work and/or overall productivity |
| Yes | No | Uncertain | There are other important benefits or disadvantages that should have an important role in judgments of the value of this intervention: ____ |

| Are any of the following contextual considerations important in assessing this intervention’s long-term value for money? | | | Contextual Considerations |
|--|----|-----------|--|
| Yes | No | Uncertain | This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life |
| Yes | No | Uncertain | This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness |
| Yes | No | Uncertain | This intervention is the first to offer any improvement for patients with this condition |
| Yes | No | Uncertain | Compared to “the comparator,” there is significant uncertainty about the long-term risk of serious side effects of this intervention |
| Yes | No | Uncertain | Compared to “the comparator,” there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention |
| Yes | No | Uncertain | There are additional contextual considerations that should have an important role in judgments of the value of this intervention: ____ |

Source: [Overview of the ICER value assessment framework and update for 2017-2019](#)

APPENDIX A2. ICER'S CALCULATIONS DERIVING A THRESHOLD FOR POTENTIAL BUDGET IMPACT FOR NEW DRUGS (2017-2019)

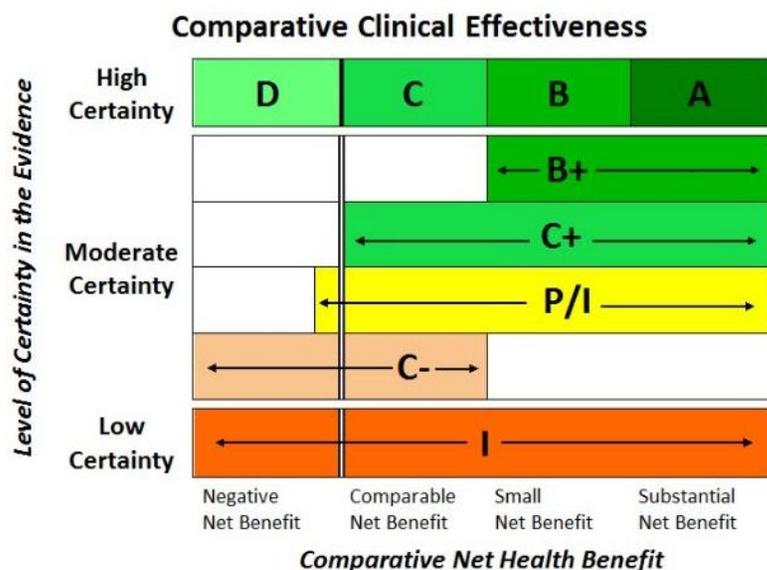
| Item | Parameter | Estimate | Source |
|------|---|-----------------|---|
| 1 | Growth in U.S. GDP, 2018 (est.) +1% | 3.5% | World Bank, 2018 |
| 2 | Total personal medical health care spending, 2017 (\$) | \$2.88 trillion | CMS National Health Expenditure, 2018 |
| 3 | Contribution of drug spending to total health care spending (%) | 17% | CMS National Health Expenditures, 2018; Altarum Institute, 2017 |
| 4 | Contribution of drug spending to total health care spending, 2016 (\$) (Row 2 x Row 3) | \$481 billion | Calculation |
| 5 | Annual threshold for net health care cost growth for ALL drugs (Row 1 x Row 4) | \$16.8 billion | Calculation |
| 6 | Average annual number of new molecular entity approvals, 2016-2017 | 34 | FDA, 2018 |
| 7 | Annual threshold for average cost growth per individual new molecular entity (Row 5 ÷ Row 6) | \$495.3 million | Calculation |
| 8 | Annual threshold for estimated potential budget impact for each individual new molecular entity (doubling of Row 7) | \$991 million | Calculation |

Note: Calculations are updated once per year based on new data for GDP growth, FDA approval volume, and the ratio of prescription drug costs to total health expenditures.

Source: [Overview of the ICER value assessment framework and update for 2017-2019](#)

APPENDIX A3. ICER'S CLINICAL BENEFIT RATING CATEGORIES

ICER uses an Evidence Rating Matrix™ to evaluate the quality of available evidence and the level of net health benefit from reviewed therapies. The matrix presents the magnitude of the difference between a therapeutic agent and a comparator as net health benefit on the horizontal axis, taking into account clinical benefits and risks, as well as adverse effects; the matrix differentiates between low, moderate, and high certainty evidence on the vertical axis.



