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Navigating the Inflation Reduction Act

BY STEVE USDIN, WASHINGTON EDITOR

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The Inflation Reduction Act is reconfiguring the commercial landscape so profoundly that a deep understanding of the law, and effective strategies for adapting to it, will become critical success factors for biopharmaceutical companies. IRA strategies are essential, regardless of a company's size or geographic location, say investors, pharma CEOs, consultants, attorneys and former senior government officials who spoke with BioCentury.

Making plans for adapting to the changing environment is made more difficult by the discretion Congress gave CMS to implement the drug price-setting provisions of the law. The agency hasn't announced its IRA policies, or whether and how it may seek public input as it develops them.

Given the time scale of drug development, it is not possible to wait for certainty. Capital allocation and pipeline prioritization decisions are being made now based on the known and imagined impacts of the IRA.

IRA strategies will have to account for direct effects of Medicare price cuts, as well as fallout from cuts in the prices of competitive drugs in a therapeutic class.

While the price-setting provisions of the IRA have attracted a great deal of attention, the law's redesign of Medicare Part D also presents opportunities and challenges for biopharma companies.

Caps on out-of-pocket costs for products covered by Medicare Part D, which covers drugs dispensed at retail pharmacies, and elimination of co-insurance for adult vaccines, will enhance adherence to prescriptions, leading to increased market sizes and revenues for some drugs.

At the same time, greater manufacturer liability for discounts on high-priced drugs, combined with penalties for increasing prices above consumer inflation levels, will attenuate revenues for other drug classes.

Temporary exemptions to aspects of the Part D redesign and price-setting provisions for small companies add another layer of complexity.

Every biopharma needs an IRA strategy

Multinational pharmas have teams combing through the IRA, their portfolios and pipelines, gaming potential responses to the legislation. The first impressions from some of the largest companies suggest the law will reduce investments in small

molecule drugs, bolster investments in biologics, and cause companies to consider deferring U.S. launches of drugs for smaller indications if there is a potential for later launches of larger indications.

In September, David Ricks, chair and CEO of Eli Lilly and Co. (NYSE:LLY), told BioCentury the IRA will halve the values of small molecule drugs, reducing the valuations of companies that are developing them. He predicted that therapies, both small molecules and biologics, that could have been medically useful and commercially viable will be left on the cutting room floor — and some biotechs that are developing them will be forced to close their doors.

Vas Narasimhan, Novartis AG (SIX:NOVN; NYSE:NVS), told BioCentury in September that Novartis is undertaking a review of the IRA's effects on its business. He predicted that the law will make it more difficult to develop small molecules for conditions affecting Medicare populations, reduce investments in drugs treating large, chronic conditions, and present challenges to pursuing new indications with approved therapies.

The IRA establishes maximum prices for drugs that are subject to its negotiation provisions but does not mandate a floor. Ricks and Narasimhan said they assume CMS will set prices that are equivalent to those that occur with generic competition, while some stakeholders believe price cuts will be less severe.

Concerns about the IRA are not, or should not be limited to large companies. Many of the biotech executives who will gather in San Francisco for the JP Morgan meeting hope to partner with or sell their assets to multinational pharmaceutical companies that are reevaluating commercial strategies to take the IRA into account.

Investors also have their eyes on the IRA.

"All investment calculations are based on the concept of net present value of future profits, and the IRA has a lot to say about future profits," Peter Kolchinsky, managing partner at RA Capital Management, told BioCentury.

"Nothing could be more wrong than the idea that a drug development company of any size or shape doesn't have to worry about the IRA," he added. "It would be like telling early-stage companies not to worry about their launch prices or whether insurance will cover their product someday or even about FDA approval, because that's all far in the future."

Supporters of the IRA point to a Congressional Budget Office assessment that predicted it will result in 15 fewer drugs over a decade, a cost that they contend is an acceptable tradeoff for lower prices. Biotech executives, however, say the CBO failed to consider the effect of price-setting on investment decisions.

