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Economic Evaluation

Do Cost-Effectiveness Analyses Account for Drug Genericization? A Literature Review and Assessment of Implications

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ABSTRACT

Objectives: We investigated how health technology assessment (HTA) organizations around the world have handled drug genericization (an allowance for future generic drug entry and subsequent drug price declines) in their guidelines for cost-effectiveness analyses (CEAs). We also analyzed a large sample of published CEAs to examine prevailing practices in the field.

Methods: We reviewed 43 HTA guidelines to determine whether and how they addressed drug genericization in their CEAs. We also selected a sample of 270 US-based CEAs from the Tufts Medical Center's CEA Registry, restricting the sample to studies on pharmaceuticals published from 1991 to 2019 and to analyses taking a lifetime time horizon. We determined whether each CEA examined genericization (and if so, whether in base case or sensitivity analyses), and how inclusion of genericization influenced the estimated incremental cost-effectiveness ratios.

Results: Fourteen (33%) of the 43 HTA guidelines mention genericization for CEAs and 4 (9%) recommend that base case analyses include assumptions about future drug price changes due to genericization. Most published CEAs (95%) do not include assumptions about future generic prices for intervention drugs. Only 2% include such assumptions about comparator drugs. Most studies (72%) conduct sensitivity analyses on drug prices unrelated to genericization.

Conclusions: The omission of assumptions about genericization means that CEAs may misrepresent the long run opportunity costs for drugs. The field needs clearer guidance for when CEAs should account for genericization, and for the inclusion of other price dynamics that might influence a drug's cost-effectiveness.

Keywords: cost-effectiveness analysis, drug pricing, generics, health technology assessment, patents.

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Introduction

Health economists have debated whether and how to incorporate into cost-effectiveness analyses (CEAs) an allowance for future generic drug entry and subsequent drug price declines after a brand-name drug's patent or exclusivity period expires. Omitting assumptions about drug genericization seems incongruous with consensus recommendations that CEAs should take a societal perspective and thus reflect the full cost and health consequences of alternative interventions or strategies.[1–3] As Shih et al[4] observed in 2005, "Incorporating generic drug entry into pharmacoeconomic models will yield more accurate projections of the incremental cost-effectiveness ratio and lead to better decision making." The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Drug Cost Task Force in 2010 concurred, noting " if a 25-year model is prepared, it should reflect the expected market realities of price changes, if any, during the patent-protected period and the impact of generic entry and its related price erosion."[5] The Second Panel on Cost-Effectiveness in Health and Medicine in 2017 also agreed, stating that "Anticipating price changes that may occur with the loss of patent in the future should be accounted for in the analysis."[1]

Although the occasional CEA has included assumptions about genericization and other pricing dynamics,[6–8] most seem to exclude such scenarios. In 2008, Hoyle[9] reported no guidance in the literature about what practitioners should assume regarding future drug prices in economic evaluations. Moreover, Hoyle's review of 12 CEAs published in *BMJ* and *Pharmacoeconomics* found no discussion of assumptions for future drug prices; instead, the author noted, the analyses had simply assumed that the real, inflation-adjusted price of any given drug would remain constant over time.[9] Some health technology assessment (HTA) bodies, such as the Institute for Clinical and Economic Review (ICER), have chosen to omit genericization assumptions in their CEAs.[10]

Although a comprehensive treatment of all avenues of future price dynamics, including how current pricing may affect the development of long-term drug innovation, and their implications for CEA is needed, in this article, we focus on price changes due to future generic entry. Failure to consider eventual genericization—for a brand-name drug under investigation and, if relevant, its drug comparator—could distort results of CEAs by misrepresenting total drug costs and not reflecting real-world conditions.[8] The problem may be particularly acute in the American healthcare setting, in which generics comprise 90% of all prescriptions,[11,12]

Table 1. Overview of genericization in HTA guidelines.

