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WHITE PAPER

Global Market Access Trends: 2022 Edition

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Introduction

The year 2021 brought about key changes to the pricing and reimbursement landscape globally, motivated in part in response to global changes brought about by the pandemic and its resultant economic pressures. In 2022, we found that major changes to the pricing and reimbursement landscape have continued to prevail across all markets as regulators and payers continue to evolve their strategies amidst accelerated development processes and the rapid evolution of therapeutic standards.

In this white paper, Trinity's Evidence, Value, Access and Pricing experts identify the trends emanating from 2022 that will lay the foundation for the opportunities and challenges that pharmaceutical manufacturers may face in 2023 and beyond.

Key Global Market Access Trends of 2022

1 Evolving Evidence Expectations

Value demonstration for products with early evidence continues to encounter challenges as payers and regulators attempt to catch up.

2 Spreading of Joint Health Technology Assessment

While several middle-income countries are in the early phases of introducing health technology assessment (HTA) bodies, HTAs are becoming increasingly collaborative across countries where HTAs are already well established.

3 Increasing Price Transparency Regulation

Greater net-price transparency is an ongoing goal of legislators and payers, but 2022 saw some of the strongest implementations and rhetoric deployed to date.

4 Persisting Appraisal Challenges Associated With Cell and Gene Therapy Expansion

The entry of new cell and gene therapies, as well as the expansions of existing therapies, is altering the pricing and reimbursement landscape for cell and gene products.

5 Changing Early and Orphan Access Opportunities

New policies have been introduced globally to manage the high budget impact of therapies with early and orphan access designations.

Payer Perspectives

A survey was conducted in September 2022 to capture payers' insights about the trends that have been identified in this white paper.

The sample consisted of 11 U.S. payers and 24 payers from global markets across 4 continents.

U.S. payers (n=11)
ex-U.S. payers (n=24)

Country of Respondent	Number of Respondents (n)
Brazil	2
Canada	2
China	2
France	2
Germany	3
Italy	3
Mexico	3
Spain	5
United Kingdom	2
United States	11

Insights from this survey have been included with each trend, including the mean average score within **U.S. and ex-U.S. payer groups** about their perception of impact for each category.

Evolving Evidence Expectations

Value demonstration for products with early evidence continues to encounter challenges as payers and regulators attempt to catch up.

Under the 21st Century Cures Act, the U.S. Food and Drug Administration (FDA) now accepts Real-World Evidence (RWE) as part of the manufacturer's submission package, with increasing requests for real-world evidence in innovative technology launches (e.g., demonstrating unmet needs in a market prior to a new therapy launch and/or leveraging cost analyses to characterize current healthcare resource utilization and cost of care).

U.S. payers have rated their organizations to be more receptive to considering real-world evidence in their review of new products compared to ex-U.S. payers, signifying an opportunity for U.S. manufacturers to provide more robust evidence as part of their submission packages as well as on-going value communications with payers.

With respect to higher evidence expectations, one drug that had high coverage in the news in 2022 was Biogen's Aduhelm (aducanumab) due to the decision from Centers for Medicare & Medicaid Services (CMS) to restrict coverage until further efficacy evidence was provided.

Aduhelm received its FDA accelerated approval in July 2021 as the first amyloid beta-directed antibody in the Alzheimer's Disease (AD) space.[1] Although the final decision by the FDA noted that the surrogate endpoint was "reasonably likely to predict a clinical benefit to AD patients," this approval was mainly driven by champions of the product given that the majority on the FDA advisory panel had opposed the drug's approval. Members of the advisory panel noted skepticism around the validity of the surrogate endpoint.[2]

> "We have seen more cellular therapies and increased rare diseases which have been more difficult to predict. We have [also] seen combination therapies which have increased overall expense beyond initial predictions as well. [As a result] we have utilized more real-world evidence in our decision making [this year]."
>
> **U.S. Payer**
> **Large Regional Healthcare System**

Payer Perspectives

How impactful do you perceive evolving evidence expectations to be in 2022?

