



ScienceDirect

Contents lists available at sciencedirect.com
Journal homepage: www.elsevier.com/locate/jval

Health Policy Analysis

A Review of Current Approaches to Defining and Valuing Innovation in Health Technology Assessment



Sarah Hofmann, Dipl-Vw, Jennifer Branner, MSc, Arpit Misra, PhD, Hannah Lintener, BSc

ABSTRACT

Objectives: The growing focus on the value of new drugs for patients and society has led to a more differentiated notion of innovation in the context of pharmaceutical products. The goal of this article is to provide an overview of the current debate about the definition and assessment of innovation and how innovation is considered in reimbursement and pricing decisions.

Methods: To compile the relevant literature, we followed a 2-step approach. First, we searched for peer-reviewed literature that deals with the definition of pharmaceutical innovation. Second, we reviewed health technology assessment (HTA) guidelines of 11 selected countries (Australia, Belgium, Canada, England, France, Germany, Italy, Japan, Norway, Sweden, and The Netherlands) regarding aspects of innovation that are currently considered as relevant by the respective HTA bodies.

Results: All countries in our sample use 1 of 2 types of reward mechanism for novel drugs that they consider provide some sort of benefit. Generally, the focus is on the therapeutic benefit of a drug, whereas, depending on the exact arrangement, other aspects can also be taken into account. A reduction in side effects and aspects of treatment convenience can be invoked in some of the countries. Mostly, however, they are not considered unless they are already captured in the clinical outcomes used to measure the therapeutic benefit.

Conclusion: Our review shows that although the health economic literature discusses a range of aspects on how innovation may generate value even without providing an immediate added therapeutic benefit (or on top of it), these are only selectively considered in the reviewed HTA guidelines. For most part, only the added therapeutic value is crucial when it comes to pricing and reimbursement decisions.

Keywords: health technology assessment, innovation, pharmaceuticals, value-based pricing.

VALUE HEALTH. 2021; 24(12):1773–1783

Introduction

The development of new and more effective drugs is considered an important driver of improvements in health over the past decades. They have not only contributed to increasing life expectancy but also changed the nature of severe diseases, such as HIV, cancer, and diabetes.^{1,2} To foster pharmaceutical research and development (R&D), most countries grant intellectual property rights and regulate data and market exclusivity. Rewarding temporary monopoly over new drugs enables pharmaceutical manufacturers to set profit-maximizing prices and realize a financial reward for their R&D, which in turn is supposed to encourage yet more drug innovation.^{3,4}

At the same time, although progress in drug therapies has produced undisputed benefits, the availability of ever more and effective drugs, combined with monopoly pricing, has also led to a considerable increase in drug expenditures.⁵ Besides, it has been shown that not all new drugs eventually met their claim to improve patients' health.^{6,7} Faced with the task of maintaining affordability and equitable access to therapies yet at the same

time providing incentives for the development of new medicines that offer a real benefit, many countries have implemented health technology assessments (HTAs) into their reimbursement and pricing decision making.^{7–9} HTAs systematically assess the properties and effects of a health technology to determine its value at different points in its lifecycle.¹⁰ Usually, the aim of pricing policies then is to ensure that prices for drugs are aligned to what the assessment concludes is the drug's value to patients and society.

This increasing focus on the value of new drugs in turn has also led to a more differentiated notion of innovation in the context of pharmaceutical products. Although, formerly, denoting a new drug as innovative was based on the drug having received patent protection or being a new molecular entity, this criterion is no longer sufficient from the perspective of many stakeholders.⁶ Rather, it became widely accepted that the central criterion to identify a drug as truly innovative should be the drug's benefit or usefulness.⁶ With usefulness being a relative quality though, innovation is often defined by the particular view of what is deemed important or valuable.¹¹

The goal of this article is to provide an overview of the current debate about the definition and the assessment of innovation in the context of HTA and how innovation is considered in pricing and reimbursement decisions. We start by reviewing current health economic literature about aspects of pharmaceutical innovation that should be taken into account when determining the value of a novel drug. We then review official HTA guidelines and related literature of 11 selected countries. We evaluate what aspects of pharmaceutical innovation are explicitly or implicitly considered as relevant and how they further play a role in the decision making of the HTA bodies and other relevant institutions to inform pricing and reimbursement decisions.

With this review, we complement previous studies that discuss different elements of value currently accounted for in HTA processes or to be possibly considered in future value assessments.^{12,13} Although these studies briefly cover innovation as 1 possible element of value, we go into more detail by providing a comprehensive review of the different notions of innovation and how they are considered in official HTA guidelines.

Methods

To compile the relevant literature for our review, we followed a 2-step approach. First, we searched for peer-reviewed literature using PubMed and the Social Sciences Citation Index. Our search strategy included English articles published from January 2010 to October 2019 (We limited our search to the years from 2010 onward for 3 reasons: First, including the years from 2000 to 2009 in an alternative search run resulted in a mere 13 additional hits, suggesting that the discussion about innovation in the context of HTA gained momentum rather after 2010. Second, several countries in our sample implemented reforms in their HTA systems between 2011 and 2014.¹⁴ To provide an up-to-date overview, we focused on the most recent literature. Third, because there exists a bulk of recent literature on the topic, we were confident that we would find all relevant older literature through reference screening in the more recent work.). Articles were included if they explicitly deal with the definition of pharmaceutical innovation or the assessment of innovation in the context of HTAs or pricing and reimbursement policies. Reference lists from the selected studies were screened for further relevant literature. Articles that deal with the pricing and reimbursement system of any of the countries covered in this study were retained for the country analysis.

In the second step, we searched the websites of international organizations and national health policy agencies for official HTA guidelines and other reports that provide information about the dimensions of innovation that considered account in the assessments of the selected countries. The dimensions of innovation were not defined a priori but were derived beforehand from the peer-reviewed literature on pharmaceutical innovation. [Table 1](#) includes a list of the 11 selected countries, the reasons for their inclusion in the study, the respective HTA bodies or other relevant institutions involved in the assessment of pharmaceutical innovations, the websites browsed, and the references used for the country analyses. The literature search took place in November 2019 and December 2019 and was validated and updated in February 2021.

The keywords, search algorithm, and the flow of the literature screening are displayed in [Figure 1](#). A full list of the articles identified as relevant can be found in [Appendix 1](#) in Supplemental Materials found at <https://doi.org/10.1016/j.jval.2021.06.006>.

