

POLITICS, POLICY & LAW | REPRINT FROM APR. 7, 2023

The IRA is coming into focus

STEVE USDIN, WASHINGTON EDITOR



BIOCENTURY & GETTY IMAGES

The Inflation Reduction Act's price-setting pathway is starting to come into focus, as are the ways it is reshaping the commercial landscape for drug development. Every company developing medicines for the U.S. market — no matter how small, and regardless of the stage of development — must consider how they will adapt.

The legislators who crafted and ratified the law are confident big pharma can easily absorb its costs. It is becoming increasingly clear to biotech industry leaders, however, that while large companies will adjust, and some biotechs will find ways to soften the blows, the IRA will punish many of the small companies that are the heart of biomedical innovation. And it will upend business models that have led to transformational medicines.

Guidance CMS issued in March points to limited opportunities for mitigating the IRA's impact, for example by developing certain kinds of combination products or encouraging biosimilar competition, and clarifies the methodology for price-determining interactions between manufacturers and CMS.

The guidance also may contain procedural flaws that open the door to litigation that would delay the start of the price-setting program.

Last week, BioCentury and Putnam convened a panel of biopharma innovators to discuss these themes and other issues associated with navigating the IRA.

Participants in the webinar included Scott Briggs, a principal at Putnam; Katie Cumnock, research lead at Patient Square Capital; Meenakshi Datta, a partner at Sidley Austin; Alex Harding, head of business development at CRISPR Therapeutics AG (NASDAQ:CRSP); Richard Pops, chairman and CEO of Alkermes plc (NASDAQ:ALKS); and Camille Samuels, a partner at Venrock.

A consensus emerged in the discussion: the IRA does not herald the end of innovation, but it will profoundly shape, and unless it is modified, circumscribe biomedical progress.

Webinar participants warned that the IRA creates a set of perverse incentives that will be bad for patients, society and the innovation ecosystem. They urged their colleagues to both devise plans for navigating the IRA and to vociferously

advocate for changes to the law and to the ways CMS implements it.

The concerns extend beyond the impacts on manufacturers of drugs that will be subject to regulated prices. The IRA will exert downward pricing pressure on therapeutic alternatives and discourage investments in the development of related drugs and adjacent indications, rendering obsolete strategies such as pipeline-in-a-product and gradually expanding indications from smaller to larger populations.

The law will change the dynamics between pharma and small biotechs, tilting the balance of power to large companies with less expensive capital and expansive marketing capabilities, the panel concluded. Because pricing power will erode more quickly, pharmas will be willing to pay less for assets and companies than they would prior to enactment of the IRA, especially for small molecule drugs.

Small biotechs will be further disadvantaged by changes in pharma priorities. The IRA, BioCentury's KOLs said, will lead pharmas to shift from investing in early-stage assets as they try to compensate for the anticipated loss of revenues from marketed products.

An opening for litigation

There is no chance that Congress will repeal or replace the IRA as long as Democrats control the White House, the Senate or the House.

However, legal challenges to the law are certain.

Lawyers working for the biopharma industry may have already found an opening for litigation in the recent CMS guidance, Sidley's Datta said.

To limit the number of issues it has to consider, the agency excluded some aspects of its guidance from public comment, including section 30, which describes procedures for the identification of drugs selected for price-setting in 2026.

Datta called these exclusions from public comment a "major defect" that could be subject to legal challenge because the Administrative Procedures Act and Medicare law require that "whenever there are material, substantive rules issued by a government agency, stakeholders in the private sector [must be given] an opportunity to comment."

Expediency and the desire to meet a tight timeline are not permissible reasons for excluding comment, according to Datta. She noted there is precedent for CMS missing statutory deadlines because it needed more time to craft policies.

"There have been dozens of instances by CMS over the years, including the Medicare Modernization Act, including the Affordable Care Act," Datta said, "where they have had statutory deadlines that they blew."

THE IRA DOES NOT HERALD THE END OF INNOVATION, BUT IT WILL PROFOUNDLY SHAPE, AND UNLESS IT IS MODIFIED, CIRCUMSCRIBE BIOMEDICAL PROGRESS.