Rating:
1 = Hardly any impact
5 = A dominating force

U.S. Payer Perception of Impact:

3.7/5

Ex-U.S. Payer Perception of Impact:

3.4/5

How receptive is your organization to considering RWE in your organization's management of new products?

Rating:
1 = No RWE consideration
10 = RWE considered similarly to clinical trial evidence

U.S. Payer Perception of Impact:

6.4/10

Ex-U.S. Payer Perception of Impact:

4.2/10

CMS made the decision to restrict coverage until additional efficacy and safety evidence is available citing similar skepticism expressed by the FDA advisory panel. These restrictions placed despite FDA approval marks a new evolution of evidence expectations for coverage on the payer side, breaking the precedence of CMS typically covering all drugs which are approved by the FDA. While this severity has only been seen in the AD space so far, such expectations may set a precedent for other disease areas. Furthermore, this action underscores payers' growing role as a check on regulatory bodies' decisions in the U.S. This development also comes at a time when the biopharmaceutical market may be approaching a significant slowdown due to biological products' patent expirations.[3]

Aduhelm was not the only case of accelerated pathway approval to come under scrutiny in recent years. 2022 is the first year where we are beginning to see a decreased number of therapies approved through the U.S. accelerated approval pathway compared to the all-time high use of this pathway in the past five years.[4,5,6]

Launched in 1992, the accelerated approval pathway was initially created as a timely mechanism to allow promising drugs to enter the market and since its implementation, it has been credited for accelerating the entry of early breakthroughs for HIV and cancer. However, it has been increasingly criticized by Congress and government watchdogs alike for allowing "expensive, unproven drugs" onto the market, particularly in the oncology space. It was found, for example, that 40% of drugs approved through this pathway had incomplete confirmatory studies. In efforts to combat this and address mounting concerns, the FDA has been reviewing their accelerated approval lists and removing approvals that have yet to satisfy confirmatory studies. How the FDA has refined the approval process itself, however, remains unknown.

Challenges associated with accelerated approval pathways are not unique to the US. Payers globally predict that more drugs will continue to be presented earlier with weaker evidence, likely in part due to these accelerated processes being highly utilized in recent years.

Consequently, alongside increased evidence expectations seen within the U.S., Germany has also released new requirements for evidence in 2022 (see Changes to Early and Orphan Access Opportunities). Payers note, however, that increased expectations have been a primary driver in Germany experiencing more market withdrawals in 2022 than typical.

Key Events for Aduhelm Along the Regulatory / Access Process

JUNE 2021
Aduhelm is granted 'Accelerated Approval' by the FDA.

JULY 2021
CMS begins National Coverage Determination (NCD) analysis.

DECEMBER 2021
Biogen applies a 50% cost reduction to Aduhelm.

APRIL 2022
CMS releases their NCD decision with heavy restrictions, and the European Medicine Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) advises Biogen of the need to supply additional clinical evidence to secure a favorable opinion of the drug in Europe.

In reaction to advice from CHMP, Biogen withdraws Aduhelm from the EMA's authorization process within the same month.

MAY 2022
In reaction to the NCD decision and advice from the CHMP, recruitment for a phase IV clinical trial begins.

SEPTEMBER 2022
Biogen and Eisai announced positive top-line data from their partnered Phase III Clarity trial where Lecanemab has hit both its primary and secondary endpoints. The final FDA accelerated approval decision date is January 6th, 2023.

Strategic Implications

U.S. payers have rated their organizations to be more receptive to considering RWE in their review of new products compared to ex-U.S. payers; signifying that RWE may have a more impactful role in U.S. markets than other markets in the near term.

