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Themed Section

The impact on cost-effectiveness of accounting for generic drug pricing: Four case studies

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ABSTRACT

Objectives: Guidance on the conduct of health technology assessments rarely recommends accounting for anticipated future price declines that can follow loss of marketing exclusivity. This article explores when it is appropriate to account for generic pricing and whether it can influence cost-effectiveness estimates.

Methods: This article presents 4 case studies. Case study 1 considers a hypothetical drug used by a first patient cohort at branded prices and by subsequent, "downstream" cohorts at generic prices. Case study 2 explores whether statin assessments should account for generic prices for downstream cohorts that gain access after the initial cohort. Case study 3 uses a simplified spreadsheet model to assess the impact of accounting for generic pricing for inclisiran, used when statins insufficiently reduce cholesterol. Case study 4 amends this model for a hypothetical, advanced, follow-on treatment displacing inclisiran.

Results: Assessments should include generic pricing even if the first cohort using a drug pays branded prices and only downstream cohorts pay generic prices (case study 1). Because eventual generic pricing for statins did not depend on decisions for downstream cohorts, assessing reimbursement for those cohorts could safely omit generic pricing (case study 2). For inclisiran (case study 3), including generic pricing notably improved estimated cost-effectiveness. Displacing inclisiran with an advanced therapy (case study 4) modestly affected estimated cost-effectiveness.

Conclusions: Although this analysis relies on simplified and hypothetical models, it demonstrates that accounting for generic pricing might substantially reduce estimated cost-effectiveness ratios. Doing so when warranted is crucial to improving health technology assessment validity.

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

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Introduction

Cost-effectiveness analysis (CEA) compares a health intervention's costs with its benefits. Cost depends on price, and for drugs, price can change substantially over time. A typical drug's life cycle can include a period after its introduction during which the drug's developer enjoys exclusive selling rights. As a "branded" drug without exact copies sold by other manufacturers, it can command high prices. Later, after the loss of exclusivity, the drug becomes a generic. If other manufacturers choose to sell copies, competition can drive the price down substantially.[1]

Nonetheless, these price dynamics rarely feature in drug CEAs, with only 5% incorporating generic pricing assumptions.[2] The reasons underlying these omissions are unclear, given that CEAs typically do not explain why they omit generic pricing. Indeed, there has been little debate. The Second Panel on Cost-Effectiveness in Health and Medicine devotes a single sentence to the issue (recommending on p. 220 that CEAs should account for anticipated future price changes).[3]

One reason for the common omission may be that CEA authors see their analyses as informing clinical decisions on a patient-by-patient basis. Because many drugs have a relatively short treatment duration, a potential price reduction many years in the future can seem irrelevant.

Omissions may also reflect uncertainty about future price changes, given that a drug's price may not follow the pattern described earlier. First, generic competition may be delayed because of slow regulatory approval, brand name manufacturers vigorously protect their patents (the "patent-thicket" problem),[4] or, for biologics, which are produced via biological processes, rather than more reliably copied chemical synthesis processes, developing a biosimilar may be impossible, or establishing interchangeability with the original drug may be difficult.[5] Second, competing manufacturers may choose not to enter a small market.[6] Finally, even with competition, prices may not fall because of high manufacturing costs.

This article presents 4 case studies to argue that CEAs should account for generic pricing. Case studies 1 (a hypothetical drug

used by a series of cohorts) and 2 (a retrospective look at statins to treat cardiovascular disease [CVD]) explore when assessments should account for generic pricing anticipated to come about only in the distant future. These case studies conclude that when near-term decisions affect the eventual availability of drugs at generic prices, assessments should account for that consequence.

Case study 3 (inclisiran, a proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitor for elevated cholesterol when statins alone are inadequate) investigates whether including generic pricing might materially affect cost-effectiveness estimates and finds that it does for a range of assumptions about the timing of eventual price declines, discount rates, and analysis time horizons. Case study 4 investigates whether this conclusion changes if a follow-on, branded drug (with initially elevated prices) eventually displaces inclisiran.

