"MANUFACTURERS ARE REALIZING THAT THIS IS GOING TO BE A FEATURE OF THE LANDSCAPE AND SOME HAVE BEGUN TO THINK ABOUT IT AS A MUTUAL OPPORTUNITY."

STEVEN PEARSON, ICER

STRATEGY

ARBITER OF VALUE

BY ERIN MCCALLISTER, SENIOR EDITOR

The Institute for Clinical and Economic Review is rapidly becoming the closest thing the U.S. has to an HTA agency.

As an independent, non-governmental body, ICER does not have the authority over reimbursement decisions accorded to European health technology assessment (HTA) agencies. U.S. payers are not required to reimburse drugs ICER determines to be cost-effective.

Yet the credibility afforded by ICER's independent status, and its inclusion of diverse stakeholder views in constructing its cost-effectiveness analyses, are leading payers and PBMs to use the analyses to establish coverage criteria, determine formulary placement and negotiate discounts from drug manufacturers.

Consultants and payers contacted by BioCentury think ICER's role should be to help companies identify value-based prices before launch, and put pressure on companies to come to the negotiating table with payers when they choose not to follow ICER's analysis.

PBMs Prime Therapeutics LLC and Express Scripts Holding Co. and regional insurer Harvard Pilgrim Health Care Inc. have said they use ICER's reports to make coverage decisions. Steven Pearson, founder and president of ICER, added Aetna Inc., Anthem Inc., CVS Health Corp. and UnitedHealth Group Inc.'s PBM unit Optum Rx to that list.

And the group's influence is increasing. "We are on the cusp of some new benefit designs coming out that will now use ICER reports not just as a piece, but as the inclusion criteria for their formularies and whether or not to link payment to the value-based price," Pearson said.

He noted New York State's Medicaid program uses ICER's value-based price as a target price, and requires drug companies to hit the target through price or supplemental rebates.

Pearson added that at least one "major" insurer will release a formulary this year that is restricted to drugs ICER has deemed cost-effective.

Some drug companies that recognize the influence ICER wields are now proactively working with the group to evaluate new drugs prior to launch.

"Manufacturers are realizing that this is going to be a feature of the landscape and some have begun to think about it as a mutual opportunity," Pearson said.

So far only Sanofi and Regeneron Pharmaceuticals Inc. have publicly disclosed that they have shared unpublished data with ICER and then used the group's analysis in price setting. The first time was prior to the partners' launch of atopic dermatitis drug Dupixent dupilumab.

The second was a re-analysis of their PCSK9 inhibitor Praluent alirocumab carried out prior to publication of results from the ODYSSEY outcomes study.

On March 10, the partners announced the study's results and said they would offer payers a new net price based on the ICER analysis if they remove barriers to access. The deal applies to a subgroup of patients who derived the greatest mortality benefit and equates to a 69% discount from list price.

According to Pearson "multiple" other companies have approached the organization to identify value-based prices for their therapies prior to launch.

"This is the role, the approach that we've worked on since ICER was founded," he said. "Our hope for the future was that these analyses wouldn't just be a two-by-four applied to the back of the head of pharma."

THINKSTOCK

CHANGE OF HEART

More often than not, ICER has determined the drugs it analyzed were overpriced. Only 22 of the 84 drugs ICER has reviewed since 2014 were cost-effective at their list prices for all analyzed indications. Three more were deemed cost-effective in some, but not all, of the indications reviewed ("see "Cold as ICER").

In ICER's first review of Praluent and competing PCSK9 inhibitor Repatha evolocumab from Amgen Inc. in 2015, it found the value-based price for the drugs across all hypercholesterolemia patients was $2,177 per year, about an 85% discount to list price.

Praluent was launched with an annual wholesale acquisition cost (WAC) of $14,600 and Repatha had an annual WAC of $14,100.

At the time, Sanofi, Regeneron and Amgen criticized ICER's assumptions, saying the group had underestimated both the underlying risk of cardiovascular events in the intended treatment population, and the estimated effect of the therapies on cardiovascular outcomes. Outcomes studies were ongoing for both drugs, and data had not been reported.

