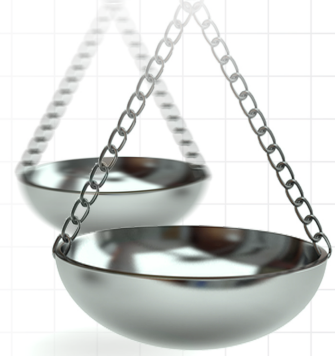
White Paper



Journal of **Comparative Effectiveness Research**

Indication-specific pricing of pharmaceuticals in the US healthcare system

Aim: To explore the potential of indication-specific pricing (ISP) of pharmaceuticals and to discuss prospects for implementation in the US healthcare system. **Materials & methods:** The Institute for Clinical and Economic Review convened a policy forum with 44 healthcare leaders from 22 payer and life sciences companies. Models of ISP were discussed. **Results:** Payers and drug manufacturers saw the potential benefits of an ISP system that balances affordability for payers, sustainability for manufacturers and access for patients. The US healthcare system presents many challenges to implementation, including potential conflicts with existing pricing policies (Medicaid Best Price, average sales price and 340B) and insufficient data systems and analytic capabilities. **Conclusion:** Possible solutions and policy recommendations for payers and manufacturers are provided.

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Keywords: health policy • indication-specific pricing • Institute for Clinical and Economic Review • multi-indication drugs • payers • pharmaceutical manufacturers • reimbursement • value-based pricing

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In the continued evolution toward a value-based US healthcare system, payers are seeking to tie healthcare reimbursement to quality and value measurements [1]. But innovations to create and test models of value-based reimbursement for drugs have, until recently, lagged behind efforts in other parts of the system [2]. Multi-indication drugs pose a particular dilemma since one drug may demonstrate superiority over existing alternatives in one indication and merely marginal benefit in another. Yet drugs are typically reimbursed in US on per unit basis with the same price paid for all covered indications, including those where benefit is marginal. Policy tools employed by payers, such as formulary tiers, step therapy rules and price benchmarks, are often driven by a single indication and may not be sufficient to address the differences in value between indications, thus leading payers to look for new policy options.

One important opportunity lies in linking the level of reimbursement of drugs to their relative clinical effectiveness across different clinical indications [3,4]. Interest in this idea of 'indication-specific pricing' (ISP) has been catalyzed in the US market by two events: the announcement by two national pharmacy benefit managers, Express Scripts and CVS Caremark that each will launch an ISP initiative in 2016 for certain cancer drugs [5,6]; and the announcement by the Centers for Medicare and Medicaid Services (CMS) that it will implement a Medicare Part B Demonstration Project which aims to change the way provider-administered drugs are reimbursed and includes ISP as a value-based pricing strategy that could be used by payers [7].

The intuitive appeal of ISP arises from the fact that the relative clinical benefit of a drug can vary widely across indications. For

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example, paclitaxel protein-bound improves median survival in metastatic breast cancer by 2.2 months over usual care, but the relative improvement in survival for metastatic non-small lung cancer is less than half of that [3]. Erlotinib, when used to treat non-small-cell lung cancer, provides a median survival gain of 3.4 months, but patients with pancreatic cancer gain only a median survival advantage of 1.4 weeks [3]. Despite these evident differences in the level of clinical benefit across indications, the drug reimbursement system in the US, rooted in a history of pricing by dosing unit, assigns a single uniform price to all drugs, no matter how they are used. As a result, price and clinical value often do not align well across multiple indications [8].

Comparative effectiveness research is in an important component of ISP. Clinical and policy decision making is more straightforward when supported by head-to-head comparisons with relevant treatment alternatives to judge the relative clinical effectiveness, risks, benefits and costs associated with a drug. However, with multi-indication drugs, such data may not be available for all indications, especially when follow-on indications are for rare diseases or for small subpopulations associated with particularly high disease burden with few alternatives. Thus, a variety of comparative effectiveness research methods and data sources will be needed to determine the relative value of a drug and the price at which it should be reimbursed.

To explore the potential for ISP to contribute to a value-based drug-pricing model, the Institute for Clinical and Economic Review (ICER) convened a Policy Summit with a group of senior medical policy figures. The purpose of the meeting was to discuss ISP of biopharmaceuticals and to explore the opportunities and challenges of ISP in the US healthcare system. In this paper, we provide a synthesis of insights collected from the literature, premeeting conversations with experts, and discussions held during the Policy Summit.