These case studies do not purport to project actual price patterns. Instead, they explore the appropriateness and potential importance of including generic pricing. The issue is important because fewer than 1 in 10 health technology assessment (HTA) guidelines recommend inclusion of generic pricing in the base case.[2] Finding that inclusion of generic pricing is appropriate and can materially influence CEA results has important implications for the conduct of HTAs.

Case Study Methods and Results

Case Study 1: Hypothetical Drug Used by a Series of Patient Cohorts

Case study 1 posits the introduction of drug used by its first cohort at branded prices and by subsequent, "downstream" cohorts at its generic price. This case study argues that an assessment of the decision to reimburse for the drug at its brand price for the first cohort should also account for the generic-priced acquisition of the drug for the downstream cohorts because the generic-priced acquisition is an incremental consequence of that initial reimbursement decision.

Figure 1 illustrates the argument. Here, a decision in the first period determines whether an initial cohort receives the drug at its branded price, designated C_B (square node at far left). If so (top branch emanating from the left-most node), then the drug is available to a second cohort in the second period at a generic cost designated C_G. A third cohort uses the drug at its generic price in the third period, and so on. Cohorts using the drug accrue health benefits designated Q. Finally, we discount costs and benefits in each period i by a factor of $\frac{1}{(1+r)^i}$, where r is the discount rate corresponding to one period.

Without reimbursement of the drug for the initial cohort (bottom branch emanating from the left-most node in Fig. 1), we incur no costs and accrue no benefits. The incremental cost-effectiveness ratio has a numerator equal to incremental costs of $C_B \times \frac{1}{(1+r)} + \sum_{i=2}^{n} C_G \times \frac{1}{(1+r)^i}$, where n is the number of periods in the analysis (ie, the analytic "time horizon"). The ratio's denominator is the incremental health benefit of $\sum_{i=1}^{n} Q \times \frac{1}{(1+r)^i}$. Importantly, the calculated cost-effectiveness ratio includes not only the drug acquisition cost for the first cohort during its branded period (the first term in the ratio's numerator) but also the drug acquisition cost for the downstream cohorts at the generic price (the summation that is the second term in the ratio's numerator).

Of course, this case study applies only if we anticipate loss of exclusivity and an eventual reduction in prices to accompany a drug's generic status. If we do not anticipate that prices will eventually fall, the distinction between branded prices and generic prices vanishes.

Even if we do anticipate price reductions to accompany generic status, a skeptic might argue that once a pharmaceutical company develops a drug, development represents a sunk cost—that is, a cost the company cannot recover—and that the drug cannot be "uninvented." Therefore, whether that drug sells at a high price that justifies its development costs is irrelevant to whether that same drug eventually goes generic. Indeed many medicines have failed to recoup their development costs and have nonetheless remained on the market because they generated at least some profit for the manufacturer and eventually went generic.[7] Figure 2 illustrates the decision problem if we assume that a drug's availability at generic prices does not depend on reimbursement at branded prices.