In the case of the IRA, "instead of blowing the deadline and doing the process the right way, which is to give stakeholders an opportunity to comment on each and every section of substantive rulemaking, including section 30 of the guidance, they're saying it's final."

She suggested that parties "need to raise your hand now" by filing public comments, if they wish to sue CMS — or support other companies in doing so — over the limited opportunities for comment.

Datta emphasized that the prospects for such litigation are uncertain but said it "may result in delaying the start of the program."

Formulations and combinations

Datta and Briggs pointed to one aspect of the guidance that highlights the importance of considering the IRA as drug companies make lifecycle plans.

"CMS will treat all drugs with the same active ingredient and the same holder of the NDA or BLA as a single drug, including different dosage, strength and formulations, even if they're marketed under different NDAs or BLAs with different approval dates," Briggs noted. This means that the timing for eligibility for price-setting — nine years for NDAs and 13 years for BLAs — starts ticking when the first version of the drug is approved.

Xarelto rivaroxaban from the Janssen Pharmaceuticals unit of Johnson & Johnson (NYSE:JNJ) "is a prime example," Briggs said. Although Xarelto's formulations are covered by three separate NDAs, two for its tablet formulations and one for an oral suspension, "for the purpose of determining price-negotiation eligibility, all of those formulations" would be lumped together based on the approval date of the first NDA.

The guidance may come as a disappointment for companies that had hoped approvals of new formulations would buy them more time, but there is good news in the guidance for manufacturers that have developed or can develop combination products.

While CMS will aggregate data across formulations and dosages of a drug, "combinations of two or more active

ingredients or moieties will be treated as separate drugs,” Datta said.

“CMS will only evaluate products together if they have the same combination of active ingredients,” Briggs said. That means, for example, that Breo Ellipta from GSK plc (LSE:GSK; NYSE:GSK) and Theravance Biopharma Inc. (NASDAQ:TBPH) and Trelegy Ellipta from GSK and Innoviva Inc. (NASDAQ:INVA) will be treated as different products for purposes of price-setting, he said. Breo Ellipta is a fixed-dose combination of the inhaled corticosteroid fluticasone furoate and the long-acting beta2-agonist vilanterol, while Trelegy Ellipta is a triple combination of fluticasone furoate, vilanterol and umeclidinium, a long-acting muscarinic antagonist.

Briggs also highlighted the implications of the CMS IRA guidance for subcutaneous formulations of mAbs, such as Rituxan Hycela or Herceptin Hylecta, that include hyaluronidase. Because hyaluronidase is “considered a separate active ingredient by CMS and is covered by a separate BLA by FDA, those would actually be considered combination products, even though many folks may consider them to be different formulations,” he said.

Commercial implications of the IRA

While these kinds of considerations may seem irrelevant to companies with only preclinical assets, they are very relevant to investors.

“Investors,” Pops said, “are intensely focused now on trying to understand from management teams how this legislation is going to affect their business.”

The IRA, the Alkermes CEO added, “has fundamentally affected the way we think about allocating capital in companies.”

The clearest example of the law’s impact on capital allocation flows from its differential treatment of drugs approved under the NDA and BLA pathways, which have nine and 13 years, respectively, before they can be subject to price regulation.

“The typical small molecule today actually has patent exclusivity for almost 14 years,” Samuels noted. Because it takes time to change medical practice, sales are not evenly distributed over that time.

“Losing five years of healthy margins cuts the net present value, the ultimate value of your drug, by about half,” she added. As a result, “if you go to sell your company or sell a drug asset to a big pharma, they’re going to use that as a hammer to cut your price in half.”

One response to the IRA will be the prioritization of large molecule drugs, Pops said. “The distinction between small molecules and biologics is obvious, and to the extent you’re able to shift a development program toward a biologic

“IT WILL GIVE LEVERAGE TO THE BIG COMPANIES WHO POTENTIALLY WANT TO ACQUIRE OUR COMPANIES.”