Results

Defining Rewardable Innovation

Although innovation is a widely used term, notions of what exactly constitutes an innovation in the context of pharmaceutical products differ considerably. Formerly, the term was mostly used to denote newly patented drugs or new molecular entities, thus, referring to the technological novelty of a drug.^{6,47} More recently, however, the central criterion to determine pharmaceutical innovation is the drug's value or benefit. To differentiate between these 2 concepts of innovation—technological novelty versus value of a drug—the label “true” or “rewardable” innovation is used by some to refer to the more recent concept.

A major challenge though remains to define what offers a value and, therefore, deserves reward. Although the requirements for receiving a patent in pharmaceutical research are precisely defined and globally aligned, notions of what constitutes a rewardable aspect of innovation differ.

On the one hand, there is the notion that the value of innovation derives exclusively from the effect that the innovative drug has on the therapeutic benefit. What matters most for patients is whether a drug is the best choice to achieve treatment goals. It is this basic principle that guides most of the work on how to define rewardable innovation in the context of drug value assessments.^{48–50} The main argument is that, assuming a limited budget for healthcare expenditures, valuing anything beyond this therapeutic benefit in pricing and reimbursement decisions would reduce population health by displacing more cost-effective therapies.^{51–53} Furthermore, as a consequence, pharmaceutical companies might be incentivized to increasingly invest in R&D of slightly modified but basically similar products as opposed to drugs with a potentially larger positive therapeutic impact on patients.^{54,55}

On the other hand, it is argued that there might also be other, less obvious benefits from innovation in a wider sense.^{56–58} First, there may be benefits related to health or well-being that are not captured in measures of health outcomes typically used in clinical trials. A novel drug with less side effects or one that allows a more convenient treatment, for example, oral versus intravenous administration, may have the same effect on the therapeutic outcome but still improve the subjective well-being of the patients.^{57,59}

Second, it is argued that an innovative drug may also provide nonhealth-related benefits that accrue to society at large rather than to the patients treated. For example, a drug with a new mechanism of action might contribute to the accumulation of knowledge in the scientific community, possibly leading to future innovations.^{12,58,60–62} This form of innovation is considered essential to pharmaceutical progress and to stimulate research within the therapeutic class concerned.²⁵ Individuals might further value the process of incremental innovation because it provides “peace of mind” about the potential development of treatments and cure for diseases in the future.⁵⁶

Finally, pharmaceutical innovation may also manifest in benefits completely outside of the healthcare system, for example, in more efficient production possibilities that may in turn lead to increased or secured employment in a country or to a less polluting production process.⁶³

Innovation in HTA Systems

In this section, we examine which aspects of innovation are currently considered as relevant by the HTA bodies of the selected countries and how they play a role in pricing and reimbursement

Table 1. Sample of countries and respective national HTA bodies.

Country	HTA body and institutions responsible for reimbursement and/or pricing decision (or recommendation)	Websites visited	References used for country analyses	Reason for country inclusion
	International organizations and agencies Organisation for Economic Co-operation and Development (OECD) World Health Organization (WHO) Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies ISPOR Pharmacoeconomic Guidelines around the World European Network for Health Technology Assessment (EUnetHTA)	http://www.oecd.org/health/ https://ppri.goeg.at https://tools.ispor.org/peguidelines/ http://www.eunethta.eu		
Australia	Pharmaceutical Benefit Advisory Committee (PBAC)	https://pbac.pbs.gov.au	5, 16	Significant experience in incorporating formal pharmacoeconomic assessments in decision making
The Netherlands	National Health Care Institute (ZIN)	https://english.zorginstituutnederland.nl	13, 17–19	
Sweden	Dental and Pharmaceutical Benefits Agency (TLV)	https://www.tlv.se/in-english.html	13, 20	
Norway	The Norwegian Medicines Agency (NOMA)	https://legemiddelverket.no/english	21, 22	
England	National Institute for Health and Care Excellence (NICE)	https://www.nice.org.uk	23–27	
Belgium	National Institute for Health and Disability Insurance (NIHDI-RIZIV-INAMI)	https://www.inami.fgov.be/fr/Pages/default.aspx	28–30	Explicit approval of price premiums for drugs with added therapeutic benefit
France	High Authority on Health (HAS)	https://www.has-sante.fr	31–33	
Germany	Federal Joint Committee (G-BA) Institute for Quality and Efficiency in Health Care (IQWiG)	https://www.g-ba.de/english/ https://www.iqwig.de/en/	34	
Japan	Central Social Health Insurance Council (Chuikyo) Center for Outcomes Research and Economic Evaluation for Health (C2H)	https://www.mhlw.go.jp/english/index.html https://c2h.niph.go.jp/en/	35–39	Use of mixed approaches, including both rating of added therapeutic benefit and pharmacoeconomic analysis
Canada	Canadian Agency for Drugs and Technologies in Health (CADTH)* Patented Medicine Prices Review Board (PMPRB) [†]	https://www.cadth.ca http://pmprb-cepmb.gc.ca/home	44–46	
Italy	Agenzia Italiana del Farmaco (AIFA)	https://www.aifa.gov.it/en/home	40–43	Use of rating system for innovative drugs used in price negotiations

HTA indicates health technology assessment.

*Reimbursement decisions in the province of Québec are not based on recommendations by the CADTH but the “Institut national d’excellence en santé et en services sociaux” (INESSS). We have not covered the guidelines of INESSS in this review.