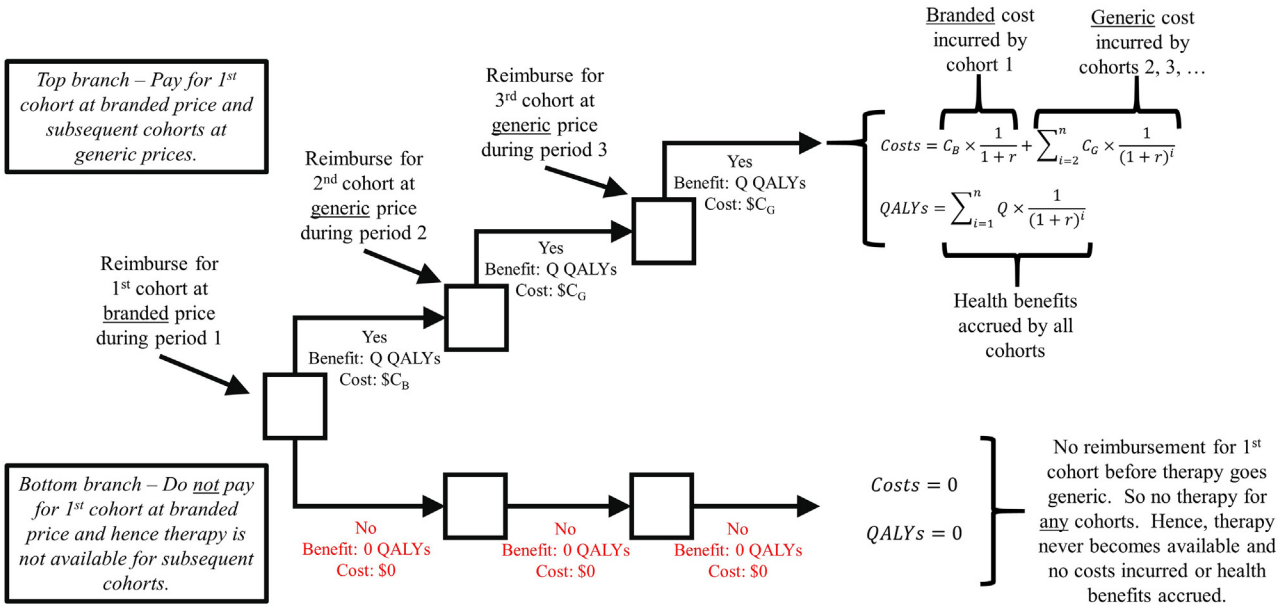
In this case, up front, branded price reimbursement does not influence a drug's downstream availability. Hence, this scenario suggests CEA should omit generic pricing because it appears in both "arms" of the decision tree from that second period onward in Figure 2. That is, generic pricing does not represent an incremental difference between the tree's 2 branches. Taking the difference between the costs in the 2 arms yields $\Delta Cost = C_B \frac{1}{1+r}$ (and $\Delta QALYs = Q \frac{1}{1+r}$). The corresponding cost-effectiveness ratio is $\frac{C_B}{Q}$, that is, the ratio of the branded price to the incremental quality-adjusted life-year (QALY) gain.

Although the Figure 2 scenario can make sense for 1 drug, it is unrealistic to assume that the private sector would repeatedly risk capital to develop drugs if payers typically refused reimbursement at branded prices and instead waited for the drugs to go generic before offering reimbursement. As the Congressional Budget Office (CBO) has noted, "Expectations about returns on R&D partly depend on expectations of prices that future drugs could command – which, in turn, partly depend on current drug prices and influences on those prices"[8] (page 12, Box 3). In turn, "Lower expected returns would probably mean fewer new drugs, because there would be less incentive for companies to spend on R&D."

CBO's analysis[9] draws on data from the Medicare Part D program for 2010 to 2018 and from research conducted by DiMassi et al.[10] That work considered the impact on innovation of the Lower Drug Costs Now Act, introduced by Representative Elijah Cummings in 2019. CBO assumed the legislation would reduce expected returns to industry by 15% to 25% for drugs with returns in the top quintile and that it would not affect returns for drugs in the remaining 4 quintiles (p. 17). Because drug discovery and development involves an extended duration, the impact on innovation emerges gradually. CBO projected that lower prices would reduce drug introductions by 0.5% during the first decade, by 5% during the second, and by 8% during the third. Although CBO does not analyze legislation imposing stricter price controls, it is reasonable to assume that substantially lower introductory prices for a broader range of drugs would have a greater impact on drug introductions and hence on the subsequent availability of drugs at lower, generic prices.

Strictly speaking, CBO does not claim that reimbursement for a particular drug at branded prices influences that drug's later availability at generic prices, but CBO does state that, in general, not paying for drugs at branded prices means that industry will not develop as many drugs in the first place. As a practical matter, we conclude that Figure 1 is more realistic than Figure 2 and hence that CEAs should assume that a drug's availability at generic prices depends on early reimbursement at branded prices. Importantly, as Figure 1 illustrates, inclusion of generic pricing is appropriate even when it accrues only to "downstream" cohorts.

Figure 1. Generic pricing follows only if branded prices are reimbursed.