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A team sport

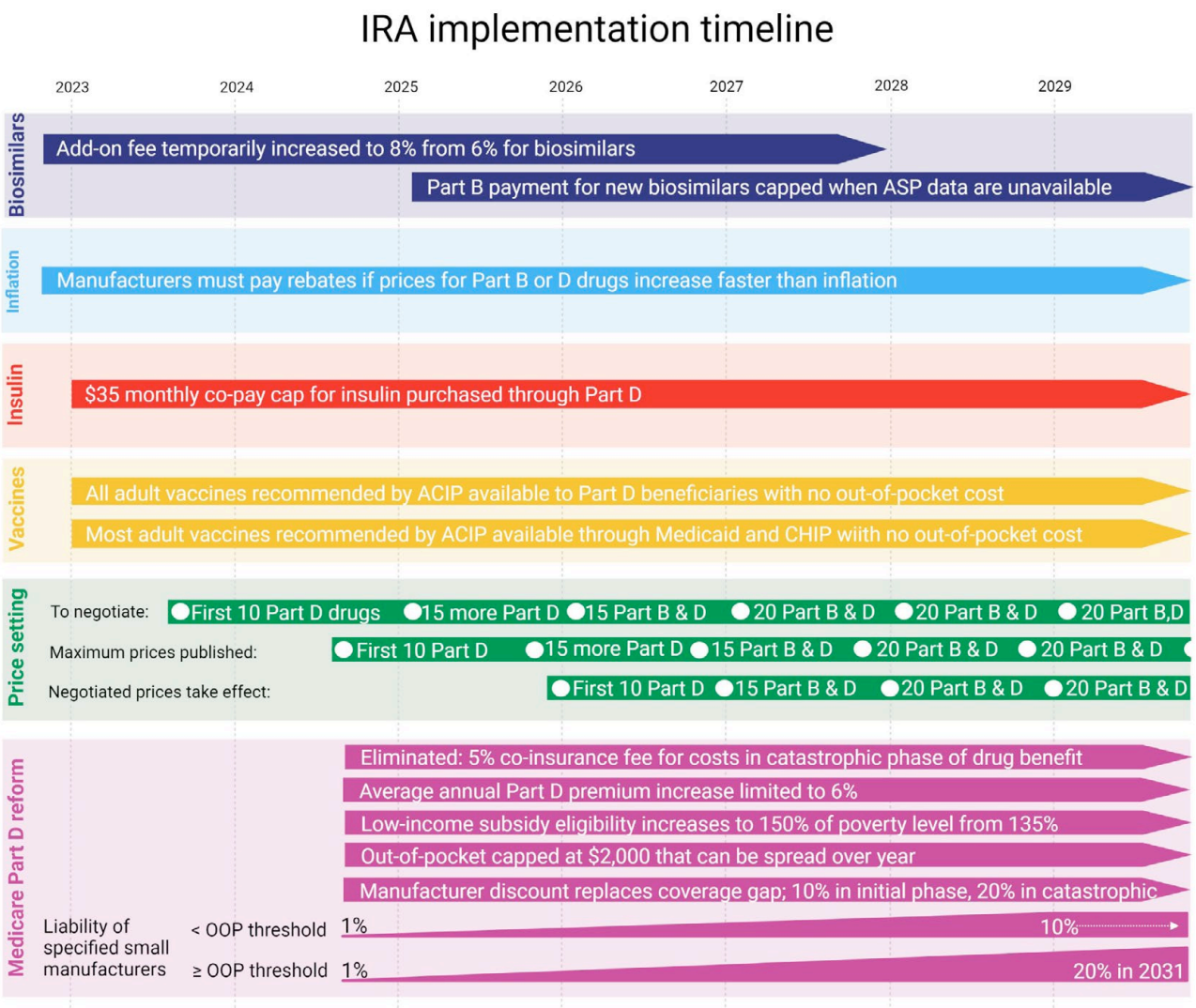
"The first thing I tell companies about the IRA is that they actually have to learn it," Alice Valder Curran, a partner at Hogan Lovells, told BioCentury. "There's no escaping having to learn it. I say that because it is not an easy hill to climb."

This advice applies to small biotechs that are so preoccupied with discovering and developing therapies they find it difficult to consider other issues, Curran said. "I understand why market access is not at the top of mind, but it is becoming impossible to ignore in a post-IRA world. Everyone has to have some understanding of it because of the impact on valuations."

The statute is long, complex and it can be difficult to integrate all the moving parts and determine what they mean for a specific product or company. Curran says companies need to be thinking about potential indications and which indications are developed first, the payer mix and pricing strategy for each indication. "Even before the IRA, you could back yourself into a corner unintentionally if you weren't mindful of those things as you develop products. Now the IRA, to quote Spinal Tap, takes that to 11 because it makes an already complicated situation even more complex."