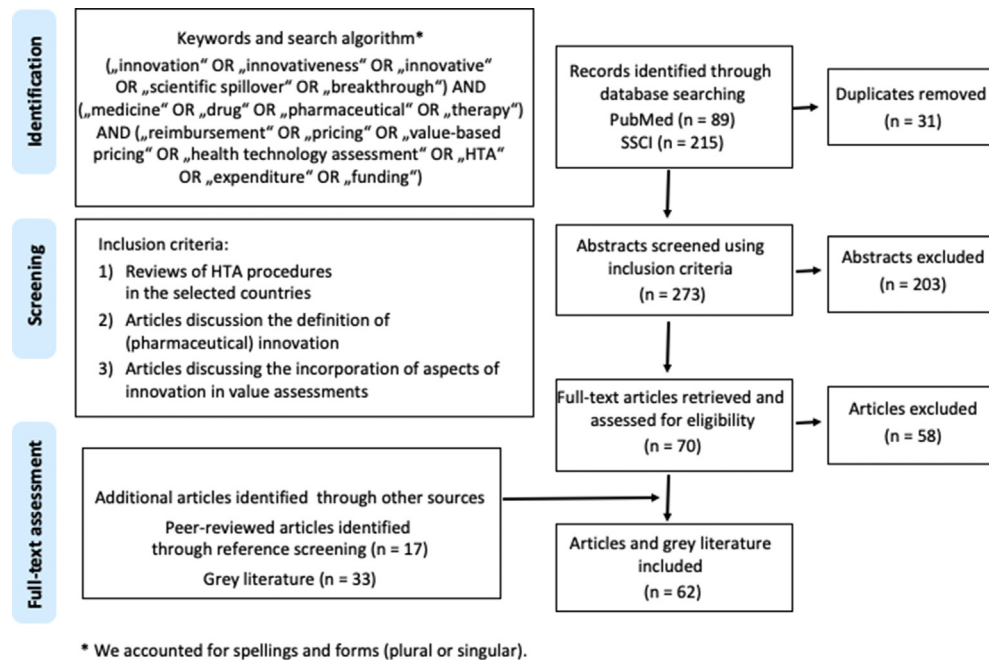
[†]PMPRB is currently making changes to the categorization of drug innovativeness; revised guidelines have not yet been published by the time of this review.

decisions. It is important to note that in the regulatory guidelines and associated documents as well as there is no uniform usage of the term “innovation.” In some countries, the term is used to explicitly refer to new drugs that fulfill certain criteria, with added therapeutic benefit generally being the most important criterion (France, Italy, and Japan). In England, on the contrary, the National Institute for Health and Care Excellence (NICE) seems to generally adopt a broader definition of innovation, stating that innovation can but “does not necessarily lead to better outcomes than the existing practice.”²⁶ Therefore, they define certain aspects of innovation that make it a rewardable innovation. The remaining countries do not use the term “innovative” or “innovation” in their guidelines or related documentation. Rather, a definition of

innovation is given only implicitly by describing what aspects of a new medicine are taken into consideration in the assessments and how these aspects translate into reimbursement decisions and into prices.

In the country-by-country analysis, we classified the factors considered as relevant by the responsible authorities according to the categories of innovation as described in the previous section: clinical/therapeutic improvement, reduced side effects, convenience of treatment, or other health-related factors and, furthermore, scientific spillovers or other nonhealth-related effects outside of the health system.

Moreover, we described how the respective factors are incorporated into pricing and reimbursement decisions and, if

Figure 1. Flow diagram of literature screening and identification process.

applicable, how they translate into a price reward. The reward mechanisms in our sample countries can be grouped into 2 types of methods, used either separately or in combination. One method is to assess the properties of a new drug compared with the best alternative treatment, and in case that the new drug represents an improvement, allow for a price that exceeds that of the comparator treatment (price premium). The other method is to apply formal economic evaluation and to limit reimbursement of a drug by defining a threshold for the incremental cost-effectiveness ratio (ICER), that is, setting a maximum reimbursable price for 1 additional quality-adjusted life year (QALY). In this case, the price reward is implicitly granted because drugs with higher effectiveness can charge higher prices without surpassing the ICER threshold. Conversely, less effective drugs are forced to charge lower prices to stay within the accepted ICER range. Both methods focus on the therapeutic benefit of a drug, whereas, depending on the exact arrangement, other aspects can also be taken into account.

France

Prices of new drugs in France are determined based on a rating of the added medical benefits (*Amélioration du Service Médical Rendu* [ASMR]) compared with the best alternative treatment (comparator). The ASMR is defined by the Transparency Commission of the High Authority on Health, the body commissioned with the medical assessment of new drugs. With a rating of 1 to 3, which can be achieved by exhibiting at least a moderate therapeutic progress in terms of mortality or morbidity, the new drug qualifies for a price premium, that is, a price above the cost of the comparator. The size of the price premium is usually determined by European reference pricing or negotiations between the manufacturer and the Economic Committee on Healthcare Products.

Next to clinical efficacy, the Transparency Commission also considers drug tolerance, quality of life effects, and the underlying medical need in its ASMR assessment.³¹

England

In England, recommendations on coverage of a new drug by the National Health Service (NHS) are made by NICE based on the results of a health economic evaluation. All drugs with an ICER below £20 000 are generally covered and reimbursed by the NHS without further deliberation.

Although health gains are the most essential aspect of innovation, manufacturers still have the possibility to invoke the “innovative nature of a health technology” as an additional decision criterion when substantial health-related benefits may not have been captured in the QALY measure.^{23,26} Although the innovative nature is not explicitly defined in the current guidance, the NICE user guide for submissions states that, to demonstrate innovation, the manufacturers must describe how a technology is a “step-change” in the management of the disease.²⁶

Furthermore, additional aspects may be considered if they relate to NICE’s principles on social value judgments, which includes, for example, reducing population health inequality.^{23,26}

Finally, the guidelines for the assessment of highly specialized treatments (treatments for very rare and chronic diseases) list additional aspects that may be taken into account (on top of the aspects that may be invoked in the standard process). These include the impact of a disease on caregivers’ quality of life, the extent and nature of current treatment options, and the “potential for long-term benefits to the NHS of research and innovation.”²⁵ Nevertheless, how these long-term research benefits are supposed to be measured is not further detailed.