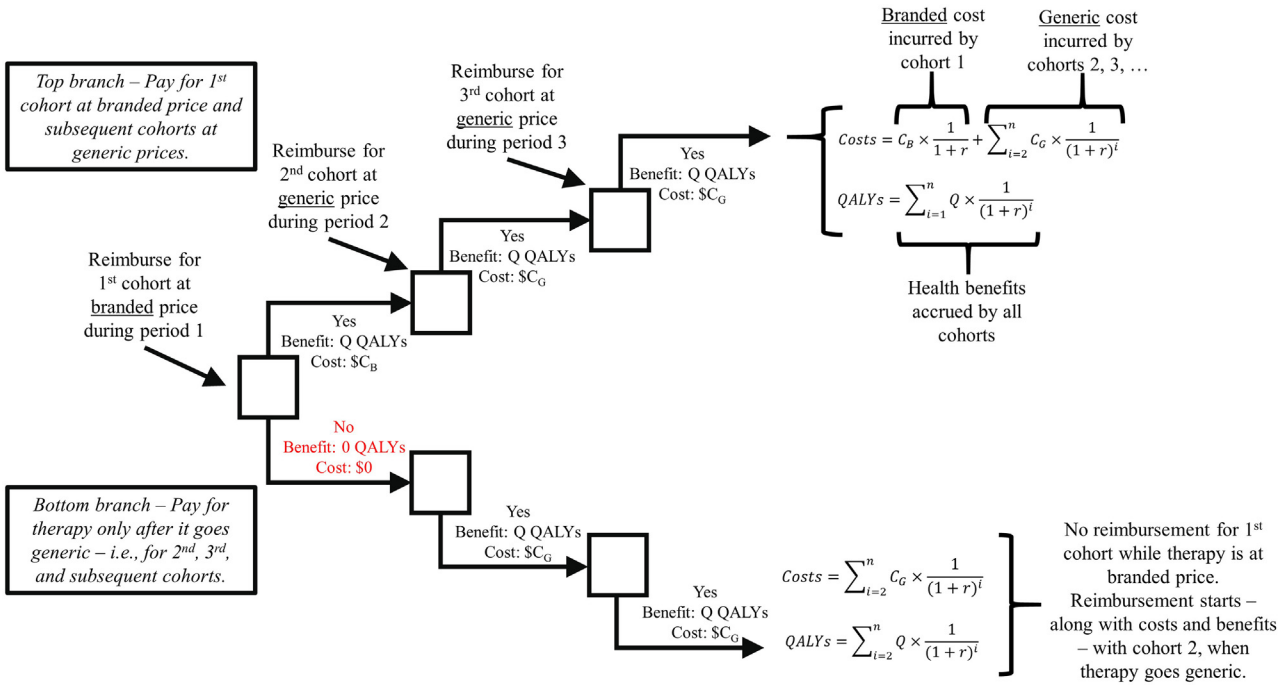
QALY indicates quality-adjusted life-year.

Case Study 2: Statins

Case study 2 looks at statins and investigates the dependence of eventual generic pricing on reimbursement at branded prices for the initial cohort of (high-risk) patients and, for later, lower-risk patient cohorts.