Analyzing the IRA is a team sport, Curran says. "It has to be a multidisciplinary exercise. The legal team can't own this. The finance team can't do it on their own. You need to have the legal team and the finance team and the regulatory team and the IP team and the transactional team and your market access team all looking at this statute because it's only by bringing together a multidisciplinary team that you will be most likely to identify all the different implications for your organization."

Curran advises biopharma companies to "think about the IRA first for your own products, and then once you think you've



got a good sense of what it's going to do for your own products and pipeline, think about it for your competitors."

The next step, she said, is to "think about how it's going to affect the market model as a whole. Through that exercise, with each one of those expanding areas of inquiry, you really start getting a sense of all the complexities, the unforeseen implications."

The process may seem never-ending, Curran said. "I think of a new implication virtually every day."

Nine versus thirteen

The most obvious set of decisions based on the IRA centers on Congress's decision to start Medicare negotiations for NDA drugs seven years after approval and at 11 years for those regulated under BLAs. The prices will come into effect two years later.

"The difference between the seven and 11 years before negotiation sets the case for biologics to be preferred and incentivized if manufacturers have a choice in development," Jake Klaisner, a consulting actuary at actuarial consultancy Milliman Inc., told BioCentury. "Obviously, for some therapeutic classes companies won't have that choice, but I think where they do, you will probably start to see things lean toward biologics."

In addition to skewing investment decisions toward biologics, the shorter runway for small molecules could lead companies to defer launching for small indications in favor of larger

indications that will generate greater revenues before being subject to Medicare price-setting.

A spokesperson for AstraZeneca plc (LSE:AZN; NASDAQ:AZN) told BioCentury the company is considering initially launching some products with smaller indications outside the U.S. and waiting to make them available to patients in the U.S. until they have obtained approval for a large indication. The pharma said IRA's nine-year threshold for setting the price Medicare pays for some drugs that were approved under NDAs is a "disincentive for us to launch a product in the U.S. first."

There are downsides to this approach, however.

"There are therapeutic areas where there are parallel advancements made by manufacturers such that there is a desire to be first to market, and that opportunity to capture even a smaller market segment and be a first mover in that space, may outweigh some of those dynamics," Klaisner said.

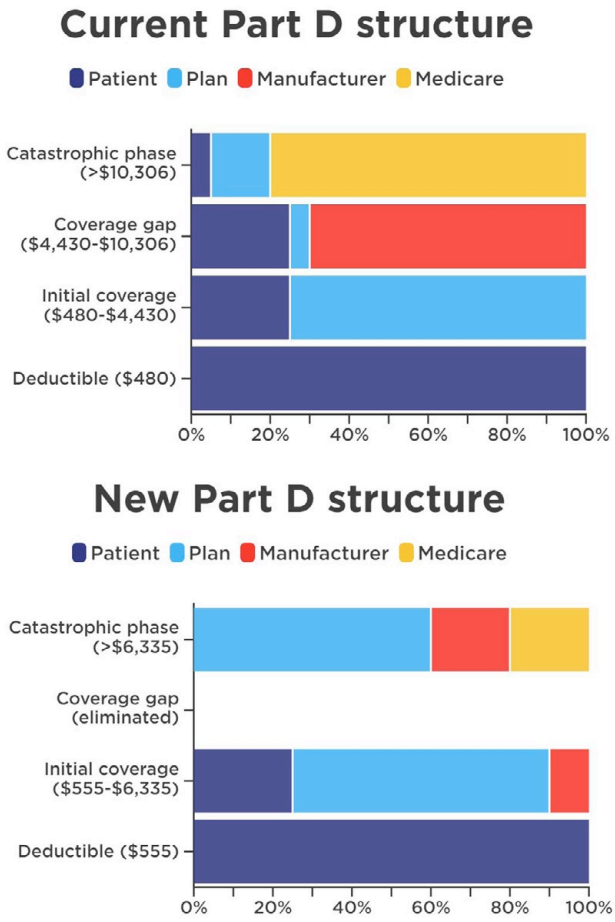
In addition to hurting patients who could benefit from smaller indications, one of the more pernicious effects of the IRA, according to Lilly CEO Ricks, is that it can make it economically infeasible to develop new indications after a drug has been approved. In some cases, drug companies will not be able to justify the costs of clinical development of new indications following launch if they are facing what is essentially a loss of exclusivity event in a few years, he said.