The Netherlands

In their decisions on reimbursement of new drugs, the Dutch National Health Care Institute applies a mixed approach, focusing on both the absolute size of the benefit of a treatment and cost-effectiveness. The 4 main principles for the assessment of a drug are the severity of the condition to be treated (necessity), the drug’s effectiveness, its cost-effectiveness, and the feasibility of including the treatment into the benefits package of the public

health insurance.¹³ There is no specified ICER threshold for the cost-effectiveness analyses. The basis generally adopted for decision ranges between €10 000 and €80 000.¹⁷ Because the societal perspective is applied for the assessments of costs, treatment convenience that results in increased productivity or savings in travel time is implicitly considered in addition to therapeutic effects captured in QALYs.¹⁸

Canada

Canada regulates the prices of all patented drugs (whether covered by public drug schemes or not) by capping prices according to the drug's therapeutic improvement. Drugs that offer an effective treatment for a particular condition with no existing treatment available are classified as "breakthrough" by the Canadian Patented Medicine Prices Review Board. They are benchmarked against prices in a set of foreign countries. Drugs with substantial, moderate, or slight or no therapeutic improvement, in contrast, are benchmarked against prices of comparator drugs in Canada (using different algorithms, respectively).⁴⁵ Primary factors considered in the classification are drug efficacy and the reduction in adverse reactions. Furthermore, Patented Medicine Prices Review Board considers several secondary factors that, on their own, can be rewarded with a rating up to moderate therapeutic improvement. Among these are route of administration, patient and caregiver convenience, and the time required to achieve the optimal therapeutic effect.⁴⁶

Reimbursement decisions, in turn, are based on recommendations by the Canadian Agency for Drugs and Technologies in Health (and the pan-Canadian Oncology Drug Review for cancer drugs) after pharmacoeconomic evaluations. Although Canadian Agency for Drugs and Technologies in Health formulates recommendations mainly based on cost-effectiveness analyses with QALYs as health outcomes, decision making by pan-Canadian Oncology Drug Review follows a more deliberative process that takes into account additional factors such as unmet therapeutic need.^{44,45}

Japan

In Japan, reimbursement prices for all medicines in the market are calculated by the Ministry of Health, Labour and Welfare according to a specified algorithm and are approved by the Central Social Health Insurance Council (Chuikyo), an advisory board for the public health insurance. If similar drugs in terms of efficacy and pharmacological properties are available, prices are benchmarked against these comparators. Otherwise, they are calculated from scratch taking into account factors, such as costs of manufacturing, marketing and administration, and a predetermined profit rate. In both cases, a price premium is added for drugs that are considered innovative. The size of the premium is defined based on the degree of innovation, which, in turn, depends on whether 1 or all of the following criteria are met: a new action mechanism, higher efficacy or safety, improvement of treatment, and a beneficial drug formulation.^{36,37}

Since 2019, cost-effectiveness analyses are used in addition to the established price setting, that is, reimbursement prices are adjusted according to the ICER determined in the cost-effectiveness analysis. The current cost per gained QALY threshold is set at ¥5 million (\$45 000) for standard drugs and ¥7.5 million (\$67 500) for specialized drugs used to treat complex conditions including oncologic, pediatric, or rare diseases. Apart from health outcomes measured in QALYs, there are no further aspects to be considered in the economic evaluations.^{35,38}

Norway

In Norway, decisions on reimbursement of new drugs are made by the Norwegian Medicines Agency based on pharmacoeconomic evaluations. To be reimbursed, the incremental costs per QALY gained in comparison with the best alternative available must not exceed NOK 275 000 (\$32 000). A higher ICER threshold may be applied for severe conditions.²² Besides the therapeutic benefit captured by QALYs, caregivers' quality of life may be presented as an additional aspect in the analysis. Furthermore, because the societal perspective is applied for the assessments of costs, duration of treatment administration or travel time for patients and caregivers can be indirectly considered if they provide cost savings.²¹

Belgium

In Belgium, the Commission for Reimbursement of Medicinal Products, a body of the National Institute for Health and Disability Insurance recommends reimbursement of a drug based on an assessment of the therapeutic value, the importance of the drug with regard to therapeutic and social needs, the impact on healthcare expenditure, and the relation between projected costs and therapeutic value.¹⁴ For drugs with an added therapeutic benefit (categorized as "class 1"), prices are then negotiated between the manufacturer and the Price Department of the Federal Public Service for Economic Affairs.¹⁴ To this end, manufacturers are required to submit pharmacoeconomic evaluations, where they assess incremental costs per QALY gained (though there is no specified ICER threshold).²⁸ Furthermore, applicability and user-friendliness are indicated as elements of therapeutic value that should be reflected on or provided in a separate analysis if they are relevant and not already captured in the assessment of additional health benefit.²⁸

Germany

Although generally all drugs with market authorization are covered by the statutory health insurance, maximum reimbursement prices of new drugs must be determined within the first year after market entry. The same applies to existing drugs to be used for a new indication.

Pricing decisions are almost exclusively based on clinical criteria related to the effectiveness of the new product. The independent Institute for Quality and Efficiency in Health Care assesses the added therapeutic value of new products. Primary outcomes to be considered are mortality, morbidity, or health-related quality of life.³⁴

Depending on the existence of an added therapeutic value, the Federal Joint Committee (G-BA) decides if the drug is to be clustered in a reference price group (with a price not to exceed the group maximum) or if the medicine can charge a price premium over comparators. In the latter case, the price premium is negotiated with the National Association of Statutory Health Insurance Funds. The main criterion for the negotiation is the extent of the added therapeutic benefit as determined in the benefit assessment. Patient satisfaction might be considered additionally insofar as it refers to health-related aspects, though not as a sole criterion.³⁴

Australia

Recommendations on reimbursement and pricing of a new drug are made by the Pharmaceutical Benefits Advisory Committee based on a pharmacoeconomic evaluation of the respective drug. The relevant decision criterion is the incremental cost per QALY gained (although there is no explicit ICER threshold defined).¹⁵ Hence, a price premium is implicitly granted for drugs

Table 2. Countries and considered innovation aspects.