Note: **Negative net benefit** = the drug produces a net health benefit inferior to that of the comparator; **comparable net benefit** = the drug produces a net health benefit comparable to that of the comparator; **small net benefit** = the drug produces a small positive net health benefit relative to the comparator; **substantial net benefit** = the drug produces a substantial (moderate-large) positive net health benefit relative to the comparator; **high certainty:** A = superior, B = incremental, C = comparable, D = inferior; **moderate certainty:** B+ = incremental or better, C+ = comparable or better; P/I = promising but inconclusive, C- = comparable or inferior; **low certainty:** I = insufficient.

Source: [ICER Evidence Review Matrix: A User's Guide, 2017](#)

APPENDIX TABLE A1. VALUE FRAMEWORKS IN THE U.S.

| Framework | Purpose | Technologies | Value elements | Weights |
|-----------------------------|--|---|---|------------------------|
| ASCO | Provide doctors and patients with information about the clinical impact and financial affordability of multiple cancer drug options | Oncology drugs | <ul style="list-style-type: none"> - Clinical benefits - Toxicity - Bonus - Net health benefit - Cost | Yes (explicit formula) |
| NCCN Evidence Blocks | Provide health providers and patients information to make informed choices when selecting systemic cancer therapies | Oncologic treatments (primarily drugs) | <ul style="list-style-type: none"> - Efficacy - Safety - Evidence quality - Evidence consistency - Affordability (overall cost) | None |
| MSK Drug Abacus | Tool that could be used to determine appropriate prices for cancer drugs based on what experts tend to list as possible components of drug's value | Oncology drugs | <ul style="list-style-type: none"> - Efficacy - Toxicity - Novelty - Development cost - Disease rarity - Health burden | User-set |
| ACC-AHA | Inform clinical practice guidelines and performance measure formulations on the basis of evidence of CE | Cardiovascular treatments (primary drugs) | <ul style="list-style-type: none"> - Clinical benefit, risk - Evidence quality - Cost-effectiveness | No explicit |
| ICER | Create a "value-based price benchmark" to help payers better link prices to patient and health system benefit | Drugs, devices, and other healthcare delivery | <ul style="list-style-type: none"> - Clinical effectiveness - Cost-effectiveness - Other benefits/ disadvantages - Contextual considerations - Budget impact | No explicit |
| IVI | Platform to facilitate patient-centered value assessment of health technologies tailored to needs of individual decision makers | Rheumatoid arthritis and non-small cell lung cancer | <ul style="list-style-type: none"> - Disease outcomes, adverse events - Costs - Other factors (productivity, insurance value) | User-set |

Source: Adapted from Sorensen et al (2017) [70]