World Bank geographic classification	Number of HTA guidelines*	Number (percentage) of HTA guidelines including genericization	Countries with HTA guidelines including genericization	Countries with HTA guidelines excluding genericization
Europe and Central Asia	22	7 (32)	Belgium,[17] England,[26*] France,[28] Germany,[29] Ireland,[32] Norway,[41] Scotland,[44] Wales[26*]	Austria,[15] Croatia,[22] Czech Republic,[23] Denmark,[24] Estonia,[16*] Finland,[31] Hungary,[30] Italy,[34] Latvia,[16*] Lithuania,[16*] The Netherlands,[39] Poland,[42] Portugal,[43] Slovak Republic,[46] Slovenia,[47] Spain,[50] Sweden[51]
East Asia and Pacific	9	4 (44)	Japan,[35] New Zealand,[40] South Korea,[48] Thailand[53]	Australia,[14] Indonesia,[31] Malaysia,[36] Singapore,[45] Taiwan[52]
Latin America and Caribbean	5	0 (0)		Argentina,[37*] Brazil,[37*] Chile,[19] Colombia,[20] Cuba,[21] Mexico,[38] Paraguay,[37*] Uruguay[37*]
North America	4	3 (75)	United States[1,2,54]	Canada[18]
Middle East and North Africa	2	0 (0)		Egypt,[25] Israel[34]
Sub-Saharan Africa	1	0 (0)		South Africa[48]
Total	43	14 (33)		

HTA indicates health technology assessment.
*Note that some guidelines encompass more than one country. For example, the "Baltic guideline for economic evaluation of pharmaceuticals" includes Latvia, Lithuania, and Estonia; the National Institute for Health and Care Excellence's "Guide to the methods of technology appraisal 2013" includes England and Wales; and Argentina, Brazil, Paraguay, and Uruguay share a "Guide for Economic Evaluation Studies of Health Technologies." Additionally, the United States, lacking a centralized health technology assessment organization, is represented by 3 guidelines or recommendations from private initiatives—from the Institute for Clinical and Economic Review, the International Society for Pharmacoeconomics and Outcomes Research, and the Second Panel on Cost-Effectiveness in Health and Medicine.

although the issue is an international one (eg, generics comprise 80% of prescriptions in Germany, 47% in Spain, and 30% in France).[13]

We investigated genericization assumptions in CEAs by providing an updated and expanded review of how HTA organizations worldwide have handled the issue in their own guidelines. We also analyzed a large, updated sample of published CEAs to examine prevailing practices in the field.

Methods

HTA Guidelines

We reviewed 43 HTA guidelines to determine how they addressed assumptions regarding drug genericization in CEAs (see Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.06.014).[1,2,14-54] The sample draws upon our previous work reviewing HTA guidelines on other aspects of CEA[55] and is based on an updated search of the literature (as of September 2020) and a review of websites of HTA organizations and the ISPOR inventory of "Pharmacoeconomic Guidelines Around the World."[56] For completeness, we included 3 notable US HTA bodies or guidelines (from ICER, the ISPOR Drug Cost Task Force, and the Second Panel).[12,54] Although these practices or guidelines are not produced by government entities, they are well-known and commonly cited references for CEAs in the United States.

The 43 guidelines in our final sample represent 47 countries. In 3 cases (the MERCOSUR nations of Argentina, Brazil, Paraguay, and Uruguay[57]; the Baltic states of Latvia, Estonia, and Lithuania[58]; and the United Kingdom nations of England and Wales[59]), multiple countries share a single guideline. We characterized whether and how each guideline considered genericization for CEAs. For example, we classified recommendations according to whether they called for drug prices (for target interventions and the comparator, if relevant) to reflect pricing for generic drugs currently on the market, whether they advised the inclusion of assumptions about price declines after a drug's patent expiry, and whether they recommended consideration of genericization in base-case analyses or only in sensitivity analyses (Table 1). We also collected information about a guideline's recommended source for assumptions about drug prices (eg, wholesale acquisition cost or a measure of net price).

