Industry Update

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Journal of **Comparative Effectiveness Research**

Access in all areas? A round up of developments in market access and health technology assessment: part 2

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In this latest update, we explore the Inflation Reduction Act (IRA) enacted by the US Congress in August 2022, with the Centers for Medicare and Medicaid Services (CMS) recently releasing the list of the first ten drugs it will negotiate prices on. We also cover the consequences of price controls and rigid value assessment in Germany which have led to the withdrawal of a number of medicines. It will be important to see how the IRA balances cost-saving with holistic value assessment, incentives for innovation and patient access to treatment.

First draft submitted: 23 October 2023; Accepted for publication: 26 October 2023; Published online: 2 November 2023

Keywords: drug pricing • inflation reduction act • market access • medicare • regulatory • value assessment

The US Inflation Reduction Act (IRA), enacted in August 2022, aims to reduce financial burden for Medicare and its beneficiaries. Key changes resulting from the Act include authorizing Medicare to negotiate drug prices with manufacturers for some branded drugs, penalties for manufacturers increasing drug prices over inflation and capping of annual out of pocket costs for Medicare part D beneficiaries [1])=.

Medicare, which is the largest purchaser of prescription drugs in the US, was previously prohibited from directly negotiating drug prices. The new law authorizes the Secretary of the Department of Health and Human Services to negotiate prices for a limited number of brand-name drugs with the highest gross spending under Medicare Part B (clinician-administered) and Part D (outpatient prescription). Negotiations start in 2023 with ten Part D drugs, for prices to be applicable from 2026, with the number of drugs under negotiation cumulatively increasing each year. By 2029, negotiated prices will apply to up to 60 drugs from both Part B and Part D [1]. Moreover, the legislation aims to prevent potentially unwarranted drug price rises. From October 2022, manufacturers that raise drug prices beyond the rate of inflation will face financial penalties [2].

On 29 August 2023, the CMS (Centers for Medicare and Medicaid Services, the federal agency within Department of Health and Human Services responsible for administering Medicare and Medicaid) published their list of drugs selected for initial price negotiations for 2026 [3]. The list includes medications for anti-coagulation, diabetes, rheumatoid arthritis, haematological cancers, heart failure, psoriasis and inflammatory bowel disease (Table 1). In advance of the publication of this list, experts speculated on the most likely drugs to be selected, which have to rank high in terms of their gross cost to Medicare and be single source drugs without generic or biosimilar competition [4,5]. In addition, a drug must be at least 7 years (for small-molecule drugs) or 11 years (for biologics) past its FDA approval date. For drugs with multiple FDA approvals, CMS will use the earliest approval date to determine the number of years that have elapsed. Following CMS's publication of the list of drugs selected, there are notable differences from prior predictions. Specifically, four drugs – Farxiga, Entresto, Stelara, and Fiasp/NovoLog – were unexpected inclusions. Several commentators expressed surprise regarding Stelara's inclusion [6] as the drug is expected to face biosimilar competition in 2025 [6]. Critically, if any of the selected drugs have a biosimilar or generic competitor available by August 2024 which are meaningfully used, the original product will be exempted from price negotiation. Notably, no other drug will replace the exempted one, potentially reducing the total number

Table 1. Comparison of predicted and actual selected drugs for initial price negotiation for 2026.

Predicted drug, brand name (generic name)	Actual drug, brand name (generic name)
Eliquis (apixaban)	Eliquis (apixaban)
Xarelto (rivaroxaban)	Xarelto (rivaroxaban)
Januvia (sitagliptin phosphate)	Januvia (sitagliptin phosphate)
Imbruvica (ibrutinib)	Imbruvica (ibrutinib)
Jardiance (empagliflozin)	Jardiance (empagliflozin)
Enbrel (etanercept)	Enbrel (etanercept)
Symbicort (budesonide/formoterol)	Farxiga (dapagliflozin)
Ibrance (palbociclib)	Entresto (sacubitril/valsartan)
Xtandi (enzalutamide)	Stelara (ustekinumab)
Breo Ellipta (fluticasone/vilanterol)	Fiasp / NovoLog (insulin aspart)

Predicted drugs are those identified by Dickson and Hernandez [4] and actual drugs are those published by the CMS [3].

of drugs with negotiated prices in 2026 [6]. An additional point to note is that the Medicare spend on drugs is based on gross amounts and does not factor rebates which may currently be greater than any discount expected to be enforced from the IRA [7].

The IRA mandates that CMS considers specific manufacturer-related factors and information regarding therapeutic alternatives when negotiating a 'maximum fair price' for chosen drugs. Manufacturer-related factors include the drug research and development (R&D) costs and the extent to which these costs have been recouped, whether there has been any federal support in drug discovery and revenue and sales volume in the US. Data on the treatment itself include the degree to which the chosen medication offers a therapeutic advantage over alternative treatment options, and the cost of those alternatives. This will sound familiar to those with experience of health technology assessment (HTA); however, the IRA does not permit the use of quality-adjusted life years (QALYs) when determining the maximum fair price.