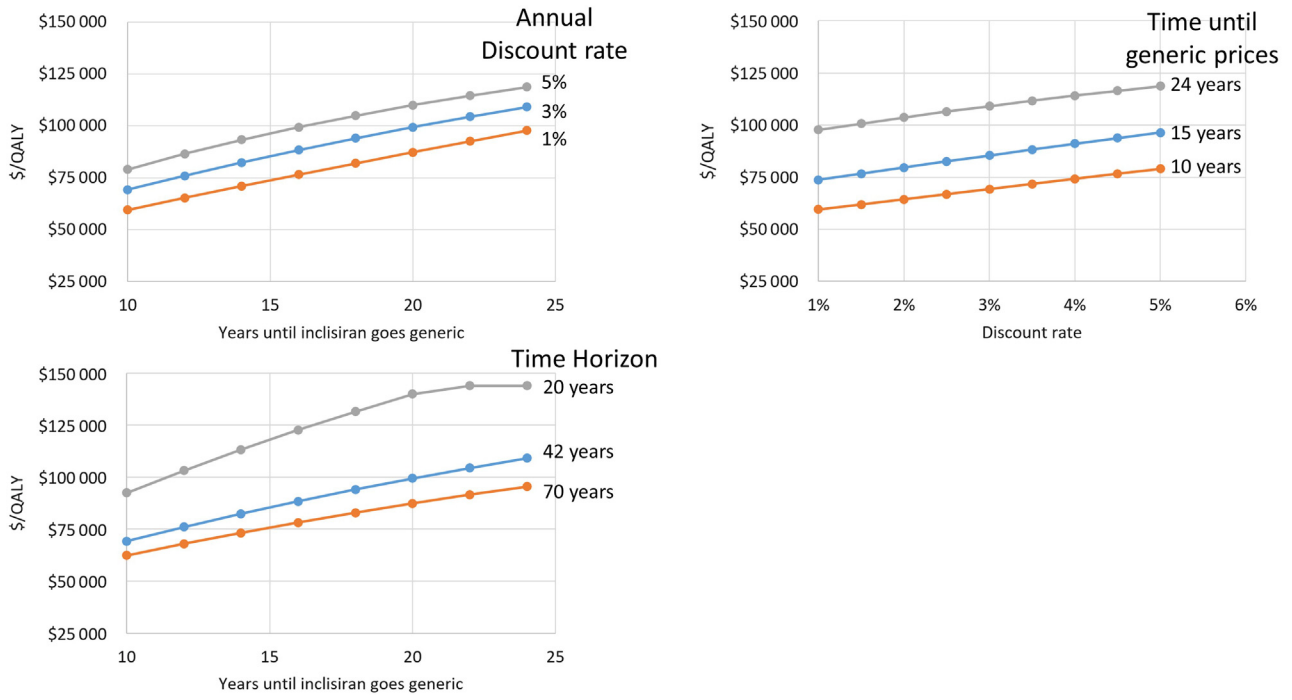
Before patent expirations ushered in generic pricing, statins cost $1 to $4 per day.[11] At those prices, cost-effectiveness for statins for primary prevention (compared with diet) ranged from $54 000 to $1 400 000 per QALY.[12] Factors affecting cost-effectiveness included sex, age, low-density lipoprotein cholesterol level (which increases risk), high-density lipoprotein cholesterol level (which reduces risk), blood pressure, and smoking status. During that period, management strategies often targeted high-risk patients—that is, patients for whom statin therapy cost-effectiveness was most favorable. Calling "the prospect of

Figure 2. Generic pricing follows whether or not branded prices are reimbursed.



QALY indicates quality-adjusted life-year.

Figure 3. Factors influencing estimated inclisiran cost-effectiveness in case study 3.



$ indicates US dollars; QALY, quality-adjusted life-year.

treating all patients at risk" of coronary heart disease "prohibitively expensive," 1 article called for measures to make statin treatment more favorably cost-effective, including increasing therapy effectiveness and improving risk prediction tools to identify individuals who would benefit most from statin therapy.[13]

Importantly, the article also argued that, "when patents expire …, substantial decreases in acquisition costs could result in greater cost-effectiveness and the possibility of treating more patients at risk."[13] That is, although the article recommended limiting treatment to individuals at the greatest risk (because their treatment is most cost-effective), it also suggested expanding treatment to others once patents expired and prices fell. This strategy entails evaluating cost-effectiveness and selecting whom to treat over time without considering how each decision affects the options available later. This approach is valid only if the options available later do not depend on choices made now.

Had payers and patients not signaled a willingness to pay for a treatment like statins at their branded prices, nevertheless (eg, by paying for drugs for other conditions and paying for medical procedures that statins prevent), drug companies may have opted not to develop statins in the first place. In that scenario, statins would never have become available at lower prices that would make them cost-effective for patients at a lower baseline risk of disease. Because paying for statins at branded prices for the first statin patients makes statins subsequently available at lower prices, a CEA of statin use for the first statin patients must reflect life cycle pricing.