APPENDIX TABLE A2. COST-SHARING AND PATIENT OUT-OF-POCKET PAYMENTS ACROSS COUNTRIES, FOCUS ON OUTPATIENT DRUGS

| | Drug coverage | Premiums and deductibles | Coinsurance and co-pays | Protection mechanisms |
|------------------|---|--|--|---|
| Australia | - Public coverage (PBS) for drugs recommended by PBAC - Other drug coverage through voluntary (supplemental) health insurance (VHI) | Deductible: none Premium: tax-funded (2% all taxpayer income; extra 1–1.5% high-income earners) | Coinsurance: none Co-pay (PBS): AU\$38.30 (US\$28.59) | Reduced co-pay for low income and children: AU\$6.20 (US\$4.63) + annual cap at AU\$372 (US\$280); Others: annual cap at AU\$1,476 (US\$1,111) then low income co-pay applies |
| Canada | - Public coverage for drugs (outpatient) varies by province and tends to focus on low income, >65, and people with specific medical conditions - Drug coverage through VHI if not eligible for public coverage | Deductible: varies by province Premium: tax-funded, varies by province (plus mandatory flat rate premium in some provinces) | Coinsurance and co-pay: vary by province | OOP caps and exemptions vary by province; Low income: various provincial programs cover OOP costs; Tax credits for individuals whose medical expenses exceed 3% of annual income |
| France | - Social insurance covers drugs on positive list - Other drugs covered through VHI | Deductible: none Premium: joint employer-employee contributions based on income level | Coinsurance: 15–100% (usually covered by VHI) Co-pay: fixed €0.5 (US\$0.56) per Rx | Exemptions: children from co-payments; patients with one of 32 severe chronic diseases exempted from co-insurance; low income (10% of population) receive free VHI; complementary VHI covers co-insurance; max OOP spending limit for non-reimbursable copay: €50 (US\$ 56) for all healthcare services |