Countries	Health-related effects				Non-health-related effects		Reward mechanism
	Therapeutic improvement	Reduced side effects	Treatment convenience	Other	Scientific spillover effects	Effects outside of the health system	
Australia	Through consideration of ICER	-	-	Clinical need for conditions with no or few other treatment options might be additionally considered	-	To some extent: Nonhealth outcomes (though not further defined) can be presented in supplementary analysis.	Through economic evaluation (QALY/ICER system): For drugs with higher clinical benefit, the charged price can automatically be higher. No specified ICER threshold. Some additional aspects considered.
Belgium	Added therapeutic benefit primary criterion for "class 1" (= added therapeutic benefit) designation	-	Applicability and user-friendliness are explicitly mentioned as elements of therapeutic value, which should be provided in a separate additional analysis.	Importance of drug with regards to therapeutic and social needs criterion for "class 1" (= added therapeutic benefit) designation	-	-	Price premium upon evidence of additional therapeutic benefit. Price premium negotiated. Economic evaluation only as additional information in negotiation.
Canada	Clinical benefit primary factor in assessment of therapeutic improvement	Reduction in adverse reactions primary factor in assessment of therapeutic improvement (by PMPRB)	Route of administration and patient and caregiver convenience are secondary factors in assessment of therapeutic improvement (by PMPRB).	Time required to achieve the optimal therapeutic effect is a secondary factor in assessment of therapeutic improvement (by PMPRB)	-	-	Price premium upon evidence of therapeutic improvement ("breakthrough"). Prices benchmarked against foreign countries (vs internal benchmarking for drugs without therapeutic improvement).
England	Through consideration of ICER	-	-	ICER threshold increased to 50 000 for treatment at the end of life; ICER threshold increased to up to 300 000 for rare diseases. For highly specialized treatments: impact on care of persons' quality of life (included in deliberation)	For highly specialized treatments: Potential for long-term benefits of research and innovation (included in deliberation about reimbursement)	Reduction in population health inequalities (included in deliberation about reimbursement)	Through economic evaluation (QALY/ICER system): For drugs with higher clinical benefit, the charged price can automatically be higher. Specified ICER threshold. Increase of threshold for special drugs (end of life, rare diseases, highly specialized treatments)

continued on next page

Table 2. Continued

Countries	Health-related effects				Non-health-related effects		Reward mechanism
	Therapeutic improvement	Reduced side effects	Treatment convenience	Other	Scientific spillover effects	Effects outside of the health system	
France	Clinically relevant effect in terms of mortality or morbidity main criterion for determination of ASMR	Tolerance additional criterion for determination of ASMR	-	Unmet medical need and quality of life additional criterion for the determination of ASMR	-	-	Price premium upon evidence of additional medical benefit (ASMR); premium on the basis of EU5 reference pricing and/or negotiation Economic evaluation as additional information in negotiation
Germany	Mortality, morbidity, and health-related quality of life primary outcomes for determination of therapeutic added value			Patient satisfaction can be considered insofar it refers to health-related aspects.			Price premium upon evidence of additional therapeutic benefit Size of premium negotiated Economic evaluation as additional information in negotiation
Italy	Therapeutic benefit an important criterion for reimbursement and for innovation designation	-	-	Unmet therapeutic need a criterion for innovation designation	-	-	Economic advantages for innovative drugs (exempt from mandatory discount + immediate coverage in all drug plans guaranteed) Multicriteria approach for price negotiation Economic evaluation important for price negotiation
Japan	Higher efficacy and improvement of treatment an important criteria for innovation designation	-		Beneficial drug formulation explicitly mentioned as a criterion for innovativeness price premium.	-	-	Price premium upon evidence of additional therapeutic benefit Premium defined according to algorithm Economic evaluation (including ICER threshold) used in addition

continued on next page

Table 2. Continued

Countries	Health-related effects				Non-health-related effects		Reward mechanism
	Therapeutic improvement	Reduced side effects	Treatment convenience	Other	Scientific spillover effects	Effects outside of the health system	
Norway	Through consideration of ICER	-	Difference in duration of treatment administration or travel time for patients and caregivers can be presented as costs.	ICER threshold increase possible for severe conditions	-	-	Through economic evaluation (QALY/ICER system): For drugs with higher clinical benefit, the charged price can automatically be higher. Specified ICER threshold. Increase of threshold for severe diseases
Sweden	Through consideration of ICER		Societal perspective in CE analyses can include cost set-offs due to easier drug administration.	Medical need and disease severity are the main principles for drug reimbursement			Through economic evaluation (QALY/ICER system): For drugs with higher clinical benefit, the charged price can automatically be higher. No specified ICER threshold
The Netherlands	Therapeutic value most critical criterion for reimbursement; further through consideration of ICER		Societal perspective in CE analyses can include cost set-offs due to easier drug administration (productivity, savings in travel time).	Necessity and burden of disease main criterion for drug reimbursement			Through economic evaluation (QALY/ICER system): For drugs with higher clinical benefit, the charged price can automatically be higher. No specified ICER threshold

Note. A review of current approaches to defining and valuing innovation in HTA. ASMR indicates Amélioration du Service Médical Rendu; CE, cost-effectiveness; HTA, health technology assessment; ICER, incremental cost-effectiveness ratio; PMPRB, Patented Medicine Prices Review Board; QALY, quality-adjusted life-year.

that offer clinical benefits captured by the health outcomes used for the calculation of QALYs. In addition to the ICER, the committee considers clinical need (ie, whether there are other treatment options available) as a relevant factor.¹⁵ Furthermore, it does allow for nonhealth outcomes to be presented in a supplementary analysis,¹⁵ but these nonhealth outcomes are not detailed further..

Italy

In Italy, once a drug has received market authorization by the European Commission, manufacturers can apply for reimbursement to the Italian Medicines Agency. The Technical Scientific Committee decides on reimbursement based on the therapeutic

value of the drug. Furthermore, it determines whether the product can be considered as innovative based on the following 3 criteria: an unmet therapeutic need in the condition to be treated, a therapeutic benefit (added value) compared with available alternatives, and the quality of the evidence.^{40,41} Innovative medicines enjoy economic advantages in that they are exempt from mandatory discounts and that nationwide access to them must be guaranteed immediately, whereby regional approval processes are avoided.^{41,43}

After the reimbursement decision, price negotiation between the manufacturer and the Prices and Reimbursement Committee take place. For the negotiation, a multicriteria approach is applied,

with cost-effectiveness analyses being an important factor (although there is no specified ICER threshold).^{14,42} According to Paris and Belloni¹⁴, “pharmacological or technological innovation that is not a therapeutic advantage over existing products” is also considered as 1 of the several criteria in the pricing process. Nevertheless, we could not confirm this finding based on more recent references.

Sweden

In Sweden, The Dental and Pharmaceutical Benefits Agency decides simultaneously on pricing and reimbursement for new medicines. Besides the medical need and the severity of the condition, an acceptable cost-effectiveness ratio is the main criterion for coverage in the public benefits scheme.²⁰ There is no explicit ICER threshold defined, though. In the assessment of a drug's effectiveness, only outcomes that result in a measurable therapeutic benefit are taken into account. Nevertheless, the societal perspective, which is applied for the assessment of costs, allows for the consideration of additional aspects, for example, easier drug administration that leads to gains in productivity or spare time.¹⁴

Table 2 provides an overview of the innovation aspects that are considered in each of the studied countries and of the reward mechanisms in place.