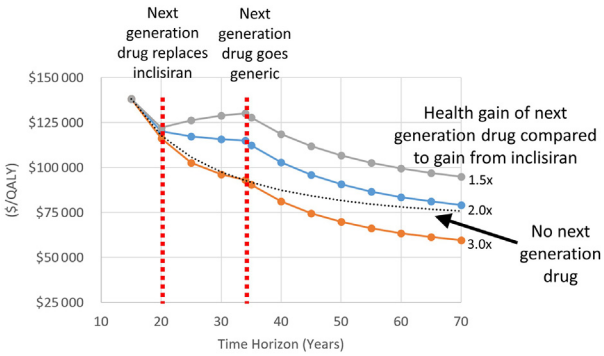
Nevertheless, the downstream availability of statins at generic prices does not depend on payment of branded prices for all potential users of these drugs. It is instead enough for a sufficiently large number of initial patients to pay branded prices for a sufficiently long duration (because investors consider total expected returns and returns depend on price and sales volume). Eventually, statin prices declined because of both competition among brand name versions and, later, the introduction of generic statins.[14] For the first statin cohort, accounting for generic pricing that would benefit downstream groups made sense. For later groups using statins—that is, individuals with lower baseline risks of coronary events—reimbursement at branded prices had no impact on the therapy's availability after patent expiration; with or without reimbursement for these later groups, statins would have eventually become available at generic prices. Hence, CEAs could evaluate reimbursement for these groups at branded prices without accounting for later, generic pricing.

Case Study 3: Inclisiran

When introduced in 2015, PCSK9 inhibitors cost approximately $14 000 per year.[15] Despite a price reduction to $5900 per year,[16] which fell within the range recommended by the Institute for Clinical and Economic Review (ICER),[17] demand remained weak, perhaps because the initial version of these drugs required administration by injection every 2 to 4 weeks.[18]

In December 2021, a new type of PCSK9 inhibitor based on small interfering ribonucleic acid (si-RNA) technology and known as inclisiran received Food and Drug Administration approval.[19] The si-RNA PCSK9 inhibitors have 3 advantages over the original antibody versions. First, because they are synthetic chemicals, they could more readily go generic in the future because competitors could replicate the chemical manufacturing process, unlike the antibody PCSK9 inhibitors, which are biologics and harder to copy. Second, producing an si-RNA-based therapy is less expensive than producing a biologic, which means prices could fall further than the price of a biologic if subject to enough competition.[18] Finally, because they are long acting, si-RNA PCSK9 inhibitors require injections only every 6 months.[20] These characteristics mean that si-RNA therapy might eventually be more widely used than the antibody PCSK9s and, once generic, become

Figure 4. Impact of next-generation drugs on cost-effectiveness in case study 4.



$ indicates US dollars; QALY, quality-adjusted life-year.

available at a more modest per-patient cost after their loss of exclusivity.

This case study compares a conventional CEA for inclisiran that assumes static pricing with an expanded analysis that includes eventual generic pricing. Both CEAs used a simple model (see Appendix in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.09.011) based loosely on the analysis of earlier generation PCSK9 inhibitors conducted by the ICER in 2015.[17] ICER used the Harvard CVD Policy Model, a discrete-event, Markov simulation for the US population at the age of 35 years and older.[17] For the 605 000 people in the United States with familial hypercholesterolemia,[17] this article's simple model reproduces ICER's population lifetime incremental costs and QALY gains for these earlier generation PCSK9 inhibitors if we assume that patients live for 42 years after treatment initialization and that each year, compared with statins alone, PCSK9 incremental costs and health gains amount to $14 350 and 0.045 QALYs, respectively. (Because patients treated with PCSK9 inhibitors also use statins, the PCSK9 inhibitor price also represents its incremental cost.)

To estimate inclisiran's incremental cost-effectiveness assuming static pricing, we preserve the 42-year time horizon and 0.045 QALY incremental gain per year used to reproduce ICER's results (previous paragraph), but we reduce inclisiran's annual price to $6500—the price Novartis charged at inclisiran's launch.[21] For the alternative scenario, which envisions eventual generic pricing, we assume inclisiran's price remains $6500 after introduction, but that it goes generic after 15 years,[22] at which point its annual price declines by 80%, to $1300. This scenario is plausible for a manufactured molecule, especially one with many generic competitors.[23] The time horizon of 42 years and the QALY gain of 0.045 QALYs per year remain the same. All analyses use an annual discount rate of 3%.