CAMILLE SAMUELS, VENROCK

embodiment of the biology you’re trying to exploit, that’s probably worth on the order of twice as much as doing it in a small molecule.”

That’s cold comfort to most small biotechs, according to Samuels, because they are usually focused on a specific modality. If they are developing a small molecule, they may not have the capacity to pivot to a biologic.

Even if companies find ways to shift development from small molecules to biologics, the result will almost certainly be worse for patients and society because biologics are usually more difficult and time-consuming to administer and are always more expensive.

Second-order effects

There are numerous second-order effects from the IRA that will reshape the commercial environment for both small molecule and biologic drugs.

Because the law creates revenue cliffs, there will be more pressure to reach peak sales as quickly as possible. This creates a competitive advantage for big pharmas, which have greater marketing resources and less expensive capital than small companies that are funded through equity capital, Pops said.

The IRA creates an arbitrage opportunity for large companies that can put more resources into a launch, and that are acutely aware of the fixed window of nine or 13 years, Pops explained. “If I can deploy more capital early for a more square-wave launch within that period of time, that drug is actually worth more to me than to the public company and its owners who can only deploy capital at a certain rate.”

Because the competitive dynamic is being shifted to favor large companies, Pops expects them to become “much more predatory to take advantage of those arbitrage situations as they present themselves.”

Samuels, who serves on the boards of several biotechs, amplified those concerns. “It will give leverage to the big companies who potentially want to acquire our companies because they can invest in the larger indications quickly, more profitably than we can.”

Harding cited the pending acquisition of Seagen Inc. (NASDAQ:SGEN) by Pfizer Inc. (NYSE:PFE) as an example of how “biologics companies are going to be favored in terms of acquisition targets.”

He also highlighted a bigger trend.

In addition to compensating for lost revenue from upcoming patent cliffs, pharmas will need to compensate for unanticipated revenue losses from drugs subject to IRA price-setting. Together, the two forces could push pharmas to shift their gaze from early-stage biotechs to companies with products that could be marketed relatively soon, Harding said. “They’re doing their five-year forecast and seeing that they have a revenue gap coming up in the future, and they’re looking for later stage assets that have the potential to plug that gap, which comes at the expense of earlier stage deals, discovery stage deals.”

Another set of second-order effects involves the spillover of Medicare pricing to the commercial market and to products that haven’t been on the market long enough or that do not have large enough Medicare sales to trigger price-setting.

“If you look at a Medicare Advantage or Medicare Part D plan that is all of a sudden paying 25, 30 or 40% less for a drug, we would expect that drug to be preferred on those formularies, and we would expect other drugs within the same therapeutic class to need to be offering payer rebates to those organizations to maintain parity access,” Briggs said.

This spillover effect could make it difficult to develop new drugs in a therapeutic class, Cumnock said. Launching a drug into a class that includes more mature products always creates requirements to differentiate the new product, she said. Demonstrating superiority “becomes much more important if the drug in front of you may be negotiated well in advance of you hitting your peak sales.”

Datta suggested that the IRA “raises the question of whether you should be second to market,” even with a better product, because the law may slash the prices payers are willing to accept for an entire therapeutic class.

Still, Pops and Samuels cautioned against exaggerating the law’s impacts. Biotechs will continue to turn scientific discoveries into medicines — but the windows of opportunity may be narrower, and companies will need to adopt new business strategies.

“If we meander into something that yields an opportunity to make a medicine that could help elderly patients with dementia, and we knew that we only had nine years to make money on it but it was going to really be important medicine we would develop, we would just try to figure out what the business model is that supports doing that,” Pops said.

“THERE WILL NEVER BE ANOTHER KEYTRUDA.”

RICHARD POPS, ALKERMES

The IRA isn’t necessarily going to lead her to pull the plug on companies, Samuels said. “I happen to have already invested in a seed-stage company that could be drugging the undruggable. I’m not going to withdraw my investment, even though it’s a small molecule company, frankly, whose first indications are oncology.” She added, however, “I am concerned that the ultimate exit valuation of the company will be impacted. I have to be concerned about it.”