Scott Briggs, a principal at Putnam, a consulting firm that is part of Inizio Advisory, told BioCentury he has heard from clients about "cases where manufacturers may forgo second or third indications if the runway between when that indication would receive approval and when negotiation will ultimately occur is not long enough to justify the development costs."

The problem should stimulate FDA and CMS to provide more regulatory clarity on ways drug companies can use real-world evidence and conduct pragmatic trials, Mark McClellan, director of the Duke-Margolis Center for Health Policy, told BioCentury. This would make it possible to slash the cost and time required to generate data on new indications, which could offset the decreased period of free pricing.

McClellan, who served as FDA commissioner and CMS administrator in the George W. Bush administration, said unleashing greater use of real-world evidence could be coupled with flexibility granted to CMS to renegotiate prices based on the approval of new indications. McClellan serves on the boards of Johnson & Johnson (NYSE:JNJ), Cigna Corp. (NYSE:CI) and other healthcare companies.

"There would have to be a threshold" for increasing prices because "not every modification of a drug or indication is all that valuable. You can have a sensible discussion on that,"



McClellan said. He added, however, that it is not clear whether CMS will be willing to have those discussions.

Klaisner also pointed to uncertainty about whether and how CMS will be willing to increase prices in response to approval of new indications. "There's likely a reason why Congress carved that out explicitly in the text of the statute in a way that at least leaves the door open for [renegotiating a higher price]," he said. On the other hand, "CMS certainly could take the position that a new indication expands the volume of sales, that's good for the manufacturer, but we don't have a different price on the table for that."

Second- and third-order effects

"A lot of people are over-focusing on the price negotiation piece" of the IRA, Briggs said.

While it is a large driver of change, "the second- and third-order effects of price negotiations are likely to be as significant or more significant," Briggs said.

A company's product may not be a potential target for negotiation, but pricing power will be affected if competitive drugs in the same class are subject to price negotiation. It will be important for companies to have an "understanding of how that might impact payer management and provider choice around different products within the class," Briggs said.

Alex Busch, a partner at Putnam, told BioCentury that companies should consider scenario planning based on the different ways CMS could implement the law. "There are still a lot of unknowns: how are drugs going to be selected; what are the negotiation points; and what are the ultimate outcomes going to look like? Planning for the different paths this can take as CMS figures out what they are doing with this legislation is going to be a critical component of being successful."

Single orphans

The IRA provides an exemption from price-setting for drugs that are approved for a single orphan condition, but that exemption disappears if the drug is approved for any other indication.

Alnylam Pharmaceuticals Inc. (NASDAQ:ALNY) has said that it has paused plans to conduct a Phase III study of its Amvuttra vutrisiran for Stargardt disease because the drug is approved for another orphan condition, polyneuropathy associated with hereditary TTR-mediated amyloidosis (ATTR-PN).

To avoid losing the single-orphan exemption, Alnylam plans to develop and conduct clinical trials of another molecule to treat Stargardt, a process that could create substantial delays in patient access, Ben Shaberman, VP for science communications at the Foundation Fighting Blindness, told BioCentury.

BioCentury has identified18 other drugs from 17 other manufacturers that were approved for a single orphan indication in 2021 or 2022 and are being studied in clinical trials for at least one additional indication. If the law is not modified to expand the single-orphan exemption, manufacturers will be forced to choose between retaining the single-orphan exemption from price-setting and continuing to develop indications that could help patients.

"We've heard from a number of clients and prospective clients, both big pharma and small biotech" that are considering how the IRA will impact clinical development plans for new products, Briggs told BioCentury. Companies that are "looking to enter the clinic with potentially one or two molecules targeting a couple of different indications that each separately might have orphan drug status [are considering whether] it makes sense to continue pursuing those indications for one molecule versus potentially splitting those among molecules to insure against price negotiation."

Small company phase-ins

The IRA provides for temporary exceptions from price-setting and phase-ins for subsidy payments for small companies.

"It is critical for small companies to wrap their heads around the Part D redesign and understand what it means for their business," Lindsay Bealor Greenleaf, VP of ADVI Health, a consulting firm that specializes in commercialization and market access strategies, told BioCentury.