| Germany | - Statutory health insurance OR - VHI | Deductible: none Premium: joint employer-employee contributions based on income level | Coinsurance: 10% (€5–€10 or US\$5.5–\$11) per Rx Co-pay: none | Exemptions: children <18; max cost-sharing (does not apply to OOP above reference prices) limit of 2% of annual income (1% for patients with chronic conditions) |
| Japan | - Statutory health insurance - Supplemental VHI | Deductible: none Premium: varies by plan/municipality based on income tax | Coinsurance: 30% (20% for children <6; 10-20% for ages 70+ with lower income) Co-pay: none | Reduced cost-sharing for young children, older people, chronic conditions, mental illness, and disabilities; co-insurance reduced to 1% after JPY80,100 (US\$761) monthly cap depending on enrollee age and income; Low income: cap at JPY35,400 (US\$337)/month |
| U.K. | - NHS covers drugs on NICE positive list - Supplemental VHI | Deductible: none Premium: tax-funded | Coinsurance: none Co-pay: GBP8.40 (US\$10.2) per item for outpatient Rx | Exemptions: children <16, low income, certain diseases, ages 60+ for prescriptions; annual cap on prescriptions co-payment (prepayment certificate costing GBP104/US\$150) |
| U.S. | Medicare (Part B and Part D); Medicaid; commercial insurance | Deductible and premium: vary by plan | Employer plans: coinsurance 17–32%, co-pay US\$11–93; Medicare: varies by plan Medicaid: varies by state | No uniform limit on patient costs |

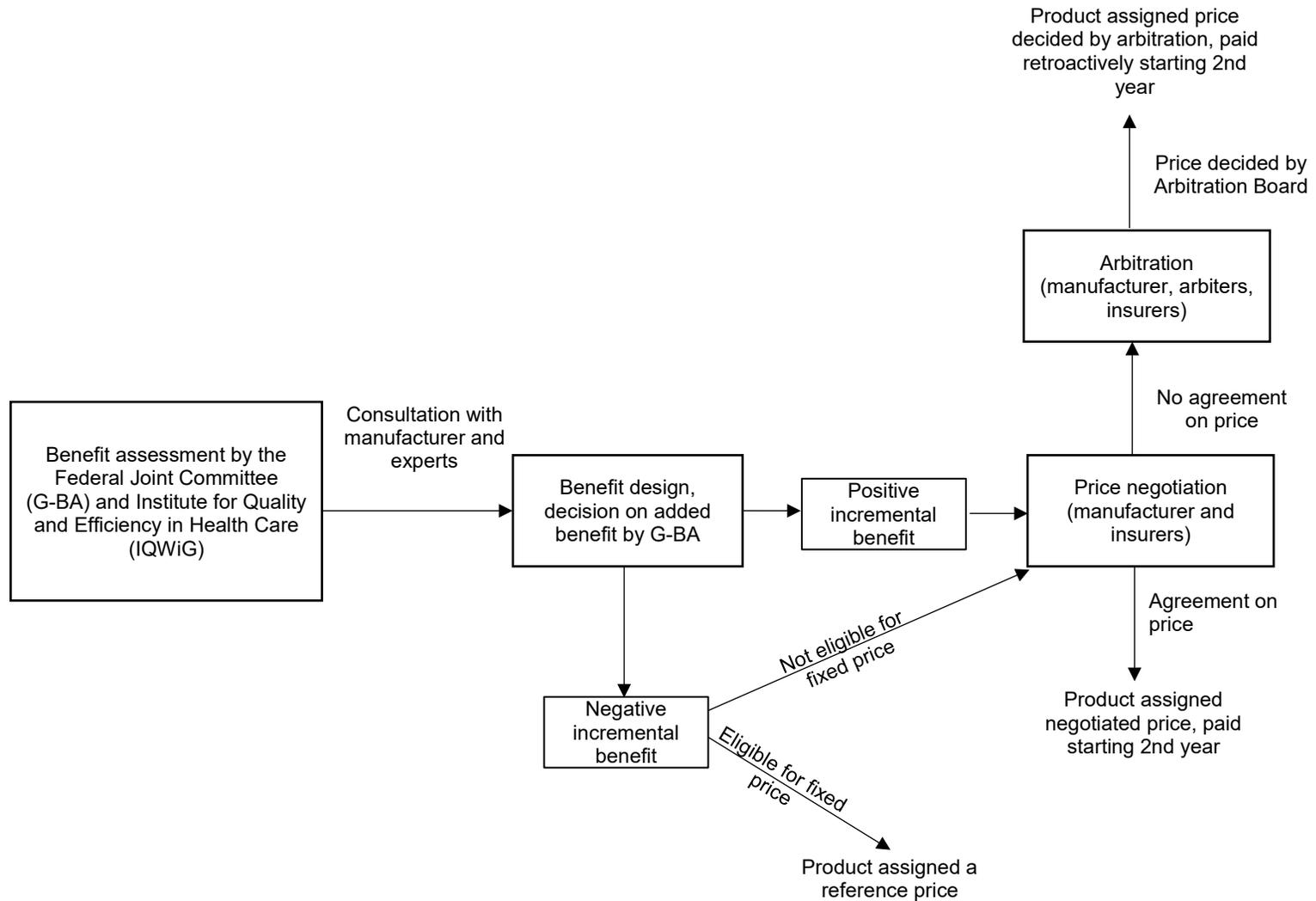
Note: All systems, except the US, offer universal coverage and voluntary (supplemental) health insurance is available for excluded services. PBAC=Australian HTA body.