Discussion

The results of this review are generally in line with findings in other studies that analyze the elements taken into account in value assessments of new drugs.^{2,13,52,64} It is important to note that our analysis is limited to the definitions and processes as described in the official HTA guidelines. We do not provide an assessment of how HTA bodies interpret the guidelines or deviate from the guidelines in real practice.

A reduction in side effects and aspects of treatment convenience can be invoked in some of the countries. Mostly, however, they are not considered unless they are already captured in the clinical outcomes used to measure the therapeutic benefit. Still, these aspects might become more important in the future when HTAs are more frequently based on real-world evidence. For example, low adherence is widespread outside clinical trials and is associated with increased hospitalizations and higher mortality.^{65–67} Improving ease of use in medications, in turn, may positively affect adherence and, thus, health outcomes.⁶⁸ Furthermore, experiences from the recent coronavirus disease pandemic that has strained many complex healthcare systems (eg, overloaded intensive care units or inpatient capacity) may shift the way a healthcare system or regulatory body values medicines. For example, the mode of administration, such as oral, subcutaneous, or intravenous, might be valued not only in terms of comfort for the patient but also in terms of the wider public health benefits such medicines bring, for example, through tying up less resources.

Where aspects beyond the added therapeutic value are mentioned, they are mostly not detailed further and guidance on how to include them in decision making is vague. This may be attributable to the fact that there are no generally accepted approaches to quantify benefits that are neither monetary nor measurable in standard health outcome units such as QALYs. There have been several methods proposed to accommodate multiple elements within 1 value assessment, each of them offering different advantages but none of them established in healthcare decision making yet.^{69,70} The extent to which these wider aspects of innovation should be rewarded will eventually be

a societal and political decision and cannot be answered straightforwardly.

Conclusion

Our review shows that, although the health economic literature discusses a range of aspects on how innovation may generate value even without providing an immediate added therapeutic benefit (or on top of it), these are only selectively considered in the reviewed HTA guidelines. For most part, only the added therapeutic value is crucial when it comes to pricing and reimbursement decisions.

Supplemental Material

Supplementary data associated with this article can be found in the online version at <https://doi.org/10.1016/j.jval.2021.06.006>.

Article and Author Information

Accepted for Publication: June 6, 2021

Published Online: August 14, 2021

doi: <https://doi.org/10.1016/j.jval.2021.06.006>

Author Affiliations: WifOR Institute, Darmstadt, Germany (Hofmann, Branner, Misra, Lintener) and Cytel/Ingress, Rotterdam, Netherlands (Misra).

Correspondence: Sarah Hofmann, Dipl.-Vw, WifOR Institute, Rheinstrasse 22, Darmstadt 64283, Germany. Email: sarahmaria.hofmann@gmail.com

Author Contributions: *Concept and design:* Hofmann, Misra
Acquisition of data: Hofmann, Branner, Lintener
Analysis and interpretation of data: Hofmann, Branner, Lintener
Drafting of the manuscript: Hofmann, Branner, Misra, Lintener
Critical revision of the paper for important intellectual content: Hofmann, Branner
Obtaining funding: Misra

Conflict of Interest Disclosures: Ms Hofmann, Branner, Lintener, and Dr Misra reported receiving grants from Roche during the conduct of this study.

Funding/Support: The present study was funded by Roche (Roche Pharma AG, Basel, Switzerland).

Role of the Funder/Sponsor: The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the article for publication.

REFERENCES

1. Buxbaum JD, Chernew ME, Fendrick AM, Cutler DM. Contributions of public health, pharmaceuticals, and other medical care to US life expectancy changes, 1990–2015. *Health Aff (Millwood)*. 2020;39(9):1546–1556.
2. OECD. Pharmaceutical Innovation and Access to Medicines. <https://www.oecd.org/health/pharmaceutical-innovation-and-access-to-medicines-9789264307391-en.htm>. Published November 2018. Accessed December 14, 2019.
3. Frank R, Ginsburg P. Pharmaceutical industry profits and Research and Development | health affairs. <https://www.healthaffairs.org/action/showDoPubSecure?doi=10.1377%2Fhblog20171113.880918&format=full>. Accessed December 12, 2019.
4. 't Hoen E. EU review of pharmaceutical incentives: recommendations for change. *Medicines Law & Policy*. Published <https://medicineslawandpolicy.org/2019/06/eu-review-of-pharmaceutical-incentives-recommendations-for-change/>. Accessed December 12, 2019.
5. OECD. Health at a Glance 2015: OECD Indicators. https://www.oecd-ilibrary.org/social-issues-migration-health/health-at-a-glance-2015_health_glance-2015-en. Published 2015. Accessed December 12, 2019.