Methods

The ICER Policy Summit was held on 9–11 December 2015 with 44 healthcare leaders from 22 leading insurers, pharmacy benefit management firms and drug manufacturers that compose the ICER membership group [9]. Supplementary Table 1 lists all the attendees. A background paper was developed by ICER staff in advance of the meeting. The Policy Summit was conducted under Chatham House rules, whereby participants are able to share comments and heard perspectives at the meeting, but commit to not identify the person or organization making the statement [10]. Thus the insights in this paper are not linked to any one individual person or company but rather represent the authors' synthesis of key perspectives on ISP.

Results

Models of ISP

ISP is based upon a central principle of setting a different price for each indication, it can be administered through varying mechanisms. Three major options are described below:

Distinct product differentiation, authorized & marketed under different brand names with different prices

Some manufacturers have addressed the challenge of marketing a single drug with widely differing clinical uses by gaining regulatory approval for different brands for each indication. For example, sildenafil was initially approved for male erectile dysfunction under the brand name Viagra® (Pfizer, NY, USA) in 1998, but in 2005, it gained separate approval for the treatment of pulmonary arterial hypertension, and marketed for this use under a new brand – Revatio® (Pfizer, NY, USA) [11,12]. Viagra has an average wholesale price of $57.93 per 25 mg tablet and Revatio has an average wholesale price of $43.66 per 20 mg tablet [13]. This multiple-brand approach facilitates separate value assessments and provides a mechanism for different pricing for each indication of the same compound. It has been used selectively in the US either when the indications are distinctly different and separate brands are viewed as commercially attractive to help define the market for each or when two manufacturers license the same compound for different uses. For similar indications, however, such as treatment of different forms of cancer, multiple brands may be too burdensome or contribute unnecessary confusion.

No brand differentiation, distinct, separate discounts are applied for each indication

This option establishes different prices for each indication and administers these through a direct link to drug usage. We are unaware of any examples of this approach in the US, however, work by the Office for Health Economics in England suggests that Italy has had the most experience with this approach [14]. For example, in Italy, separate risk-sharing agreements apply on an indication-by-indication basis for the cancer drug bevacizumab, with a specific additional 7% discount applied when used in advanced colorectal cancer. This approach, though conceptually simple, can be difficult to implement, as it requires robust data systems for successful execution.

No brand differentiation, a single 'weighted-average' price is developed using estimates of indication use across the population, with

possible retrospective reconciliation through rebates based upon actual use

Instead of trying to capture indications to assign differential pricing, an alternative is to use *ex ante* population estimates to establish a single weighted-average price, and then through retrospective review of actual utilization across all indications adjust the rebate accordingly. This approach may address payer concerns about 'overuse' for lower value indications while still providing access for higher value indications.

The weighted-average method appears to be administratively simpler than other approaches and may be easier to communicate to other stakeholders such as clinicians, patients and the public. However, since this approach requires retrospective review of claims to determine reconciliation based upon actual usage by indication, it may be best suited for organizations with robust data capabilities.

Challenges to implementation

Medications are distributed and purchased in bulk without knowledge of their ultimate use and this makes linking prices with indications extremely difficult in practice. The payment transaction between a payer (e.g, health plan, insurance company, or pharmacy benefit manager) and a drug manufacturer occurs at a different point than when drug is administered or dispensed to an individual patient for a specific indication [15]. For manufacturers and payers interested in developing an ISP strategy within the complex US healthcare environment, several specific challenges must be considered.

Insufficient data systems & analytic capabilities

Capturing indication information in a precise and reliable manner can be problematic. Clinicians are not always required to provide the indication while prescribing a drug and pharmacies may not know or record the indication for which the drug is prescribed, even if the prior authorization process required by the insurer needs the information. Even when the indication is known at the point of dispensing, it may need to be verified for accuracy with the physician if it is the subject of a manufacturer rebate agreement. Medical claims may have this information but lag time and dissociation from the pharmacy benefit may limit usability. Thus, few payers currently have the data capabilities to implement ISP models that require patient-level indication information.

Drug formulary tier structure limitations & difficulty linking ISP to differential patient cost-sharing

Drug formularies are typically organized by drug category and may not have the capability to place the same drug in different tiers per indication. Administrative challenges of implementing more flexible formulary designs may make it difficult to align patient cost-sharing with value-based pricing in a transparent fashion. In principle, patients prescribed a drug for a 'higher' value indication should not face the same cost-sharing as patients prescribed the same drug for a 'lower' value indication.

Potential misalignment with Medicare provider reimbursement for office-administered drugs

Prescribing physicians and hospitals purchase certain drugs from the manufacturer (or an intermediary) at a set price per milligram in a process uncoupled from indication. Reimbursement is based upon a CMS-issued volume-weighted average sales price (ASP) derived from data submitted by manufacturers 6 months earlier [16]. Because of this delay and dissociation from actual use, circumstances could arise where the medicare reimbursement rate could be lower than the acquisition cost for some indications.