Source: Adapted from Rice et al (2018) [71]

APPENDIX TABLE A3. REFERENCED AGENCIES ACROSS COUNTRIES

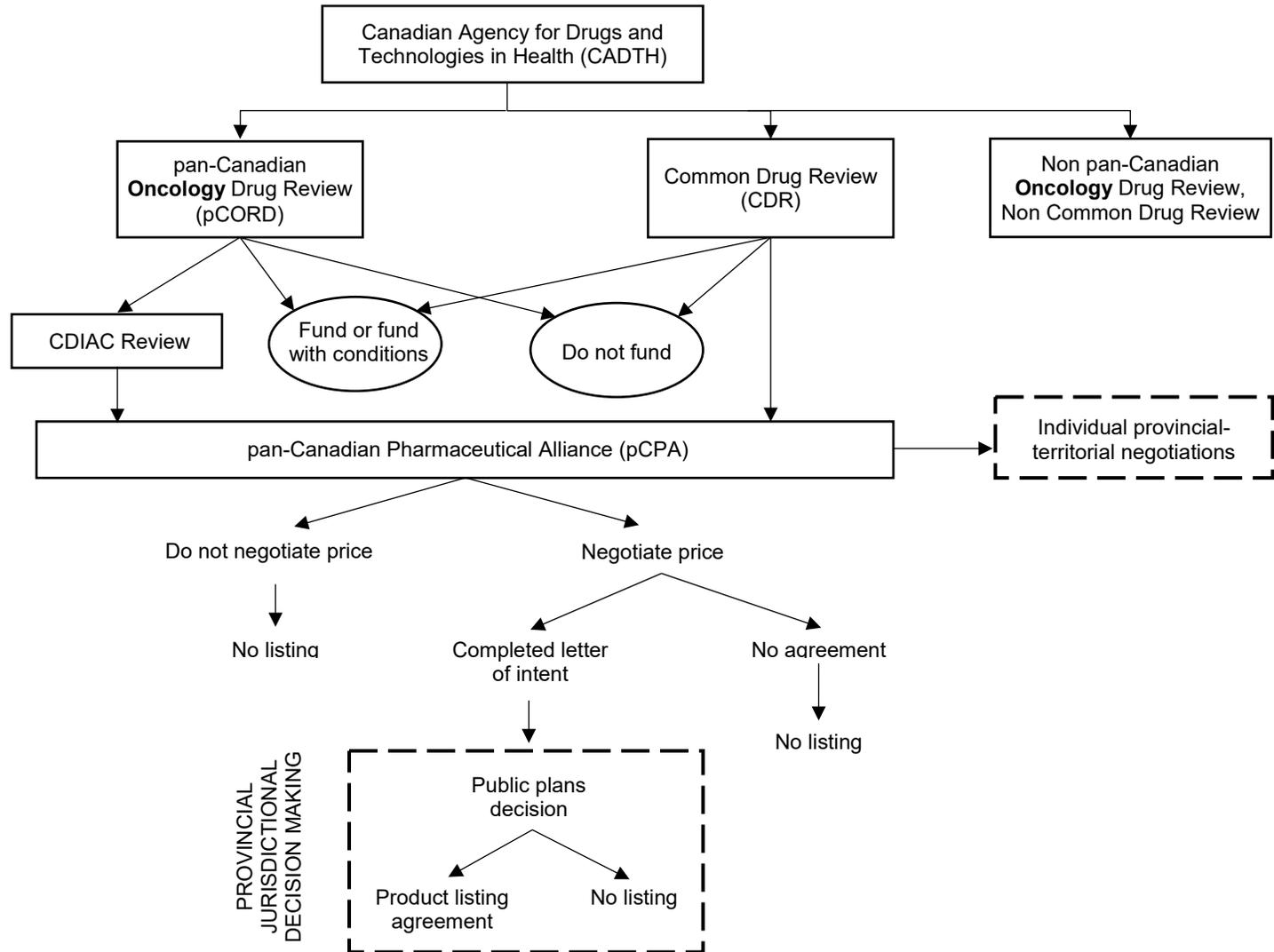
| | Referenced agencies | |
|------------------|---------------------|---|
| Australia | MSAC | Medical Services Advisory Committee, www.msac.gov.au |
| | PBS | Pharmacy Benefit Scheme, www.pbs.gov.au |
| | PBAC | Pharmaceutical Benefits Advisory Committee, www.pbs.gov.au/info/industry/listing/elements/pbac-meetings |
| | PBPA | Pharmaceutical Benefits Pricing Authority, www.pbs.gov.au/info/industry/pricing/pbs-items/pba-policies-procedures |
| Canada | CADTH | Canadian Agency for Drugs and Technologies in Health, www.cadth.ca |
| | CDEC | Canadian Drug Expert Committee, www.cadth.ca/collaboration-and-outreach/advisory-bodies/canadian-drug-expert-committee-cdec |
| | CDIAC | Cancer Drug Implementation Advisory Committee, www.capca.ca/current-issues/the-pan-canadian-cancer-drug-funding-sustainability-initiative/cancer-drug-implementation-advisory-committee-cdiac |
| | CDR | Common Drug Review, www.cadth.ca/about-cadth/what-we-do/products-services/cdr |
| | pCODR | pan-Canadian Oncology Drug Review, www.cadth.ca/pcodr |
| | pCPA | pan-Canadian Pharmaceutical Alliance, www.canadaspremiers.ca/pan-canadian-pharmaceutical-alliance |
| | PMPRB | Patented Medicine Prices Review Board, www.pmprb-cepmb.gc.ca |
| France | CEESP | Commission Evaluation Economique et de Santé Publique, www.has-sante.fr/jcms/c_419565/fr/commission-evaluation-economique-et-de-sante-publique |
| | CEPS | Le Comité économique des produits de santé, www.solidarites-sante.gouv.fr/ministere/acteurs/instances-rattachees/article/ceps-comite-economique-des-produits-de-sante |
| | HAS | Haute Autorité de santé, www.has-sante.fr |
| | UNCAM | Union Nationale des Caisses d'Assurance Maladie |
| Germany | G-BA | Gemeinsamer Bundesausschuss, www.g-ba.de |
| | IQWiG | Institute for Quality and Efficiency in Healthcare, www.iqwig.de |
| | SHI | National Association of Statutory Health Insurance, www.gkv-spitzenverband.de |
| Japan | Chuikyo | Central Social Insurance Medical Council |
| | MHLW | Ministry of Health, Labor and Welfare, www.mhlw.go.jp |
| | NIPH | National Institute of Public Health, www.niph.go.jp |
| | PMDA | Pharmaceutical and Medical Devices Agency www.pmda.go.jp |
| U.K. | ABPI | Association of the British Pharmaceutical Industry, www.abpi.org.uk |
| | NHS | National Health Service, www.nhs.uk |
| | NICE | National Institute for Health and Care Excellence, www.nice.org.uk |