For the static pricing scenario (annual costs remain at $6500), per-patient-on-treatment costs total $158 000 and health benefits 1.1 QALYs, both over 42 years, yielding cost-effectiveness of $144 000 per QALY. Assuming generic pricing after 15 years, per-patient-on-treatment costs total $95 000, and health gains 1.1 QALYs, both over 42 years, yielding cost-effectiveness of $86 000 per QALY.

In sensitivity analysis, extending the time horizon to 70 years (base case 42 years) yields accumulated, discounted costs of $102 000 and accumulated, discounted health benefits of 1.3 QALYs and hence cost-effectiveness of $76 000 per QALY. Figure 3 illustrates sensitivity analysis for the analytic time horizon (20-70 years) and other assumptions, including the discount rate (base case 3%, alternatives of 1% and 5%), years until inclisiran goes generic (base case 15 years, alternatives of 10 and 24 years).

Case Study 4: Advanced Follow-On Treatment

This case study considers a hypothetical, advanced follow-on treatment that displaces inclisiran. It assumes the next-generation drug becomes available in year 20, 5 years after generic inclisiran becomes available. Its branded, annual price ($9750) corresponds to an incremental cost 50% greater than the branded inclisiran price ($6500), and its incremental health benefit over statins alone (0.090 QALYs) is twice inclisiran's (0.045 QALYs). Fifteen years after its introduction (simulation year 35), the advanced treatment goes generic, with its price falling immediately to $1300 per year, matching inclisiran's assumed generic price.

In case study 4, the "treatment" is inclisiran up to year 20, with the hypothetical follow-on treatment taking over in year 21. The case study's "comparator" is statins alone. The fact that the follow-on treatment appears only in the "treatment" arm of this CEA implies that the decision to reimburse inclisiran at the scenario's start triggers the development and introduction of the follow-on drug in year 21. Without that reimbursement (the comparator arm), drug companies never develop the follow-on drug.

The dependence of the follow-on drug's future development on inclisiran's reimbursement reflects the assumption that (as in other industries) drug manufacturers invest in a product when they expect that investment to yield a return. Darius Lakdawalla of the University of Southern California has stated that for the drug industry, "Innovation investment is driven by expectations of future revenues … the mechanism works through expectations about the future policy and market environment, and how these are likely to influence the revenues that can be earned when a pipeline drug is eventually launched."[24] It is reasonable to assume that reimbursement for inclisiran increases the expectation that payers will reimburse for follow-on treatments addressing the same indication and that a lack of reimbursement would suggest the opposite. Although many factors influence investment decisions, real-world experience suggests the same conclusion. For example, payer coverage for cancer treatments is more generous than coverage for other diseases,[25] and drug manufacturer investment in cancer therapies is both large and has grown more quickly than investment in other areas.[26]

Sensitivity analysis explores the impact of altering the assumed relative effectiveness of the follow-on treatment (base case—follow-on yields 2x inclisiran's incremental benefits, compared with statins alone, alternative scenarios of 1.5x or 3.0x inclisiran's benefits). The sensitivity analysis retains the base case assumptions for the follow-on drug's price.

With a 70-year time horizon, per-patient-on-treatment costs total $158 000 and health gains 2.0 QALYs, yielding cost-effectiveness of $79 000 per QALY. That result is modestly less favorable than the cost-effectiveness estimate for the 70-year scenario without the next-generation drug ($76 000 per QALY in case study 3), that is, in which inclisiran enters the market, goes generic, and never declines in use because no follow-on drug enters the market.

Figure 4 illustrates how a next-generation drug affects cost-effectiveness, taking into account the analysis time horizon (from 15 to 70 years, as designated by the figure's horizontal axis) and the next-generation drug's assumed health benefit. The black, dashed line shows the relationship between time horizon and cost-effectiveness without the next-generation drug—that is, reflecting inclisiran only, as in case study 3. The other 3 curves in Figure 4 illustrate the sensitivity analysis—that is, the relationship between time horizon and cost-effectiveness with the introduction of a next-generation drug that improves health by a factor of

1.5 (gray line), 2.0 (blue line), or 3.0 (orange line), compared with inclisiran.