But payers pushed back and put onerous prior authorization criteria in place to limit access.

As a result, both drugs have had meager sales. Last year, Praluent's reported sales were $195 million, Repatha's were $319 million.

Regeneron and Sanofi, which declined to provide interviews for this story, have since then changed their tack.

Last year, ahead of the launch of Dupixent, they provided ICER with detailed, unpublished data from clinical trials, and in exchange got to see ICER's cost-effectiveness analysis before it was published, using it in discussions with payers prior to launch.

The partners launched Dupixent at an average net price that fell within the range of cost-effectiveness established in ICER's report.

The list price was $37,000, and the average net price was in the low $30,000s. ICER said the drug was cost-effective at prices of $17,369, $30,632 or $43,895 depending on whether the cost-effectiveness threshold was set at $50,000, $100,000 or $150,000 per QALY.

Express Scripts praised the companies' approach to the launch as "responsible" and immediately included Dupixent on the National Preferred Formulary.

Similarly, when ODYSSEY showed Praluent lowered the risk of major adverse cardiovascular events (MACE), Regeneron and Sanofi shared the unpublished data with ICER for use in a planned update to the group's cost-effectiveness assessment.

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The reduction in all comers was 15% (HR=0.85; CI: 0.78, 0.93; p=0.0003). In a prespecified high-risk subgroup of patients with baseline LDL-C levels at or above 100 mg/dL, there was a 24% reduction in the risk of MACE (HR=0.76; CI: 0.65, 0.87) and a 29% reduction in the risk of all-cause mortality (HR=0.71; CI: 0.56, 0.90).

Pearson told BioCentury the prespecified subgroup analysis in ODYSSEY provided rigorous results to support a cost-effectiveness analysis.

ICER determined Praluent was cost-effective in the high-risk population at a price of $4,500-$8,000 per year. The value-based price was $2,300-$3,400 per year if used to treat all patients who met the trial eligibility criteria.

ADAPTING TO VALUE

The ODYSSEY data, ICER report and price concessions were announced simultaneously on March 10.

"You have to have your head in the sand — deep in the sand — to think that doctors aren't concerned about the price of the product," said Regeneron President and CEO Leonard Schleifer on an investor call to discuss the announcement. "So we thought it would be a good idea to see what ICER had to say and see whether or not it could overlap with what we had to say about value."

Sanofi and Regeneron said they would offer a net price that corresponded with the ICER analysis in patients with LDL ≥ 100 mg/dL if payers removed access barriers, such as prior authorization criteria requiring documentation that patients have been maintained on maximally tolerated statin doses for at least six months, or documentation that their statin regimens have been optimized.

On the investor call, Sanofi CEO Olivier Brandicourt said the pharma is committed to working with value assessment groups around the world. In the U.S., ICER is "very respected," he said, "and we have to try and we are trying here, clearly, to work with them."

Harvard Pilgrim and Express Scripts are reviewing their coverage of Praluent.

"We will re-examine our coverage criteria to see if they are still relevant. Overall, we are encouraged to hear Regeneron and Sanofi are willing to reduce the price of this medication to make it more accessible for patients," said Express Scripts spokesperson Jennifer Luddy in an emailed statement to BioCentury.

Harvard Pilgrim CMO Michael Sherman said the payer will consider revising its coverage policy "if we think the decision makes sense from a clinical as well as economic lens."

It will not remove all prior authorization requirements, however. Physicians "would still need to check with us to ensure that their patients meet the hypothetically expanded policy," Sherman said. He did say the amount of documentation required could be lessened.

Prime said it would review the data, but declined to comment further.

HTA REALITIES

U.S. payers, PBMs and reimbursement consultants said ICER's credibility stems from its focus on value rather than cost, and its practice of determining value based on input from multiple stakeholders.

European HTA agencies like the U.K.'s NICE frequently exclude from their models benefits on quality of life or social impact that patients and caregivers find important. ICER includes them.