APPENDIX FIGURE A1. NEGOTIATING PRICES FOR NEW DRUGS IN GERMANY



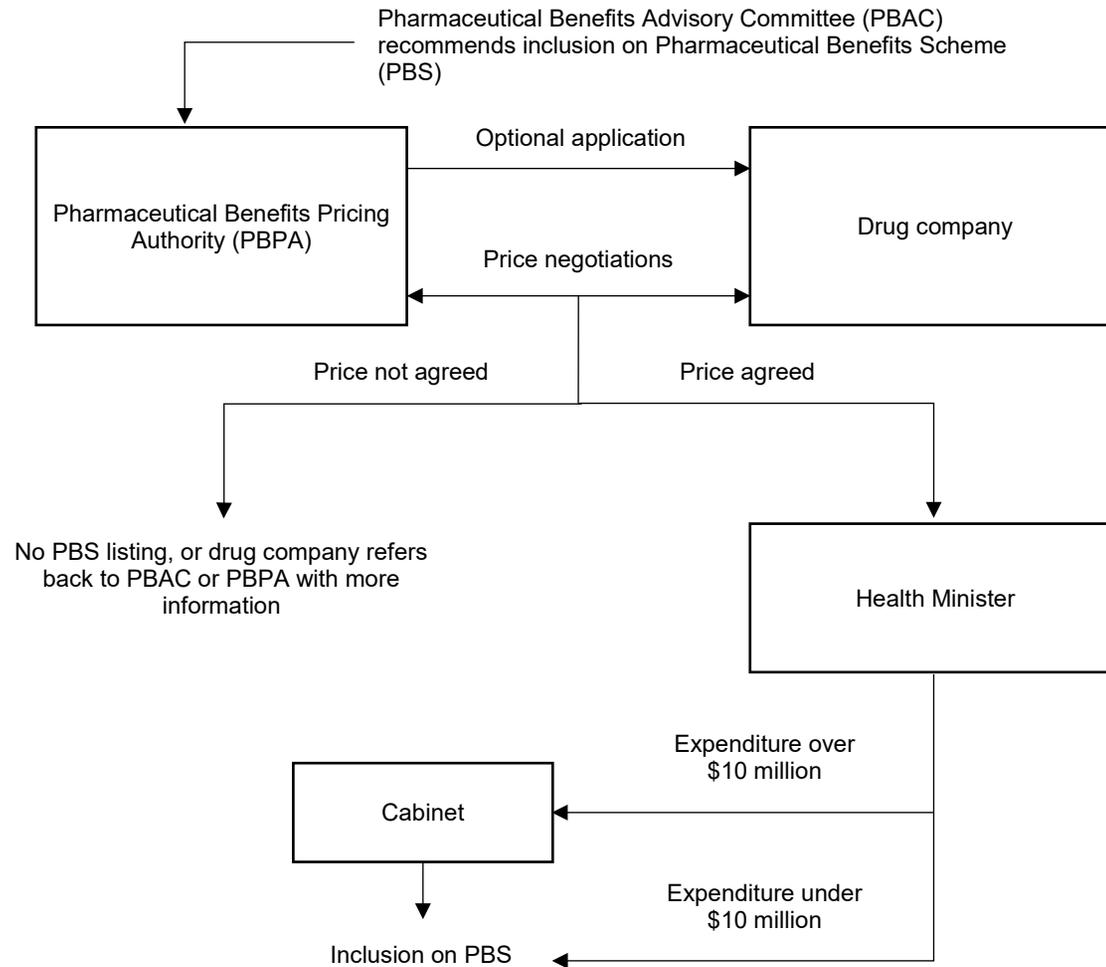
Source: Adapted from Institute for Quality and Efficiency in Health Care (IQWiG) [Involvement of people affected in the dossier assessment](#)