CEA Registry

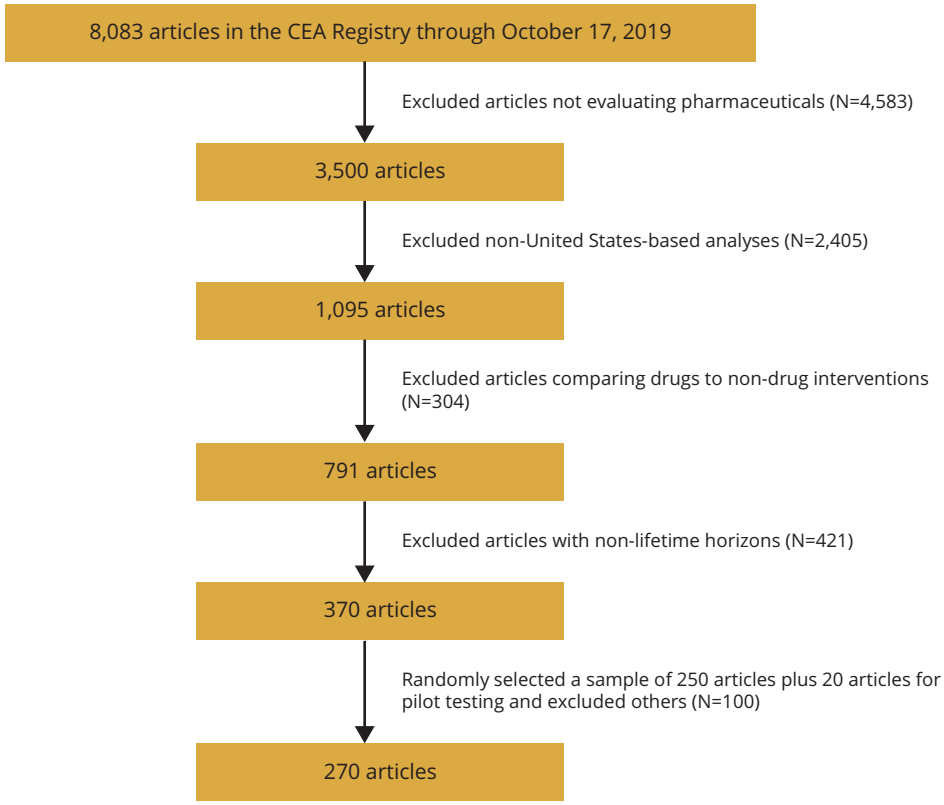
The CEA registry

To investigate customary practices among health economists, we analyzed data from the Tufts Medical Center CEA Registry, a regularly updated database of more than 8000 published, English-language cost-utility analyses.[60] At the time of our analysis, the Registry contained data on CEAs published through mid-October 2019.

Creating a sample

Given our focus on drug genericization, we restricted our sample to CEAs pertaining to drugs or biologics and to those in which the comparator was also a drug or biologic. To restrict the analysis to one jurisdiction with a single set of laws, we further limited the sample to studies conducted for the United States. We also selected studies that included a lifetime time horizon for base-case analyses, given that these analyses would most likely confront analysts with decisions about how to incorporate a drug's genericization. The various restrictions left a sample of 370 CEAs (Fig. 1). From these, we randomly selected 270 analyses for detailed analysis (mentioned later).

Figure 1. Selecting the sample from the CEA registry.



Developing a data collection form

We created a data collection form to capture salient information. Similar to our methods for analyzing HTA guidelines, we collected information on a number of factors related to genericization, including whether genericization was examined at all and, if so, whether in base-case or sensitivity analyses. We also recorded the price changes assumed after a drug's genericization and how the change influenced the resultant incremental cost-effectiveness ratios.

Two researchers pilot tested the form on 20 randomly selected CEAs from our sample and made minor changes to the form based on the results. Appendix 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.06.014 includes the final form. Two researchers then abstracted data on a full random sample of 250 CEAs, which together with the 20 pilot articles we retained yielded a final sample of 270 articles. The researchers abstracted data independently and subsequently met to resolve any differences. We linked the data gathered from each article as part of this review to data on each article already residing in the CEA Registry.