Sweet spots and no-fly zones

Oncology drug development will be hit hard by the pricing cliffs because drug companies will have to abandon the strategy of gaining initial approvals in smaller populations of patients, typically those whose disease has progressed after several lines of standard treatments, and expanding the size and number of indications over time.

“There will never be another Keytruda,” Pops said, referring to the strategy taken by Merck & Co. Inc. (NYSE:MRK) that rapidly expanded indications for the PD-1 inhibitor, via the accelerated approval pathway. “You cannot think about bringing a drug to the market and then building indications over a decade as you expand the potential utility in different cohorts of patients. Patients lose in that regard.”

Panelists had different perspectives about the kinds of products the IRA has made more attractive for investors.

Harding, who stressed that he was expressing his personal opinion, not CRISPR’s official position, said the law and the guidance CMS issued are good news for developers of cell-based therapeutics. “My interpretation is that any product that’s derived from blood cells, such as the products that CRISPR has, would be excluded from price-setting under the IRA.”

Given the exemption from price-setting for drugs with a single orphan indication, “the ideal product to put venture money behind right now,” Pops said, is a small or large molecule “with a big orphan population where there’s a burned-in regulatory pathway and where there’s a burned in payment pathway.”

He added: “The incentives are shifting towards non-mass market, high-priced injectable drugs, which is a totally perverse outcome from a bill that’s purportedly oriented toward advancing the public health and lowering cost.”

Briggs pointed out that in addition to creating a price-setting regime, the IRA restructured Medicare Part D, including by

creating an uncapped 20% liability for drug manufacturers for the most expensive medicines.

The Part D redesign means that for many small molecules that are subject to price-setting, the 20% liability will come on top of whatever discount CMS imposes.

The interaction of the Part D redesign and the IRA has created a new sweet spot, he suggested, for general medicine drugs that are not expensive enough to trigger either the 20% manufacturer liability or price-setting. “There might be an interest in potentially renewed development of those general medicine drugs because they’re subject to lower Medicare rebates, even prior to a potential price negotiation.”

Cumnock pointed to immunology as an area that could become attractive because it provides opportunities for marketing to non-Medicare populations, shielding drugs from price-setting under the IRA. “There’s a lot of activity in immunology right now, and a fair number of the indications that you could target in the immunology population fall into a predominantly commercial payer population.”

While younger patients will age into the Medicare market, “if you are thoughtful in the way that you do your indication sequencing and what you go after, there’s a fair bit of opportunity in some of these disease areas within the adult, but younger adult, population,” Cumnock said.

Mixed messages for biosimilars

The IRA is a mixed blessing for biosimilars.

By slashing the cost of biologics, it could cut the legs from under biosimilars manufacturers that typically plan to offer discounts of about 40% from the list prices of original biologics.

There are two aspects of the IRA that could boost the market for biosimilars.

Cumnock noted a provision that for five years provides an additional 2% reimbursement for biosimilars on top of the 6% of average sales price (ASP) CMS pays providers under Medicare Part B.

In addition to juicing the reimbursement, the IRA could be positive for biosimilars because only single-source drugs are subject to price-setting, so the launch of a biosimilar exempts the reference product. As a result, manufacturers may be less inclined to take measures to stymie biosimilars competition, Briggs said. “If you look at biosimilar markets where there are three, four or more biosimilars in the market, those tend to start looking like generic markets.” On the other hand, biologics manufacturers retain both pricing power and market

share when faced with fewer biosimilar competitors. “If there are one or two biosimilars in the market, that could certainly be more advantageous than taking a 40, 50 or 60% haircut off the price of the drug,” Briggs said.

As a result, he predicted that there will be situations “where manufacturers will be less aggressive in pushing back on and defending against biosimilar entry than they would’ve been historically.”

Expecting the worst, advocating for better

All of the panelists said it makes sense to assume that the loss of revenue resulting from the IRA process will be similar to those that occur when a product loses exclusivity.