Unintended pricing effects related to Medicaid best price provisions

In exchange for coverage in state Medicaid programs, manufacturers enter an agreement with the Department of Health and Human Services to provide a quarterly rebate to state Medicaid programs based upon a statutory formula: for 'innovator' products, the base rebate amount per each unit is 23.1% of the average manufacturer's price, the price that manufacturers charge retail pharmacies before any negotiated discounts. However, if the manufacturer offers a rebate to any qualified purchaser in excess of 23.1%, Medicaid must also receive that 'best price' rebate [17,18]. ISP agreements with commercial payers could interfere with the Medicaid Drug Rebate Program if one of the indications is linked to a discount that exceeds the basic Medicaid rebate; this would trigger a new 'best price' for all uses of the drug in all state Medicaid programs and would impact the mandated price to 340B eligible entities [17,18]. Absence of an explicit exemption to the best provision from CMS, some manufacturers may be unwilling to enter into a commercial ISP contract.

Restrictions on negotiations related to off-label indications

Manufacturers can only negotiate reimbursement contracts for FDA-approved indications. Drugs that have significant off-label uses, including ones that may be supported by research, guidelines and compendia, are unlikely to be suitable candidates for ISP since a decision must be made regarding which price will

be used for off-label uses, and manufacturers cannot enter contract negotiations that give the perception of promoting off-label use.

Anti-kickback laws creating legal concerns

A federal Anti-kickback Statute prohibits offering or receiving remuneration to induce or reward referrals for items or services paid for by federal healthcare programs [19]. It is possible that an ISP arrangement under which the manufacturer accepted risk for 'overuse' of a drug for a lower value indication could be viewed as remuneration offered to encourage the health plan to favorably cover the manufacturer's product. Statutory and regulatory safe harbors protect certain arrangements from Anti-kickback Statute liability, but it is unclear how enforcement agencies would apply these safe harbors to ISP contracts.

Discussion

Possible solutions & policy recommendations

Although ISP may appear to clash with the US healthcare system, several approaches may help to address the challenges that any ISP program would face. Recommendations for payers and manufacturers are summarized in Table 1 and presented in detail below.

Payers can use prescription claims & improve data systems to capture indication information

Whether using a single weighted-average price or separate, differential discounts by indication, ISP requires robust data capabilities that are not available system-wide today. Nonetheless, some payers have the data capture capabilities and cross-platform integration to support innovative reimbursement models that depend upon claims information. Other payers can seek to improve these capabilities.

Drug markers or ICD-10 codes from claims data could be used as surrogates to help identify the indication, but this would be limited to indications that can be clearly identified and are easy to distinguish from each other, such as rheumatoid arthritis and cancer. Prescribing physicians, either through prior authorization, as part of a new prescription format or both, could be required to report the indication for each patient receiving a drug. Specialty pharmacies that serve as intermediaries between manufacturers and patients have extensive data tracking capabilities that could be adapted to capture indication.

For infused products, the issuance of different billing codes for physician-administered drugs (usually referred to as J codes and issued by CMS) for different indications could be a simple way to differentiate uses. For oral products, National Drug Codes are the universal product identifier assigned post-FDA approval and used to bill payers [20]. Creation of additional National Drug Codes for billing purposes would be difficult and is less realistic than the assignment of different J codes.

Payers can work with existing formularies

The inflexibility of drug formulary tiers *can* be addressed in the short run by selecting drugs for which pricing can vary by indication but formulary tier remains consistent.

Manufacturers & payers can focus ISP programs on oral drugs with indications across different conditions & by using a single weighted-average price approach

Although oral drugs are not entirely unaffected by ISP, oral drugs are more likely to avoid entanglement with infusion-based ASP-plus pricing policies that might create financial losses for practitioners using the drug for its lower value indication. To address concerns about ASP, infused drugs could be distributed and coded based on their separate indications to accommodate the process of physicians and hospitals buying and then billing after the drug is administered. But this approach would require extensive administrative work.

Payers & manufacturers will need to work to understand the potential implications of CMS including ISP in the Medicare Part B Demo

It is unclear whether CMS will proceed with its proposed National Part B demonstration program in which regions of the country would be randomized to either retain the current ASP + 4.3% payment structure or shift to an ASP + 2.5% + a fixed-fee model. With either model clinicians risk losing money if they predominantly prescribe a drug for its 'lower value' indication in an ISP approach.