Results

Analysis of HTA Guidelines

Of the 43 HTA guidelines we reviewed, 14 (33%) mention genericization for CEAs (Table 1). Roughly one-third of the guidelines for countries in the Europe and Central Asia region do so, including those in Belgium,[17] England,[26] France,[28] Germany,[29] Ireland,[32] Norway,[41] Scotland,[44] and Wales,[26] whereas some in countries with long HTA traditions, such as Denmark,[24] The Netherlands,[39] Spain,[50] and Sweden,[51] do not. Some HTA bodies in the East Asia and Pacific region (eg, in Japan,[35] New Zealand,[40] South Korea,[49] Thailand[53]) provide at least some guidance on genericization, whereas some in countries with considerable HTA experience (eg, Australia[14]) fail to do so. In the United States, guidance from the Second Panel[1] and ISPOR's Drug Price Task Force[54] mention genericization.

Four of the 43 HTA guidelines (9%)—from New Zealand,[40] Norway,[41] and the United States (ISPOR,[54] Second Panel[1])—recommend that base-case analyses include assumptions about future drug price changes due to genericization (Table 2). Table 2 further classifies HTA guidelines based on whether they include recommendations for base-case or sensitivity analysis and on whether they recommend using generic prices for brand-name drugs before their genericization (if a generic substitute in the therapeutic class is available), after they go generic, or both. In 9 instances (21%), HTA guidelines recommend simply that base-case analyses use current within-country generic drug prices (if generics are available). HTA guidelines in Belgium specify that analyses should use the "lowest price product…even if not frequently used in Belgium."[17] In contrast, South Korea's Health Insurance Review and Assessment Service recommends against using generic drug prices owing to a distrust of drug quality.[49] In 7 cases (16%) (eg, in France[28] and Germany[29]), HTA guidelines recommend that in sensitivity analyses analysts should consider the role of generics (whether for future generics [6 guidelines] or currently available generics [2 guidelines]).

Analysis of the Cost-Effectiveness Literature

Table 3 describes the sample of studies drawn from the CEA Registry. Most of the analyses had academically-affiliated authors and used a healthcare payer perspective. Leading funding sources

Table 2. Analysis of countries' HTA guidance on drug genericization by type of recommendation.

Guidance pertains to base-case or sensitivity analysis	Use generic prices if there is currently a generic substitute for the brand-name drug	Make assumptions regarding future price declines after genericization
Base-case analysis	Belgium[17] England and Wales[26] Germany[29] Ireland[32] Japan[35] South Korea[49]* Thailand[53] United States (ICER)[2] United States (ISPOR)[54]	New Zealand[40] Norway[41] United States (ISPOR)[54] United States (Second Panel)[1]
Sensitivity analysis	Scotland[44] Thailand[53]	France[28] Germany[29] New Zealand[40] Norway[41] Scotland[44] United States (ISPOR)[1]

Note: Table excludes the 29 guidelines that make no recommendations regarding generics.
HTA indicates health technology assessment; ICER, Institute for Clinical and Economic Review; ISPOR, International Society for Pharmacoeconomics and Outcomes Research.
*Recommends against use of generics in baseline analysis due to concerns over quality.

included the pharmaceutical industry (40%) and government (31%).

Most published (95%) CEAs did not include assumptions about future genericization (Table 4). Only 5% included assumptions about future generic prices for intervention drugs and even fewer (2%) included such assumptions about comparator drugs. Nine studies presented results with and without genericization assumptions for the intervention drug. On average, inclusion of genericization decreased ICERs by 43% (range 16%-77%). In 2 cases, inclusion of genericization caused the ICER to move from above to below the commonly used $100 000/quality-adjusted life-year benchmark. In addition, most studies (72%) conducted sensitivity analyses on the drug's price without specifically targeting genericization. The percentage of studies considering future genericization was roughly the same for analyses funded by the drug industry versus those funded by nondrug industry sources (6% vs 4%) (Table 5).