APPENDIX FIGURE A2. OVERVIEW OF THE PUBLIC SYSTEM REIMBURSEMENT DECISION PATHWAY FOR NEW MEDICINES IN CANADA



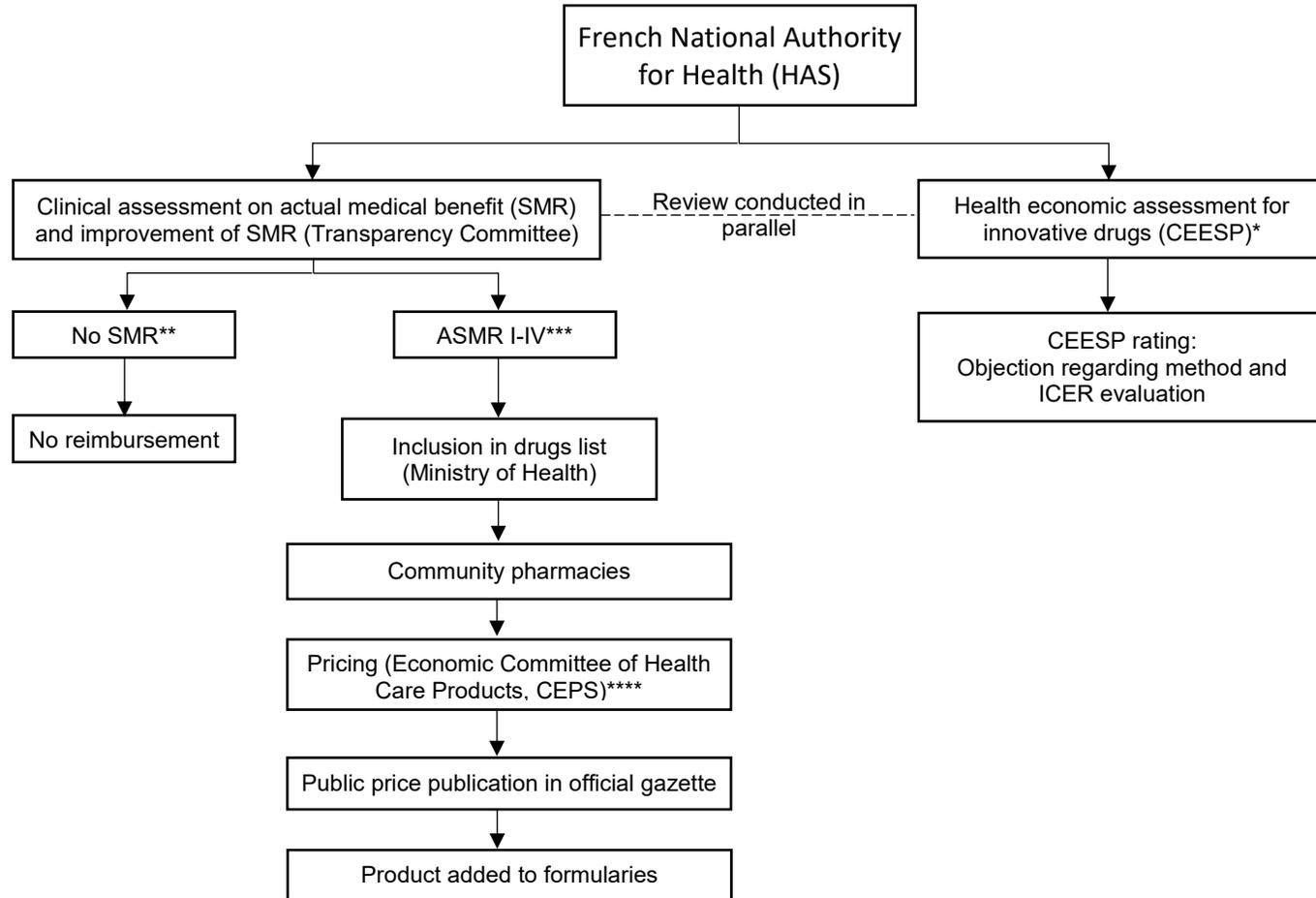
*Note: CDIAC = Cancer Drug Implementation Advisory Committee
Source: Adapted from Salek et al (2019) [68]*