6. Kesselheim AS, Wang B, Avorn J. Defining "innovativeness" in drug development: a systematic review. *Clin Pharmacol Ther.* 2013;94(3):336–348.
7. OECD. New Health Technologies: Managing Access, Value and Sustainability. <https://www.oecd.org/health/managing-new-technologies-in-health-care-9789264266438-en.htm>. Published January 2017. Accessed October 10, 2019.
8. Directorate-General for Competition (European Commission). Competition enforcement in the pharmaceutical sector (2009–2017): European competition authorities working together for affordable and innovative medicines. European Commission. http://publications.europa.eu/publication/manifestation_identifier/PUB_KD0718081ENN. Published May 2019. Accessed August 29, 2019.
9. Panteli D, Eckhardt H, Nolting A, Busse R, Kulig M. From market access to patient access: overview of evidence-based approaches for the reimbursement and pricing of pharmaceuticals in 36 European countries. *Health Res Policy Syst.* 2015;13:39.
10. O'Rourke B, Oortwijn W, Schuller T, International Joint Task Group. The new definition of health technology assessment: a milestone in international collaboration. *Int J Technol Assess Health Care.* 2020;36(3):187–190.
11. Claxton K, Longo R, Longworth L, McCabe C, Wailoo A. *The Value of Innovation*. London: National Institute for Health and Care Excellence (NICE); May 22, 2009.
12. Lakdawalla DN, Doshi JA, Garrison Jr LP, Phelps CE, Basu A, Danzon PM. Defining elements of value in health care - a health economics approach: an ISPOR special task force Report [3]. *Value Health.* 2018;21(2):131–139.
13. Angelis A, Lange A, Kanavos P. Using health technology assessment to assess the value of new medicines: results of a systematic review and expert consultation across eight European countries. *Eur J Health Econ.* 2018;19(1):123–152.
14. Paris V, Belloni A. *Value in Pharmaceutical Pricing*. Paris, France: Organization for Economic Co-operation and Development (OECD); 2013.
15. Paris V, Belloni A. Value in pharmaceutical pricing. Country Profiles: Australia. Organization for Economic Co-operation and Development (OECD). <https://www.oecd.org/els/health-systems/Value-in-Pharmaceutical-Pricing-Australia.pdf>. Accessed August 29, 2019.
16. Australian Government Department of Health. Guidelines for preparing a submission to the pharmaceutical benefits advisory committee. Version 5.0. <https://pbac.pbs.gov.au/>. Accessed August 28, 2019.
17. ZIN. Cost-Effectiveness in Practice. Zorginstituut Nederland; 2015. Available at: <https://english.zorginstituutnederland.nl/binaries/zinl-eng/documents/reports/2015/06/16/cost-effectiveness-in-practice/Cost-effectiveness+in+practice.pdf>. Accessed October 10, 2019.
18. ZIN. Guideline for economic evaluations in healthcare. Zorginstituut Nederland; 2016. Available at: <https://english.zorginstituutnederland.nl/binaries/zinl-eng/documents/reports/2016/06/16/guideline-for-economic-evaluations-in-healthcare/Guideline+for+economic+evaluations+in+healthcare.pdf>. Accessed October 10, 2019.
19. Delwel GO. *Guidance for Outcomes Research for the assessment of the cost-effectiveness of in-patient medicines*. Diemen, the Netherlands: Healthcare Insurance Board; 2008.
20. Pontén J, Rönnholm G. *PPRI Pharma profile Sweden 2017*. Stockholm: the Dental and Pharmaceutical Benefits Agency; 2017.
21. NoMa. Guidelines for the submission of documentation for single technology assessment (STA) of pharmaceuticals. Norwegian Medicines Agency; 2018. Available at: <https://legemiddelverket.no/Documents/English/Public%20funding%20and%20pricing/Documentation%20for%20STA/Guidelines%20151018.pdf>. Accessed December 12, 2019.
22. NoMA. PPRI Pharma profile: Norway. <https://ppri.goeg.at/sites/ppri.goeg.at/files/inline-files/PPRI%20Norway%202018.pdf>. Published 2018. Accessed December 13, 2019.
23. National Institute for Health and Care Excellence (NICE). *Guide to the methods of technology appraisal 2013*. London, UK: National Institute for Health and Care Excellence; 2013.
24. National Institute for Health and Care Excellence (NICE). The principles that guide the development of NICE guidance and standards. <https://www.nice.org.uk/Media/Default/About/Who-we-are/NICE-principles-consultation-2018.pdf>. Accessed December 13, 2019.
25. National Institute for Health and Care Excellence (NICE). Interim process and methods of the highly specialised technologies programme updated to reflect 2017 changes. Accessed March 8, 2021.
26. Who we are. Our principles. NICE. <https://www.nice.org.uk/about/who-we-are/our-principles>. Accessed February 27, 2021.
27. Charlton V, Rid A. Innovation as a value in healthcare priority-setting: the UK experience. *Soc Justice Res.* 2019;32(2):208–238.
28. Cleemput I, Neyt M, Van de Sande S, Thiry N. *Belgian Guidelines for Economic Evaluations and Budget Impact Analyses. Health Technology Assessment (HTA)*, 2nd ed. Brussels, Belgium: The Belgian Health Care Knowledge Centre (KCE); 2012.
29. Cleemput I, Van Wilder P, Vrijens F, Huybrechts M, Ramaekers D. *Guidelines for pharmacoeconomic evaluations in Belgium. Health technology assessment (HTA)*. Brussels, Belgium: The Belgian Health Care Knowledge Centre (KCE); 2008.
30. KCE. *Threshold values for cost-effectiveness in health care*. Brussels, Belgium: The Belgian Health Care Knowledge Centre; 2008.
31. HAS. Évaluation Des Médicaments - Doctrine de La Commission de La Transparence - principes d'évaluation de la CT relatifs aux médicaments en vue de leur accès au remboursement. https://www.has-sante.fr/upload/docs/application/pdf/2021-03/doctrine_ct.pdf. Accessed March 8, 2021.
32. Toumi M, Rémuzat C, El Hammi E, et al. Current process and future path for health economic assessment of pharmaceuticals in France. *J Mark Access Health Policy.* 2015;3. <https://doi.org/10.3402/jmahp.v3.27902>.
33. HAS. Choices in Methods for Economic Evaluation. https://www.has-sante.fr/upload/docs/application/pdf/2012-10/choices_in_methods_for_economic_evaluation.pdf. Accessed February 20, 2021.
34. IQWiG. Allgemeine Methoden Version 6.0. https://www.iqwig.de/methoden/allgemeine-methoden_version-6-0.pdf. Accessed February 20, 2021.
35. C2H. *Guideline for Preparing Cost-Effectiveness Evaluation to the Central Social Insurance Medical Council*. Center for Outcomes Research and Economic Evaluation for Health, National Institute of Public Health C2H; 2019.
36. Medical Economics Division, Health Insurance Bureau, Ministry of Health, Labour and Welfare (MHLW). Full scale introduction of cost-effectiveness evaluations in Japan, overview (2/20/2019). https://c2h.niph.go.jp/tools/system/overview_en.pdf. Accessed December 13, 2019.
37. Shirowai T, Fukuda T, Ikeda S, Takura T. New decision-making processes for the pricing of health technologies in Japan: the FY 2016/2017 pilot phase for the introduction of economic evaluations. *Health Policy.* 2017;121(8):836–841.
38. Shirowai T. Cost-effectiveness evaluation for pricing medicines and devices: a new value-based price adjustment system in Japan. *Int J Technol Assess Health Care.* 2020;36(3):270–276.
39. Shibata S, Uemura R, Suzuki T. Factors that affect the acquisition of reward premiums for promotion of innovative drug discovery in Japan. *Ther Innov Regul Sci.* 2016;50(1):56–65.
40. AIFA. Criteri per La Valutazione Dell'innovatività. https://www.aifa.gov.it/documents/20142/241044/Allegato_1_1.pdf/66558a13-543c-9643-e67b-85be01547465#:~:text=Potranno%20essere%20considerati%20innovativi%20i,qualit%C3%A0%20delle%20prove%20E2%80%9CAIta%E2%80%9D. Accessed February 19, 2021.
41. Prada M, Rossi L, Mantovani M. Time to reimbursement and negotiation condition in Italy for drugs approved by the European Medicines Agency during the period 2014–2019. *Aboutopen.* 2020;7(1):89–94.
42. Villa F, Tutone M, Altamura G, et al. Determinants of price negotiations for new drugs. The experience of the Italian Medicines Agency. *Health Policy.* 2019;123(6):595–600.
43. Adami S, Ciampalini S, Dell'Aera M, et al. Defining innovations of therapeutic interventions: a position paper by the Italian Society of Hospital Pharmacists. *Int J Clin Pharm.* 2012;34(2):259–262.
44. CADTH. Guidelines for the Economic Evaluation of Health Technologies: Canada. <https://cadth.ca/about-cadth/how-we-do-it/methods-and-guidelines/guidelines-for-the-economic-evaluation-of-health-technologies-canada>. Accessed December 5, 2019.
45. Paris V, Belloni A. Value in pharmaceutical pricing. Country Profiles: Canada. Organization for Economic Co-operation and Development (OECD). <https://www.oecd.org/els/health-systems/Value-in-Pharmaceutical-Pricing-Canada.pdf>. Accessed December 19, 2019.
46. About the PMPRB. Patented Medicine Prices Review Board Canada. <http://pmprb-cepmb.gc.ca>. Accessed December 5, 2019.
47. Stiller I, van Witteloostuijn A, Cambré B. Do current radical innovation measures actually measure radical drug innovation? *Scientometrics.* 2021;126(2):1049–1078.
48. Morgan S, Lopert R, Greyson D. Toward a definition of pharmaceutical innovation. *Open Med.* 2008;2(1):e4–e7.
49. Aronson JK. Something new every day: defining innovation and innovativeness in drug therapy. *J Ambul Care Manage.* 2008;31(1):65–68.
50. Kennedy I. Appraising the value of innovation and other benefits. A short study for NICE. <https://www.nice.org.uk/Media/Default/About/what-we-do/Research-and-development/Kennedy-study-final-report.pdf>. Accessed December 13, 2019.
51. Jena AB, Philipson T. Cost-effectiveness as a price control. *Health Aff (Millwood).* 2007;26(3):696–703.
52. de Solà-Morales O, Cunningham D, Flume M, Overton PM, Shalet N, Capri S. Defining innovation with respect to new medicines: a systematic review from a payer perspective. *Int J Technol Assess Health Care.* 2018;34(3):224–240.
53. Bryan S, Lee H, Mitton C. 'Innovation' in health care coverage decisions: all talk and no substance? *J Health Serv Res Policy.* 2013;18(1):57–60.
54. Jena AB, Calfee JE, Mansley EC, Philipson TJ. "Me-too" innovation in pharmaceutical markets. *Forum Health Econ Policy.* 2009;12(1):5.
55. Régnier S. What is the value of 'me-too' drugs? *Health Care Manag Sci.* 2013;16(4):300–313.
56. Jena AB, Neves L, Burkholder R. Do value frameworks fully capture the value of innovation? <https://www.healthaffairs.org/doi/10.1377/hblog20180409.228386/full>. Accessed August 29, 2019.
57. Aronson JK, Ferner RE, Hughes DA. Defining rewardable innovation in drug therapy. *Nat Rev Drug Discov.* 2012;11(4):253–254.
58. Sweeney N, Goss TF. The value of innovation in oncology: Recognizing emerging benefits over time. Boston Healthcare White Paper. Available at: https://www.phrma.org/-/media/Project/PhRMA/PhRMA-Org/PhRMA-Org/PDF/A-C/bha_value_of_cancer_innovation-whitepaper.pdf; 2015. Accessed August 11, 2021.