Discussion

Generics have become ubiquitous in American medicine cabinets, their supply and use encouraged by a variety of laws. From angiotensin-converting enzyme inhibitors (for high blood pressure) to statins (hyperlipidemia) to antiretroviral agents (HIV), generic drugs often provide health benefits at low cost long after the patent expiration of the brand-name products they replace.[13] One study reported that Americans save more than $300 billion annually by receiving drugs that have gone generic and sell for a lower price than when they were branded.[61]

Still, most HTA guidelines for economic evaluation do not mention drug genericization, and only a few recommend that base-case analyses include assumptions about future drug price changes. Moreover, 95% of published United States-based pharmaceutical CEAs with lifetime time horizons make no assumptions about future drug price reductions after a drug's loss of exclusivity. These results are not entirely surprising, because they build on earlier, smaller studies that reached similar conclusions.[4,7,9] Nonetheless, our confirmation of these trends in larger samples, along with their persistence, is notable.

The omission of assumptions about genericization may have important implications for CEAs. It suggests that analyses may be misrepresenting the opportunity costs of drugs in the long run. In many cases, this could mean that new treatments will appear less cost-effective than they actually are, although in cases in which a comparator drug loses exclusivity before the new treatment, failure to consider genericization may make new treatments seem more cost-effective than they are.[4,62] The inclusion of genericization assumptions could alter intervention rankings based on cost-effectiveness and could even change payer decisions in countries that use cost-effectiveness benchmarks to inform coverage and reimbursement.[8,9,62] For example, after considering potential price reductions after genericization, the conclusions of a CEA of fingolimod versus intramuscular interferon beta-1a in relapsing-remitting multiple sclerosis changed from cost-effective at $118 434 per quality-adjusted life-year gained to cost-saving (ie, fingolimod improved health and reduced costs).[8] The impact on cost-effectiveness ratios should be greater for drugs that experience larger price reductions after patent expiry, for drugs with high costs relative to total health costs, for drugs that lose exclusivity earlier, and for drugs that patients take over longer time periods—for example, for chronic conditions, such as multiple sclerosis.[8,9,62] Although most studies conduct sensitivity analyses on drug prices, those adjustments tend to reflect simple increases or decreases of launch prices and do not capture the timing and nature of actual life-cycle pricing dynamics.

The lack of attention to genericization is noteworthy given that patents and exclusivity lie at the heart of the pharmaceutical enterprise. Omitting future price reductions seems inconsistent with the intent of CEAs, which is to reflect future costs and consequences as realistically as possible.

Why then does the practice persist? One reason may be uncertainty regarding the timing of generic drug entry and the degree to which prices actually fall after the patent or exclusivity period ends. For example, ICER has argued that it "does not as a rule consider such 'dynamic pricing' approaches in its modeling unless there is known timing for patent expiry and certainty around expected changes in price."[10] ICER has further noted that, as a practical matter, it is difficult to predict the timing of generic drug entry because drug companies often engage in tactics to

Table 3. Articles sampled from the Cost-Effectiveness Analysis (CEA) Registry.

Item	Description		Percent
Number of articles selected		270	
Year published	Range	1991-2018	
Type of prevention	Tertiary	211	78%
	Secondary	42	16%
	Primary	37	14%
Author affiliation*	University/academic	240	89%
	Pharmaceutical/medical device industry	95	35%
	Healthcare organization	84	31%
	Contract research organization/consultant	81	30%
	Government organization	39	14%
	Other	7	3%
Study sponsorship/funding*	Pharmaceutical company	109	40%
	Government	84	31%
	Not stated/could not be determined	44	16%
	Other	21	8%
	None	21	8%
	Foundation	16	6%
	Healthcare organization	13	5%
	Professional membership organization	3	1%
Perspective (as assessed by CEA Registry readers)*	Healthcare payer	213	79%
	Societal	34	13%
	Not stated/could not be determined	4	2%
	Limited societal†	13	5%
	Healthcare sector	3	1%
	Other	3	1%
Discount rates			
Costs			
	3%	257	95%
	5%	8	3%
QALYs			
	3%	256	95%
	5%	7	3%