APPENDIX FIGURE A3. SETTING DRUG PRICES IN AUSTRALIA



Source: Adapted from [Stephen Duckett \(2013\)](#)

APPENDIX FIGURE A4. OVERVIEW OF MARKET ACCESS IN FRANCE



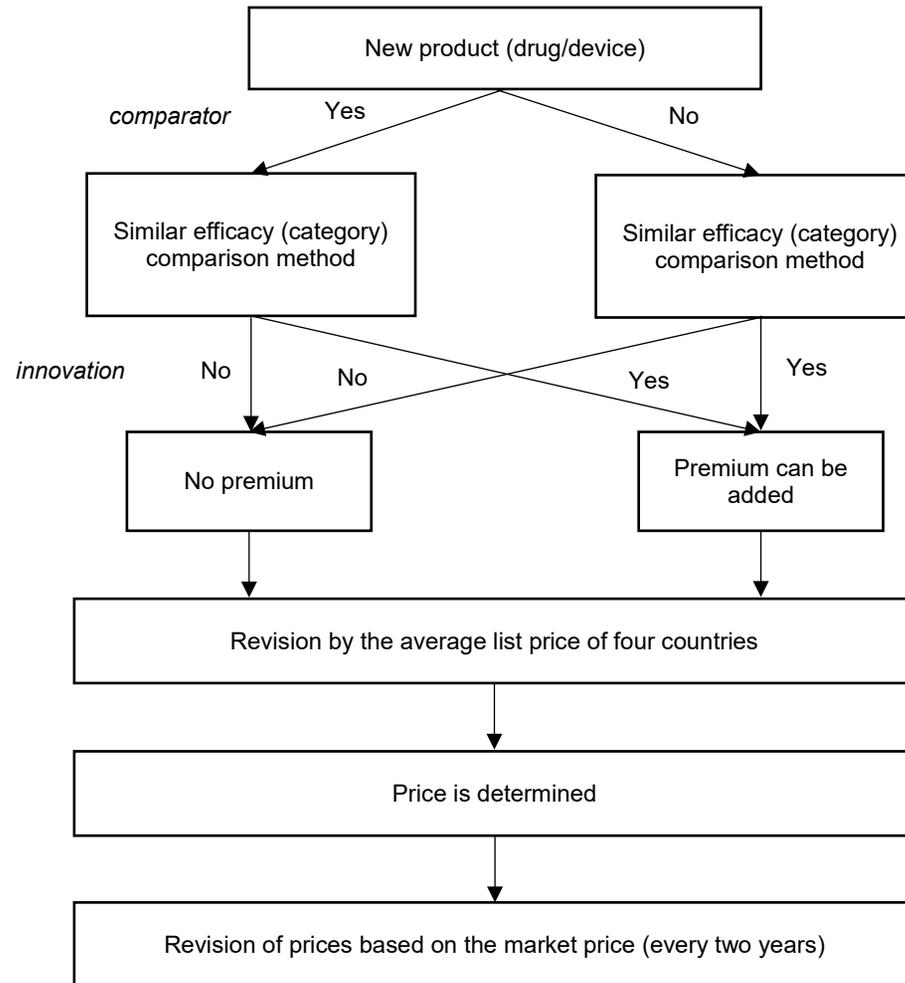
Notes: *Health economic assessment required if ASMR I-III claimed **AND** turnover (including tax) in year 2+ is €20 million **OR** healthcare organization modification.

** Pricing depends on comparator and target population. *** Reimbursement level set by National Association of Health Insurance Funds (UNCAM) on SMR.

**** Pricing negotiations based on product ASMR level and international reference pricing; fast track pricing negotiations (30 days instead of 90) possible for products with ASMR levels I-III.

Source: Adapted from MAP BioPharma [Market Access Overview](#)

APPENDIX FIGURE A5. FRAMEWORK FOR PRICING DRUGS AND DEVICES IN JAPAN



Source: Adapted from Shiroiwa et al (2017) [41]