59. Pekarsky B. Should financial incentives be used to differentially reward 'me-too' and innovative drugs? *Pharmacoeconomics*. 2010;28(1):1–17.
60. Cueni TB. Can Europe afford innovation? *Eurohealth*. 2008;14(2):8–10.
61. Morgan SG, Bassett KL, Wright JM, et al. "Breakthrough" drugs and growth in expenditure on prescription drugs in Canada. *BMJ*. 2005;331(7520):815–816.
62. Garrison Jr LP, Kamal-Bahl S, Towse A. Toward a broader concept of value: identifying and defining elements for an expanded cost-effectiveness analysis. *Value Health*. 2017;20(2):213–216.
63. Ferner RE, Hughes DA, Aronson JK. NICE and new: appraising innovation. *BMJ*. 2010;340:b5493.
64. Tutone M, Villa F, Addis A, Trotta F, Tafuri G. How do drug regulatory bodies deal with potential innovative therapies? *Ther Innov Regul Sci*. 2020;54(1):195–199.
65. Riegel B, Knafelz G. Electronically monitored medication adherence predicts hospitalization in heart failure patients. *Patient Prefer Adherence*. 2013;8:1–13.
66. Roebuck MC, Liberman JN, Gemmill-Toyama M, Brennan TA. Medication adherence leads to lower health care use and costs despite increased drug spending. *Health Aff (Millwood)*. 2011;30(1):91–99.
67. Sokol MC, McGuigan KA, Verbrugge RR, Epstein RS. Impact of medication adherence on hospitalization risk and healthcare cost. *Med Care*. 2005;43(6):521–530.
68. Sabaté E, World Health Organization. Adherence to Long-Term Therapies: Evidence for Action. https://www.who.int/chp/knowledge/publications/adherence_full_report.pdf. Accessed November 5, 2019.
69. Sussex J, Towse A, Devlin N. Operationalizing value-based pricing of medicines: a taxonomy of approaches. *Pharmacoeconomics*. 2013;31(1):1–10.
70. Brazier J, Tsuchiya A. Improving cross-sector comparisons: going beyond the health-related QALY. *Appl Health Econ Health Policy*. 2015;13(6):557–565.