As the largest payer of provider-administered drugs, any changes to Medicare reimbursement in the buy and bill system is likely to have a big impact on the healthcare system overall. Thus, commercial payers may be reluctant to make significant changes until more is known about the Medicare Part B Demo. If CMS opts to use ISP itself for some Part B drugs, private insurers and manufacturers to follow suit for those drugs. If CMS does not move forward with ISP, payers and manufacturers interested in trying to implement ISP contracts for provider-administered drugs should work together to present to CMS formal requests to create exemptions to the ASP-based reimbursement mechanisms that currently obstruct ISP pilots.

Similarly, the Medicaid Best Price policy could be modified to accommodate ISP models by specifying

an allowance for different best prices for different indications, and that any new, lower best price created by an ISP agreement will affect only the best price for that indication. The consequence of this modification would allow ISP contracts without affecting Medicaid best price for drug prices that are undifferentiated by indication.

Payers & manufacturers can minimize the challenge presented by off-label use through drug selection & by using the weighted-average ISP model

Communication between payers and manufacturers regarding off-label use of pharmaceuticals is an ongoing area of debate: policies are unclear and

Table 1. Summary of challenges and potential solutions for indication-specific pricing programs in the US market.

Challenges	Potential solutions
Insufficient data systems and analytic capabilities	Use claims data and improve data systems to capture the indication for each prescription use
Limitations of drug formulary tier structure and difficulty linking ISP to differential patient cost-sharing	Select drugs for which pricing can vary by indication but formulary tier can remain consistent
Potential misalignment with Medicare provider reimbursement for office-administered drugs	Focus ISP pilots on oral drugs with indications across different conditions and use a single weighted-average price approach Request that federal policy makers include ISP in Medicare Demonstration projects
Unintended pricing effects related to Medicaid best price provisions	Focus ISP pilots on oral drugs with indications across different conditions and use a single weighted-average price approach Request that federal policy makers include ISP in Medicare Demonstration projects that include exemptions from Medicare and Medicaid pricing provisions Request changes to Medicaid best price provisions so that best prices are linked to specific indications
Restrictions on negotiations related to off-label indications	Select drugs for ISP that have minimal off-label use, apply price adjustments only to labeled indications, and use a weighted-average approach to ISP
Anti-kickback statutes create legal concerns	Both payers and manufacturers should be mindful of anti-kickback laws forbidding certain kinds of contractual promotion of products that are reimbursable by federal healthcare programs

ISP: Indication-specific pricing

Table 2. Legal and regulatory challenges for indication-specific pricing.

Regulatory and legal issues affecting indication-specific pricing	Corresponding statutes/regulations	Ref.
Medicare average sales price 2	42 U.S.C. Sect. 1395w-3a 42 C.F.R. Sect. 414.804	[5]
Medicaid best price rebate program	42 U.S.C. Sect. 1396r-8 42 C.F.R. Sect. 447.505	[1,22]
Office of Inspector General, Federal Anti-kickback Statute	42 U.S.C. Sect. 1320a-7b(b)	[23,24]
Health Resources and Services Administration, 340B Drug Pricing Program	42 U.S.C. Sect. 256b	[17]
Off-label promotion of drugs	21 C.F.R. Sect. 312.7	[22]

C.F.R.: Code of Federal Regulations; Sect.: Section; U.S.C.:United States Code.

challenging to interpret [21]. However, off-label use should not be an insurmountable barrier to ISP. Recognizing that limitations exist on promotion of off-label indications, and that some utilization will fall outside the FDA-approved drug label, payers and manufacturers can address these concerns by selecting drugs for ISP that have minimal off-label use, by applying indication-specific price adjustments only to labeled indications, and by using a weighted-average approach to ISP.

Both payers & manufacturers should be mindful of anti-kickback laws forbidding certain kinds of contractual promotion of products that are reimbursable by federal healthcare programs

Table 2 presents a cumulative list of the statutes and regulations that may impinge on ISP agreements.

Conclusion

The 2015 ICER Policy Summit set out to explore the potential benefits and risks of ISP for pharmaceuticals in the US healthcare system, to understand the barriers to its implementation and to explore potential solutions and policy recommendations. Payers and manufacturers both saw the potential of ISP as a mechanism to align their efforts for better patient access to innovative medicines at prices that achieve the twin goals of affordable healthcare system and a sustainable business model. However, ISP is but one of many possible policy tools available to payers and manufacturers. Some payers feel that they may be able to achieve the broader goals of ISP through the application of existing medical policy tools, such as step therapy policies, tiered formularies and vigorous price negotiation using some form of value-based price benchmarks. And payers were clear that ISP, by itself, does not meet challenges to affordability.