Note. Articles included in the analysis focused on pharmaceutical interventions and comparators, used a lifetime time horizon, and were conducted from a US perspective.
QALY indicates quality-adjusted life-year.
*Categories not mutually exclusive.
†The "limited societal" perspective accounts for any costs not unique or specific to the healthcare sector, such as unpaid caregiver time, productivity impacts, or patient time. It does not include spillover costs to nonhealthcare sectors, such as education.

delay patent expiration and that, even after market exclusivity ends, the timing of generic introductions is uncertain. Moreover, ICER has observed that although loss of market exclusivity can substantially reduce prices, it might not do so for drugs treating diseases with relatively small populations, such as cystic fibrosis,[10] because smaller markets may attract less generic competition.[63]

Nevertheless, making assumptions and using sensitivity analysis to assess the contribution of each to overall uncertainty are a hallmark of economic evaluation and recommended in leading consensus guidelines.[1] By apparently prohibiting any assumptions about price declines accompanying a drug's loss of patent protection,[63] ICER effectively assumes that prices will remain at their current brand-name levels even after a drug goes generic, which would misrepresent a drug's long-term cost to society. Such an omission is akin to assessing the cost-effectiveness of a finite mortgage yet assuming that the payments continue indefinitely, such as rent.[13] At the very least, analysts could use sensitivity analyses to examine how results change with plausible assumptions about genericization.

Another factor could be a concern that incorporating genericization will be used to justify what some may consider excessive brand-name drug prices (although even most drug industry-funded CEAs have conformed to the convention of omitting genericization assumptions). An analyst might pretend that a drug's price will never decrease because doing so prevents justification of a high price during the drug's branded period (ie,

Table 4. Inclusion of genericization assumptions in published cost-effectiveness analyses (n = 270).

Description of study assumptions	Articles (n = 270)
How (and whether) the study considered generic drug prices	
Used current generic price for intervention drug if a generic is available	23 (9%)
Used current generic price for comparator drug if a generic is available	15 (6%)
Included assumptions about future generic pricing for intervention drug	13 (5%)
Included assumptions about future generic pricing for comparator drug	4 (2%)
Authors explicitly stated they chose not to consider generic pricing	0 (0%)
Other	8 (4%)
Study did not mention generics	218 (81%)
Included assumptions in base-case analysis about drug price *changes* before patent expiry	7(3%)
Conducted sensitivity analysis on drug prices without mentioning genericization	195 (72%)
Included assumptions about future generic pricing of *intervention* drug in:*	
Baseline analysis	4 (2%)
Sensitivity analysis	11 (4%)
Inclusion of assumptions about future generic pricing made incremental analyses:	
More cost-effective	3 (2%)
Less cost-effective†	2 (1%)
Did not change incremental analyses	1 (0.4%)
Study did not present analyses without genericization	7 (2%)
Assumption about time until loss of patent/exclusivity (years):	
Average	9.2 years
Range	1-25 years
Assumption about declines in drug price after genericization (% of branded price):	
Average	18.5%
Range	10-90%
Funding sources for articles including future genericization:	
Pharmaceutical/medical device company	6 (2%)
Government	3 (1%)
Healthcare organization	1 (<1%)
None	3 (1%)
Could not be determined	1 (<1%)
Source for assumptions on drug prices	
Wholesale acquisition cost	60 (22%)
Average wholesale price	50 (29%)
Average sales price	40 (15%)
Average wholesale price/wholesale acquisition cost‡	39 (14%)
Net price	21 (8%)
Retail price	11 (4%)
Federal Supply Schedule	8 (3%)
Other	31 (12%)

*Some articles included assumptions in the base-case analysis, and then varied those assumptions in the sensitivity analysis.
†Two articles included genericization assumptions for a drug that was included in both the comparator and treatment regimens.
‡Several studies cited a Red Book as the source of their costs, but did not specify whether they used wholesale acquisition costs or average wholesale prices.

the drug company should not get "credit" for the drug's eventual genericization and resulting savings).[63] The problem with this position is that making drugs appear to be more costly than they actually are in the long run can cause a misallocation of healthcare resources, possibly diverting resources to other less efficient healthcare interventions.[63] In other words, including potential price effects from future genericization of the new and comparator treatment (where applicable) would appropriately reflect how the welfare surplus, arising from the use of the new drug, will be shared between the producers and the consumers. Failing to do so

Table 5. Inclusion of future genericization assumption in published cost-effectiveness analyses by type of funding source.