The CMS has given a structured timeline for drug pricing negotiations [8]. The manufacturers of these first 10 drugs had to decide by 1 October 2023 whether or not they would be participating in pricing discussions, and all have agreed to do so. Companies had to submit relevant economic and market data in support of their drug to the CMS by 2 October 2023. Meetings between the manufacturer and CMS agency officials will occur in the latter part of 2023 to discuss the data provided. The CMS also has outlined its intention to conduct listening sessions with patients for all ten drugs in question and consider this in their pricing determinations. CMS will present an initial written offer of the maximum fair price to drug manufacturers by 1 February 2024, with a justification based on their evaluation methodology. If the initial offer is not accepted by 2 March 2024, CMS and the manufacturer may engage in up to three negotiation meetings. A final written offer will be made by CMS by 15 July 2024. The negotiation process must conclude by 1 August 2024. If an agreement is not reached, manufacturers must pay an excise tax on product sales or have their products withdrawn from Medicare coverage.

Exactly how CMS will derive a maximum fair price is a concern for many stakeholders. Some have noted how the R&D costs of a specific molecule are hard to ascribe in companies working on many and that the R&D costs of all the failed trials in an indication need to be considered [9]. How a medicine will be valued compared with therapeutic alternatives is also not clear. There is no explicit guidance on how CMS should weight the various elements it has said it will consider when formulating its offer on the maximum fair price. Many have suggested that the holistic value a medicine delivers to patients, families and healthcare systems is what should be considered [10], for example using the value flower developed by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force [11]. To assess value in an unbiased and representative way, it has been proposed that multiple stakeholders – including patient organizations, healthcare providers, public/private payers, employers and the manufacturers – should be brought together to make the whole process a value-based price negotiation [12], rather than a unilateral price control.

The enactment of the IRA has the potential to influence future R&D efforts. Lowering pharmaceutical revenues leads to less R&D investment and fewer drug discoveries over time [13]. In their white paper, Goldman *et al.* gave a number of criticisms of the IRA [14], suggesting that it would disincentivize pharmaceutical manufacturers from investing in small molecule treatments given these would face price negotiations more quickly as compared with

biologics well as disincentivizing R&D into new indications for existing drugs given that the clock would not reset on time to price negotiations, being based on date of first FDA approval [14].

Price controls will ultimately influence patient access to medicines, as currently being observed in Germany. In November 2022, the German government passed the GKV Financial Stabilisation Act (GKV-FinStG) aiming to reduce pharmaceutical spending by German statutory health insurance funds (GKV). The legislation significantly changed drug price negotiations in a number of ways. These include changes to the AMNOG (Arzneimittel-marktneuordnungsgesetz) process, which assesses the additional therapeutic benefit of drugs and informs the negotiation of reimbursement prices by the statutory health insurance funds. GKV-FinStG impacts the pricing associated with Gemeinsamer Bundesausschuss (G-BA) benefit assessment, where premium prices are reserved for drugs found to have major additional benefit to comparators [15]. Following the AMNOG free pricing period (now reduced from 12 to six months), drugs found to have minor additional or non-quantifiable benefit have prices capped at the comparator's price and those with no additional benefit must price at 10% lower than their comparator [15]. Orphan drug status guarantees the added benefit rating in G-BA benefit assessment process below an annual revenue threshold; this threshold where the drug must undergo a full HTA has been reduced from €50 million to €30 million [15]. The legislation also introduces a 20% rebate for certain G-BA listed combination regimens and an increase to a mandatory rebate on patent-protected drugs outside the reference pricing system [15]. Despite aiming to improve financial stability for statutory health insurance funds, the legislation has now been linked to several pharmaceutical companies withdrawing new medicines from the market. For example, Rybrevant (amivantamab) and Tabrecta (capmatinib) have been withdrawn from the German market over the last year [16,17]. Both of these treatments were investigated in rare patient populations with the use of single-arm trials. Without randomized controlled trial comparisons, the G-BA often ascribes medicines with single arm trial data as having no additional benefit over comparators [18–20], which under the new legislation would leave them facing a maximum price obtainable lower than comparator drugs. For the manufacturers involved, this was not enough of a reward, especially as they believed that indirect treatment comparisons that were submitted to the G-BA were unfairly disregarded in their assessment.

The IRA, since its enactment in August 2022, has been a focal point of discussions within the healthcare sector. Its provisions, such as direct negotiations between Medicare and drug manufacturers, aim to alleviate financial strain on the Medicare system and its beneficiaries. Concerns about its potential to limit future innovation and impact patient access to medications have been raised by stakeholders. It will be interesting to see how CMS takes this feedback on board in their path to determining maximum fair prices of the first set of selected medicines. Hopefully the CMS implements a collaborative and transparent holistic value-based price negotiation, establishing a system conducive to innovation and patient access. Time will soon tell.

Acknowledgments

The views and opinions expressed in this article are solely those of the authors and do not necessarily reflect the views or opinions of their companies and affiliated organizations.

Financial disclosure

SV Ramagopalan has received an honorarium from Becaris Publishing for the contribution of this work. The authors have received no other financial and/or material support for this research or the creation of this work apart from that disclosed.

Competing interest disclosure

The authors have no financial and/or nonfinancial competing interests or relevant affiliations with any organization/entity to declare that are relevant to the subject matter or materials discussed in this manuscript. This includes employment, grants or research funding, consultancies, membership on scientific or other advisory boards, honoraria, stock ownership or options, paid expert testimony, patents received or pending, or royalties.

Writing disclosure

No writing assistance was utilized in the production of this manuscript.

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