Manufacturers, although encouraged by successful ISP contracts in non-US markets, were also realistic in acknowledging the many barriers to this approach in the US. It is not easy to find a payer partner with the necessary database capabilities and willingness to take on the risks associated with an ISP pilot program. Additionally, Medicaid best price provisions and ASP-based reimbursement create significant challenges for manufacturers interested in developing differential prices by indication.

Despite awareness of the limitations and risks of ISP, there remained much support for its general goals and interest in its possibilities. Many will be watching how ISP pilots undertaken by Express Scripts and CVS Caremark will fare in commercial pharmacy benefit management programs. These initiatives will provide important signals regarding the prospects for further development of ISP in the US.

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Supplementary data

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Executive summary

- Indication-specific pricing (ISP) aims to link the level of reimbursement for drugs to their relative clinical effectiveness with a different price for each indication.
- Interest in ISP has been catalyzed in the US market by two events: the announcement by two national pharmacy benefit managers, Express Scripts and CVS Caremark, that each will launch an ISP initiative in 2016 for certain cancer drugs; and the announcement by the Centers for Medicare and Medicaid Services (CMS) that it will implement a Medicare Part B Demonstration Project which aims to change the way provider-administered drugs are reimbursed and includes ISP as a value-based pricing strategy that could be used by payers.

Methods

- To explore the potential for ISP to contribute to a value-based drug pricing model the Institute for Clinical and Economic Review convened a Policy Summit with a group of 44 senior medical policy figures from 22 leading insurers, pharmacy benefit management firms and drug manufacturers that compose the Institute for Clinical and Economic Review membership group.
- The purpose of the meeting was to discuss ISP of biopharmaceuticals and to explore the opportunities and challenges of ISP in the US healthcare system.

Models of ISP

- Distinct products marketed under different brand names with different prices.
- No brand differentiation but separate and distinct discounts applied for each indication.
- No brand differentiation but a single weighted-average price is developed using estimates of indication use across the population with possible retrospective reconciliation based upon actual use.

Challenges to implementation

- In the current reimbursement system, the payment transaction between a payer and a drug manufacturer occurs at a different point than when drug is administered or dispensed to an individual patient for a specific indication, thus making it difficult to link indication to price.
- Capturing indication information in a precise and reliable manner can be problematic due to insufficient data systems and analytic capabilities.
- Drug formularies are typically organized by drug category and may not have the capability to place a drug in different tiers per indication.
- ISP may clash with existing Medicare reimbursement of office administered drugs, which is based upon CMS-issued average sales price.
- ISP agreements with commercial payers may interfere with the Medicaid Drug Rebate Program if one of the indications is linked to a discount that exceeds the basic Medicaid rebate; this would trigger a new 'best price' for all uses of the drug in all state Medicaid programs and would impact the mandated price to 340B eligible entities.
- Drugs with significant off-label uses are unlikely to be suitable candidates for ISP since manufacturers cannot enter negotiations that appear to promote off-label use.
- A federal Anti-kickback Statute prohibits offering or receiving remuneration to induce or reward referrals for items or services paid for by federal healthcare programs.

Possible solutions & policy recommendations

- Payers can use prescription claims and improve data systems to capture indication information.
- The inflexibility of drug formulary tiers can be addressed in the short run by selecting drugs for which pricing can vary by indication but formulary tier remains consistent.
- Manufacturers and payers can focus on the ISP programs on oral drugs with indications across different conditions and by using a single weighted-average price approach.
- Payers and manufacturers can minimize the challenge presented by off-label use through drug selection and by using the weighted-average price approach.
- Both payers and manufacturers should be mindful of anti-kickback laws forbidding certain kinds of contractual promotion of products that are reimbursable by federal healthcare programs.

Conclusion

- Payers and manufacturers both saw the potential of ISP as a mechanism to align their efforts for better patient access to innovative medicines at prices that achieve the twin goals of affordable healthcare system and a sustainable business model. However, ISP is but one of many possible policy tools.
- Some payers feel that they may be able to achieve the broader goals of ISP through the application of existing medical policy tools.
- Manufacturers, although encouraged by successful ISP contracts in non-US markets, were also realistic in acknowledging the many barriers to this approach in the USA.
- Despite awareness of the limitations and risks of ISP, there remained much support for its general goals and interest in its possibilities. Many will be watching how ISP pilots undertaken by Express Scripts and CVS Caremark will fare in commercial pharmacy benefit management programs. These initiatives will provide important signals regarding the prospects for further development of ISP in the USA.

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