“In the absence of more guidance, my assumption would be that there are no guardrails on CMS to hold back,” Harding said. “In the current political environment, I think the tendency would be to take as much of a discount as possible. So, if I’m modeling something, I’m going to model a loss-of-exclusivity event.”

The first prices set under the IRA will determine whether it will be politically possible for CMS to act in a restrained manner, Cumnock said. The IRA sets minimum discounts of 25-45%, based on how long a product has been on the market, but doesn’t set a floor or minimum price.

If in the first round of price-setting “we land at the ceilings that are proposed, there’s always wiggle room to go down,” Cumnock said. “But if they come in quite aggressively early on, we may see that as the new norm moving forward.”

Pops agreed that the first prices will send strong signals.

“We don’t know what a negotiated price looks like. You can imagine a world where a negotiated price accommodates some sense of its actual value, or you can imagine a world where the negotiated price is simply a bureaucratic exercise in getting to zero as fast as possible,” Pops said. “Those are two completely different conditions, and that’s why the rulemaking, the distance between the legislative language and the rule, is so important and why a number of us are focused on that actual blocking and tackling of implementing the law.” This uncertainty also explains, he said, “why the first embodiments of the price controls — or the price negotiations — are going to be so important, in setting the tone.”

That uncertainty, and the hope that advocacy can influence the outcome, are reasons for everyone with a stake in biomedical innovation to engage with CMS and Congress in the coming months and years, Pops and the other participants in BioCentury’s webinar said.

BIOCENTURY

BIOCENTURY INC.

BioCentury's mission is to provide value-added business intelligence & analysis for life science companies, investors, academia and government on the strategic issues essential to the formation, development and sustainability of life science ventures.

NEWSROOM

news@biocentury.com

SAN CARLOS, CA

+1 650-595-5333; Fax: +1 650-595-5589

CHICAGO

+1 312-755-0798; Fax: +1 650-595-5589

WASHINGTON, DC

+1 202-462-9582; Fax: +1 202-667-2922

UNITED KINGDOM

+44 (0)1865-512184; Fax: +1 650-595-5589

BioCentury®; Because Real Intelligence is Hard to Find™; BCIQ™; The BioCentury 100™; and The Clear Route to ROI™ are trademarks of BIOCENTURY INC. All contents Copyright © 2023, BIOCENTURY INC. ALL RIGHTS RESERVED. No part of BioCentury's Publications or Website may be copied, reproduced, retransmitted, disseminated, sold, distributed, published, broadcast, circulated, commercially exploited in any form or used to create derivative works without the written consent of BioCentury. Information provided by BioCentury's Publications and Website is gathered from sources that BioCentury believes are reliable; however, BioCentury does not guarantee the accuracy, completeness, or timeliness of the information, nor does BioCentury make any warranties of any kind regarding the information. The contents of BioCentury's Publications and Website are not intended as investment, business, tax or legal advice, and BioCentury is not responsible for any investment, business, tax or legal opinions cited therein or for any decision made or action taken in reliance upon such information.

All use of BioCentury and its contents by current subscribers is governed by the BioCentury User Agreement and by all

others is governed by the BioCentury Terms of Use, unless a written agreement to the contrary has been executed by BioCentury Inc.

USE OF IMAGES: Certain Images used in BioCentury Inc.'s Publications, Video Content, Websites, Services, Notices and/or Marketing Materials are licensed from Getty Images (US), Inc. Any such image of a person or object so displayed is being used for illustrative purposes only and any such person or object depicted, if any, is merely a model. For more information see "Use of Images" found under the "Legal" section on the footer of the homepage at www.biocentury.com.

PRIVACY & ADVERTISING: In accordance with its Privacy Policy, BioCentury does NOT sell its customer information or usage data to third parties. BioCentury sells advertising in its BioCentury product emails and on its website. BioCentury is pleased to acknowledge its conference and events partners and sponsors through promotional announcements, on our web site, at our events and in our product emails. BioCentury also provides advertising opportunities to partners, sponsors, and advertisers through stand-alone emails to our community.