For example, ICER used multiple models in its assessment of gene therapy Luxturna voretigene neparvovec from Spark Therapeutics Inc. One considered only the medical costs associated with the disease and the therapy. Another considered medical and non-medical costs, such as indirect costs on education, productivity loss and nursing home care.

ICER also solicits feedback from a broader audience, and frequently meets with patients early in its process to understand the endpoints and outcomes that are most important to them. During its public meetings to discuss ICER's analysis, panel members are asked to assess the overall value of the therapy as it relates to the specific concerns identified by patients. These value assessments and discussions are then incorporated into its final reports.

ICER also updates its cost-effectiveness framework every two years based on input from payers, biopharmas, patients and healthcare providers collected via public comment periods. The group increased its outreach to patients based on the feedback it received during its 2016 framework review.

"I think what ICER is trying to do is to stick more to the value tenets than a group like NICE, which is more focused on budget,"said Jack Mycka, global president and CEO of market access consultancy Medical Marketing Economics LLC.

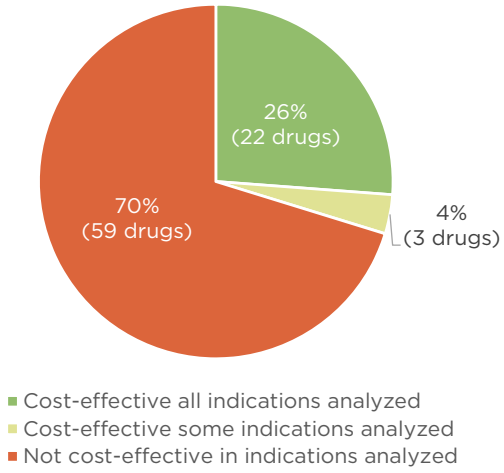
"One of the reasons that they're credible is that they have stakeholders from various sectors of life science companies, payers, etc. and the extent to which they are able to pull those parties together demonstrates their objectivity," said Sherman.

He added that he finds ICER's reports most valuable in competitive categories.

"We've been looking at the ICER reports and value propositions for years. They are an important component particularly in many cases where there are multiple choices such as insulins or PCSK9s," he said. "For high-cost drugs with few options, there is not much we can do, so the reports just tell us how much we're overpaying."

COLD AS ICER

More often than not, the **Institute for Clinical and Economic Review** (ICER) has concluded that the list prices of drugs it has reviewed exceeded the drugs' value. ICER considers therapies to be cost-effective if the cost per quality-adjusted life year (QALY) gained is $150,000 or less. Since 2014, the group has analyzed 84 drugs and determined that 70% were not cost-effective at the list price. *Source: ICER website*



ICER'S PIPELINE

The **Institute for Clinical and Economic Review** (ICER) has disclosed pending appraisals of six drug candidates that are under FDA review. ICER told BioCentury it has been approached by several drug manufacturers seeking to identify value-based prices for their products prior to launch. ICER declined to say whether any of those products are included in its appraisal pipeline, or whether any of the manufacturers for products ICER is assessing have provided data that are not in the public domain. The companies either declined to comment beyond noting that they participated in the comment period for the draft scoping report or did not respond to BioCentury's queries. *Source: ICER website, BCIQ: BioCentury Online Intelligence.*

Category	ICER draft due date	Candidate	Company	PDUFA date
Migraine	April 11	Erenumab	**Amgen Inc.** (NASDAQ:AMGN) / **Novartis AG** (NYSE:NVS; SIX:NOVN)	May 17
		Fremanezumab	**Teva Pharmaceutical Industries Ltd.** (NYSE:TEVA; Tel Aviv:TEVA)	Mid-2018
		Galcanezumab	**Eli Lilly and Co.** (NYSE:LLY)	2H18
Endometriosis	May 4	Elagolix	**AbbVie Inc.** (NYSE:ABBV)	2Q18
Amyloidosis	July 17	Inotersen	**Ionis Pharmaceuticals Inc.** (NASDAQ:IONS)	July 6
		Patisiran	**Alnylam Pharmaceuticals Inc.** (NASDAQ:ALNY)	Aug. 11

Peter Bach, director of the Center for Health Policy and Outcomes at Memorial Sloan Kettering Cancer Center, thinks ICER is setting the standard for value.