"When the Part D benefit redesign kicks in 2025, larger pharma and biotech companies will be on the hook for a 10% discount before the catastrophic coverage phase, and then a 20% discount in the catastrophic phase," Greenleaf explained. "If a manufacturer qualifies for the small biotech phase-in, the manufacturer's discount liability starts at only 1% across the whole benefit — before catastrophic and after — and it slowly ramps up through 2030 to the threshold that the larger pharma and biotech companies are going to be faced with in 2025."

The IRA provides small biotechs two separate pathways for phasing in financial liability for Part D manufacturer discounts, one that applies only to Medicare beneficiaries who qualify for low-income subsidies (LIS), and one for the entire benefit.

"For manufacturers meeting the definition of a 'Specified Manufacturer,' the discount phase-in would apply for LIS patients only, which represent about 27% of the Part D population, and for manufacturers meeting the definition of a 'Specified Small Manufacturer,' the phase-in would apply for all Part D patients," Greenleaf explained.

To qualify as a Specified Manufacturer, a company's total sales in 2021 must represent less than 1% of all Part D and Part B expenditures. Specified Small Manufacturers must meet the Specified Manufacturer criteria and have one Part D drug that represents more than 80% of spending on all of the manufacturer's Part D drugs.

The LIS phase-in is especially important for companies with product portfolios that are heavily weighted toward products used by the LIS population, such as antipsychotic drugs. In the current Medicare Part D design, manufacturers have no liability for rebates or discounts for LIS patients. The 10% discount in the initial phase and the 20% discount in the catastrophic phase represent new costs that, because of the IRA's inflation caps, cannot be offset with price increases.

"It's key to understand the nuances" of the law, Greenleaf added. "If the small biotech is currently or in the future

becomes a subsidiary of a larger company, the exemptions," along with delays in financial liabilities under the Part D redesign, can disappear.

While the price-setting exemption and phased-in Part D liabilities can help small biotechs, the fact that they vaporize when a product or company is acquired has negative implications for the value of the asset or company.

Winners and losers

Despite the complexity and unknowns of the IRA, it is clear that the Part D redesign will create winners and losers among biopharmaceutical companies.

Because their liability for subsidies will be limited to 10%, "manufacturers of lower cost drugs are going to be better off than they are with today's design," Greenleaf said. "Meanwhile, manufacturers of the more expensive, oncology or orphan drugs in part D are going to be much worse off" because the 20% liability in the catastrophic phase "goes on into perpetuity."

The added costs to manufacturers in the catastrophic phase will be mitigated by the $2,000 cap in out-of-pocket expenses. Lower costs will reduce the number of prescriptions patients leave behind at the pharmacy because they can't afford the co-pays.

Biopharma companies lobbied Congress for a lower out-of-pocket cap.

Manufacturers of adult vaccines will be another clear winner from the redesign as Medicare Part D will be required to provide all vaccines that are recommended by CDC's Advisory Committee on Immunization Practices with no co-pay.

Prospects for change

The possibility that Congress could modify the IRA adds another layer of complexity.

Some Republicans have vowed to repeal and replace the law. Experience with the Affordable Care Act suggests that it would not be wise for biopharma companies to bet that Congress will wipe the IRA's price-setting provisions off the books.

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Modifying the law is more realistic, but it is a long-term project.

A number of stakeholders, including BIO, PhRMA, No Patient Left Behind, individual biopharma companies and patient advocacy groups have already started creating dossiers that they hope will convince Congress to change aspects of the IRA.

"I think that at some point in time this will be amended, but I don't see it happening in the next Congress with the Democrats in control of the Senate" and President Joe Biden in the White House, Curran said. It may be necessary to build a case for change based on documenting the problems the law has caused, she added.

Kolchinsky is funding an advocacy organization, No Patient Left Behind, that is trying to persuade Congress that the nine-year threshold for Medicare price setting for drugs regulated under NDAs should be increased to match the 13 year threshold for BLA therapies.

This idea does not have universal support among industry lobbyists.

Some companies with portfolios that are heavy on biologics are arguing at PhRMA and BIO board meetings against trying to change the IRA. They note that there are several ways to level the playing field for small molecules and biologics and worry that Congress won't be receptive to adding four years to the NDA threshold. Rather than increase the nine years to 13, Congress may decrease Medicare pricing freedom for biologics to nine years, or by split the difference and set the threshold at 11 years for all drugs.

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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