Assumption type	Drug company-funded cost-effectiveness analysis	Funding provided by nondrug company source*	Total
Assumptions about genericization of intervention treatment (n = 13)	6 (6%)	7 (4%)	13
No assumptions about intervention genericization (n = 257)	103 (94%)	154 (96%)	257
Total	109	161	

*Other types of sponsorship included government, healthcare organization, foundation, or professional membership organization.

can erroneously increase or decrease the projected long-term producer surplus of the new drug over the control and thereby lead to a biased estimate of cost-effectiveness.

Importantly, including genericization does not mean that the drug price would be increased to the point where the drug manufacturer gets paid for all of the drug's societal benefits over the long term.[64] The cost-effectiveness of the drug (at its appropriately calculated price) should be considered against an external benchmark reflecting the marginal willingness to pay or opportunity costs. Society would pay the manufacturer for only a fraction of the drug's societal benefits in line with this assumed external benchmark. Appropriately anticipating price dynamics helps to set a starting price for the drug that allocates its "life-cycle" value properly between the manufacturer and the population.

Analyses may also omit genericization because of lingering debate and confusion about appropriate practices. For example, some might argue that even if assumptions about genericization and price changes can affect cost-effectiveness estimates, the key question is whether analyses should consider those changes in the first place and, if so, under what circumstances. A possible view is that analyses should omit genericization-related assumptions because the reimbursement of branded and generic drugs can be viewed as distinct decisions. From this perspective, analysts should conduct a first CEA that evaluates a drug at its launch price to inform decisions about reimbursement of the branded drug and a second CEA that evaluates the drug at its generic price to inform decisions about reimbursement of the off-patent drug.

This conceptualization incorrectly assumes that payers can separate decisions about reimbursing drugs at their brand-name and generic prices, choosing, if necessary, to reimburse for the drug only when it reaches generic status. Of course, if the drug company knows ahead of time that reimbursement will be forthcoming only after a drug reaches the end of its exclusivity period, it may choose not to develop the drug in the first place, thus eliminating the possibility that payers can get the drug at its generic price without having to first pay for it at its brand-name price.

Just as analysts model how a drug's effectiveness may vary over time, they should also model how resource use may vary over time, including the prices being paid in the future to acquire the treatment. More fundamentally, the division of the reimbursement question into 2 decisions—one for brand-name pricing and one for generic pricing—misses the key attribute that distinguishes drugs from other healthcare interventions, such as surgery or physical therapy. Brand-name drugs have transitorily high prices but benefits that continue after their prices decline. In contrast, the continued benefits of other interventions depend on continued payments that are unlikely to decrease.[13,63] Separating CEA into 2 decisions (the brand-name reimbursement decision and the generic pricing decision) is equivalent to analyzing a house purchase by treating it as 2 decisions—the first having to do with whether the house is worth its monthly cost before the mortgage is paid off and the second having to do with whether the house is worth its monthly cost after the mortgage is paid off.

Notably, for CEAs conducted using conventional methods, genericization will only matter when the current patient cohort would continue treatment long enough to eventually acquire the drug at a reduced, off-brand price. If, alternatively, treatment costs are all upfront, then genericization will not matter in these analyses. Although later patient cohorts access the same treatment at lower costs, a conventional CEA considers only the first cohort, which acquires the drug in the near term at higher, branded prices.

Nevertheless, an important question is whether CEA needs a broader methodology that accounts for downstream, generic pricing and, if so, whether this methodology should extend to all cases (or, eg, be excluded for one-time or short-term treatments). Importantly, because, later, lower generic prices "pay" for higher, initial brand-name prices, does it follow that society must use the generic product for an extended period and that the value benchmark for adopting a new replacement technology should be more stringent? Addressing this conflict depends on working out the role played by the current technology in incentivizing the development of replacement technologies. If the development of new replacement technologies depends on the current technology receiving reimbursement, should we "credit" the costs and benefits of next generation technologies to the current technology? If that is the case, does the current technology appear to be favorably cost-effective even if society does not acquire it at generic prices for an extended period?