"I think what's kind of amazing here is that this idea of value-based pricing is starting to take shape," he said. "I think it is fair to say that ICER has become a reference standard and probably the only reference standard currently available."

"I think this is a remarkable event that an innovative biotech company thinks that they can win if their drugs are priced based on their benefits," Bach said, referring to Regeneron and Sanofi. "Hopefully other manufacturers will see that their route to the market is wise one."

Sherman went further: "Given the fact that most drugs come out at prices higher than ICER would deem as fair market value, I would encourage it."

MORE TO COME

Pearson reports that other drug companies have contacted ICER seeking assessments of drugs prior to launch or information they can use to recreate ICER's models internally.

"I believe that they view this as a way to create a sustainable market," he said.

He declined to disclose how many companies have reached out, or whether any of ICER's planned assessments concern drugs from the companies who have. According to its website, ICER is assessing 23 drugs in six therapeutic areas.

Six of the drugs from seven different companies are not yet approved or priced (see "ICER's Pipeline").

The seven companies either did not respond to BioCentury's questions, or declined to comment, on whether they had reached out to ICER beyond commenting on its draft scoping document for the assessments. They also declined to say if they plan to take its assessments into account when setting prices.

ICER will not have the capacity to proactively inform pricing of all new drugs, and is prioritizing "high-impact, low-certainty areas," according to spokesperson David Whitrap.

Whitrap said ICER has capacity to assess "all major new drug approvals," and can "provide more frequent evidence updates for the most relevant classes as new data become available."

Mycka noted other organizations and tools are available. "I don't think that you have to meet with ICER to do that," he said. "Companies ought to be able to access that capability via consultants to do that sort of analysis."

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Roger Longman, CEO of reimbursement consultancy Real Endpoints LLC, said the analyses should come from an independent third party and be transparent.

"There needs to be more credible external analyses of the relative value of drugs, and not just how valuable is this drug relative to SOC. There is also the necessity for independent, objective and transparent analyses. Whether that analysis is done by ICER or others, the question is more one of credibility," he told BioCentury.

Real Endpoints' developed its RxScorecard to evaluate drugs for value-based pricing contracts. The tool uses algorithms developed by Real Endpoints and clinical data from company-sponsored studies. The

scoring is open and transparent, which means that the user can see how every score is derived.

Sherman added, "I've got a comfort level with ICER, but I don't think it has to be ICER. I would look at other objective analyses of value if I saw any that crossed my desk."bc

COMPANIES AND INSTITUTIONS MENTIONED

Aetna Inc. (NYSE:AET), Hartford, Conn.
Amgen Inc. (NASDAQ:AMGN), Thousand Oaks, Calif.
Anthem Inc. (NYSE:ANTM), Indianapolis, Ind.
CVS Health Corp. (NYSE:CVS), Woonsocket, R.I.
Express Scripts Holding Co. (NASDAQ:ESRX), St. Louis, Mo.
Harvard Pilgrim Health Care Inc., Boston, Mass.
Institute for Clinical and Economic Review (ICER), Boston, Mass.
Memorial Sloan Kettering Cancer Center, New York, N.Y.
National Institute for Health and Care Excellence (NICE), London, U.K.
Prime Therapeutics LLC, Eagan, Minn.
Real Endpoints LLC, Westport, Conn.
Regeneron Pharmaceuticals Inc. (NASDAQ:REGN), Tarrytown, N.Y.
Sanofi (Euronext:SAN; NYSE:SNY), Paris, France
Spark Therapeutics Inc. (NASDAQ:ONCE), Philadelphia, Pa.
UnitedHealth Group Inc. (NYSE:UNH), Minneapolis, Minn.

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