Despite its greater health benefits, the next-generation drug can slow the cost-effectiveness ratio's improvement or even make it grow less favorable (greater) because the next-generation drug adds costs after its introduction but before its going generic (scenario years 20-34—between the 2 vertical, red, dashed lines). After year 35 (to the right of the second red, dashed line), cost-effectiveness improves (falls) more rapidly because the next-generation drug contributes improved health compared with inclisiran, but its price after year 35 declines. Figure 4 illustrates that if the next-generation drug confers a QALY gain 3 times larger than inclisiran's (orange line), cost-effectiveness eventually becomes notably superior to (lower than) cost-effectiveness in the scenario without introduction of next-generation drugs (black, dashed line). Even with smaller next-generation drug health benefits (gray and blue lines), the gap between cumulative cost-effectiveness for these scenarios and cost-effectiveness for the scenario without a next-generation drug (black, dashed line) shrinks after the next-generation drug goes generic (beyond year 35—to the right of the second red, dashed line).

Discussion and Conclusions

The expiration of patent protection and the potential for their prices to decline substantially sets pharmaceuticals apart from other health interventions. As case study 1 demonstrates, if reimbursement of branded prices early on affects a drug's eventual availability at generic prices, CEAs should include those projected, downstream consequences. Nonetheless, including future price declines in CEAs makes sense only if their realization depends on up-front reimbursement decisions. For statins (case study 2), use at branded prices by the initial (highest-risk) patients incentivized development. Hence, development and availability at generic prices did not depend on reimbursement decisions for later, more marginal patient groups.

With the premise for case study 3 that reimbursement at branded prices determines the future availability of generics, this article explored how including generic pricing influenced a CEA's projected cost-effectiveness estimates for inclisiran. In the base case, including generic pricing caused projected cost-effectiveness to decline 40%, from $144 000 to $86 000 per QALY. The assumptions are uncertain, and this article used a simplified simulation to approximate the Harvard CVD Policy Model that served as the basis for the original cost-effectiveness calculation conducted by ICER, but sensitivity analysis demonstrates important impacts persist over a range of assumptions.

This analysis includes arguably conservative assumptions. Generic prices below the base case assumption of $1300 per year are plausible because inclisiran is a manufactured molecule and hence should be easy to copy and because reduced dosing frequency (every 6 months) means a large population could eventually use it, thus potentially attracting substantial generic competition. Other drugs for which prices have declined markedly after the introduction of generic copies include alendronate (Fosamax, for osteoporosis), which has declined in price by nearly 90%,[27] and fluoxetine (Prozac, an antidepressant), which declined in price by more than 80% in 3 years.[28] At this time, unbranded (biosimilar) competition does not appear to reduce prices as substantially for biologics.[29]

The discount rate's importance (Fig. 3, first panel) highlights the need to consider current guidance recommending an annual value of 3%. The decline in real interest rates over the last decade in the industrialized world and the possibility that this decline reflects a lack of investment opportunities (demand) relative to savings suggests researchers should continue to review the basis for this value.[30] The base case time horizon of 42 years in case study 3 is conservative given the ongoing, widespread use of drugs developed decades ago, including beta-blockers and statins. The substantial impact on cost-effectiveness even with the case study's conservative assumptions suggests that considering generic pricing could influence HTA findings for a wide range of therapies.

The introduction of a next-generation drug that displaces generic inclisiran may seem to make generic pricing less relevant. Nevertheless, because the next-generation drug can also go generic and because its development can depend in part on reimbursement for inclisiran, a CEA evaluating reimbursement for inclisiran should include all of these consequences. As case study 4 shows, cost-effectiveness can continue to decline (become more favorable) over the longer term, even if over a shorter period a next-generation drug's introduction can delay such improvements. It follows that the possible introduction of a new, superior drug does not obviate the need for accounting for generic pricing.

Finally, this article's case studies assume that reimbursement for drugs at present influences decisions to develop drugs later. This narrative, as expounded by Lakdawalla,[24] should have a more systematic, empirically documented basis. Understanding how reimbursement influences future investments and hence the availability of drugs at reduced, generic prices is central to understanding how HTAs should appropriately include and represent price declines attending loss of exclusivity.

Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2022.09.011.

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