There is a need for clearer guidance and more research on all of these matters. Following the recommendations of the Second Panel, analysts could conduct CEAs from both narrow and broader perspectives, where the broader perspective includes life-cycle pricing and other elements not captured under a healthcare sector perspective.[1] Policy makers could then see more clearly the difference in results under the 2 perspectives. The "enhanced" CEA should use the best information available to anticipate future price reductions after genericization because doing so best represents the drug's likely life-cycle costs. Such assumptions should apply to both the brand-name drug under investigation and its brand-name comparator drug if there is one in the analysis.

To the extent possible, assumptions on life-cycle pricing should rely on real-world experience—for example, by tailoring assumptions to a country's own experience with generics.[5,8,9,63,65] Numerous studies have shown that drug prices fall, sometimes precipitously, upon the entry of generics and that price declines are influenced by a variety of factors, including the attractiveness of the market, the complexity of the manufacturing process, the number of generic competitors, and whether the product is a small-molecule drug or a biologic.[65-68] For example, drug prices may not decline substantially until the third or fourth generic enters the market.[68]

The focus on genericization also begs a broader question about what other future price dynamics (including cost increases for nondrug health products and services) should be considered in CEAs and in what scenarios it is likely to make a difference. Genericization is only one mechanism by which drug prices change over time. Analyses could reflect the fact that net branded prices in the United States often increase substantially between a drug's launch and its eventual genericization, which will temper and could even reverse the impact of price declines after a drug's patent expiration (although other health costs, including those that may be offset by a new medication, also increase).[69-72]

Modeling scenarios should consider alternative plausible assumptions around the timing of patent/exclusivity loss and the proportion of patients switching to generics upon a drug's loss of exclusivity.[4,8,54] Analyses could also consider that drug companies sometimes extend the protection conferred by patents, for example, by delaying the entry of generics into the marketplace, thus retaining their monopolies and high prices.[63,66,67,73,74]

Predicting future events is, of course, a fraught exercise. The price of brand-name drugs may be constrained by competition, especially in drug classes with multiple agents. A generic drug such as atorvastatin might be used in new ways alongside other medications[75] (eg, the lifesaving utility of dexamethasone in treating COVID-19 was not contemplated by anyone considering the cost-effectiveness of that drug when it was branded as Decadron).[76] Even if a drug does go generic and its price falls, follow-on products may replace the original medication while

preserving and improving upon the properties of their predecessor.[63] Complicating matters, even if a new drug displaces an older drug, the original drug may have spurred the innovation, and hence, analysts might appropriately credit the original product in part for the new innovation's value—rather than simply assuming that its benefit stream fades as its use ebbs.[63]

Our study has a number of limitations, including its focus on the United States and on CEAs with a lifetime time horizon. By focusing on the United States, we aimed to control for intercountry variability in regulatory and market conditions surrounding the introduction and proliferation of generics. In addition, we restricted our analysis to CEAs that compared one drug with another drug (rather than studies that compared a drug with a device, procedure, or other intervention), and thus, we may be understating the impact of including assumptions about genericization. Finally, we assumed that genericization is relevant to all drugs in our sample, and as noted, there is debate on that question (ie, whether CEAs should exclude assumptions about genericization for one-time or short-term treatments, highly specialized therapies unlikely to go generic, or other special cases).

Trying to capture the value of future drug price changes is one of the most complex aspects of CEA. Clearer guidance for the field on appropriate methods for considering genericization and other factors that affect a drug's value would help, as would more guidance about what prices best reflect the true social marginal cost of a drug.[1,77,78] Pursuing such research and accounting for genericization will improve the utility of CEA for thinking at the societal level about a drug's far-reaching costs and benefits and about how paying for valuable drugs today incentivizes further efforts to create more such drugs, increasing the prospects for better drugs in the future.

Supplemental Materials

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