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[1] FDA grants accelerated approval for Aduhelm™ as the first and only alzheimer's disease treatment to address a defining pathology of the disease20. Biogen. (2021, June 7). Retrieved January 6, 2023, from https://investors.biogen.com/news-releases/news-release-details/fda-grants-accelerated-approval-aduhelmtm-first-and-only

[2] Sutton, S. (2022, March 22). Addressing the Aduhelm controversy. The Medicine Maker. Retrieved January 6, 2023, from https://themedicinemaker.com/business-regulation/addressing-the-aduhelm-controversy

[3] Arda Ural, P. D., Baral, S., & Sussholz, E. (2022, February 17). Ecosystems Can Help Fill the Life Sciences Innovation Gap. Ecosystems can help fill the life sciences innovation gap | EY Norway. Retrieved January 6, 2023, from https://www.ey.com/en_no/life-sciences/how-ecosystems-can-help-fill-the-life-sciences-innovation-gap

[4] Perrone, M., & Press, T. A. (2022, December 7). The FDA's Speedy approval of experimental new drugs came to a screeching halt this year. Fortune. Retrieved January 7, 2023, from https://fortune.com/2022/12/07/fda-accelerated-pathway-speedy-approval-experimental-drugs-slows-2022-this-year/

[5] Craven, J. (n.d.). FDA approved more first-in-class drugs and gave more accelerated approvals in 2021. Regulatory Affairs Professionals Society (RAPS). Retrieved January 7, 2023, from https://www.raps.org/news-and-articles/news-articles/2022/1/fda-approved-more-first-in-class-drugs-more-with-a

[6] Bio News. FDA cuts back on Accelerated Approval pathway in 2022. https://bio.news/health/fda-responds-to-misguided-criticism-cuts-back-on-accelerated-approval-pathway-in-2022/#:~:text=The%20FDA%20significantly%20cut%20back,patients%20reached%20all%2Dtime%20highs

Spreading of Joint Health Technology Assessment (HTA)

While several middle-income countries are in the early phases of introducing HTA bodies, HTAs are becoming increasingly collaborative across countries where HTAs are already well established.

Health technology assessments (HTAs) serve as the cornerstone of pharmaceutical regulation in many developed countries, meanwhile **several middle-income and developing countries are still in the early phases of introducing HTA bodies**. In this process, how the new organizations learn best practices from existing groups will have a significant impact on how pricing and market access outcomes are impacted/informed in those markets.

- Recent research in sub-Saharan Africa shows that despite growing interest in HTA organizations, awareness remains low, and HTA-related activities are uncoordinated and often disconnected from policy.[7]
- In Asia, whereas Malaysia, Singapore and Thailand have well-established processes and methods for priority setting through HTA; other countries such as Cambodia, Indonesia, Lao People's Democratic Republic, Myanmar, the Philippines and Vietnam have started to develop HTA systems by establishing nodal agencies (e.g., working groups) or conducting ad-hoc activities.[8]

Payer Perspectives

How impactful do you perceive the trend of increasing joint HTAs to be in 2022?

Rating:
1 = Hardly any impact
5 = A dominating force

U.S. Payer Perception of Impact:

2.7/5

Ex-U.S. Payer Perception of Impact:

3.3/5

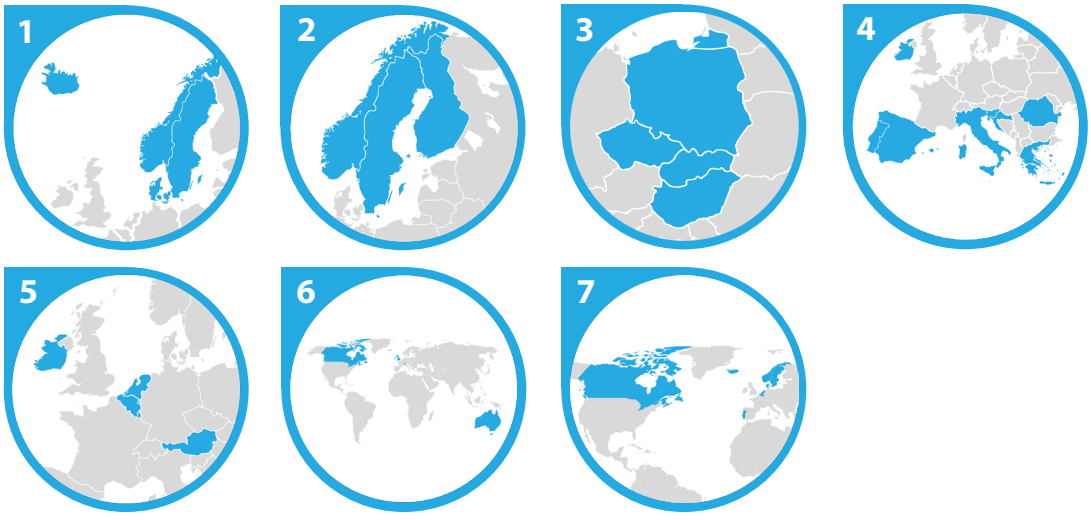
Global Collaborative HTA Systems / Initiatives

1) Nordic Pharmaceutical Forum
Iceland, Norway, Sweden, Denmark

2) FiNoSe
Finland, Norway, Sweden

3) The Visegrád Group
Czech Republic, Hungary, Poland, Slovakia

4) The Valletta Declaration
Cyprus, Greece, Italy, Malta, Portugal, Spain, Croatia, Ireland, Romania, Slovenia



5) BeNeLuxA
Belgium, The Netherlands, Luxembourg, Austria, Ireland

6) Access Consortium
Australia, Canada, Singapore, Switzerland, U.K.

7) Transcontinental Market Access Working Group
Denmark, Norway, Sweden, Iceland, The Netherlands, Belgium, Portugal, Canada

As HTA bodies continue to formalize in these aforementioned countries, increased collaboration has been observed in countries where HTA bodies are more established (see 'Global Collaborative HTA Systems' on the previous page).

The International Network of Agencies for Health Technology Assessment reached 50 members in 2022, adding both the Slovak Republic National Institute for Value and Technologies in Healthcare (NIHO)[9] & Brazil Agência Nacional de Saúde Suplementar (ANS) as members.[10,11]

The 'elephant in the room' of HTAs is the pan-European joint clinical assessment (JCA), which in 2022 began the work of aligning on a shared HTA process to begin in 2025. There are milestones in place between then and 2030 as the body slowly ramps up to assess all products entering these markets. While member countries will of course still be able to conduct their own analyses, they have until 2025 to adopt national legislation which accommodates the JCA's new presence.

As HTAs continue to collaborate explicitly, informal sharing of best practices was also on display in 2022. In particular, the use of cost-effectiveness (CE) analysis expanded to Italy and Spain as a formal part of their processes, adding an additional hurdle to successful access and reimbursement in those nations. CE is also being considered by National Committee for Technology Incorporation (CONITEC) in Brazil as an additional component of their assessments.[12] Given that existing CE markets are often those which achieve the highest discounts, the spread of this methodology could result in increased downward pricing pressure in affected markets.

Canada is also exploring joint HTA and negotiation drug pricing, with a recent partnership established between the Canadian Agency for Drugs and Technologies in Health (CADTH) and other international HTA bodies such as Healthcare Improvement Scotland, the National Institute for Health and Care Excellence (NICE), Health Technology Wales, All Wales Therapeutics and Toxicology Centre, and the Australian Government Department of Health and Aged Care. The agreement between these bodies recognized shared priorities such as the following five initial priority areas: COVID-19, futureproofing of HTA

Further Reading

EU Adopts Regulation on Pan-European Health Technology Assessment

Read Now >

> "There is a need for transparent cooperation from the very beginning of product development between regulators, payers and companies. Collaboration has always been talked about but has never really been achieved effectively."
>
> **Italy Payer**
> **National Agency for Regional Health Care**

systems, collaborating with regulators, work-sharing and efficiency gains, and digital and artificial intelligence.

In 2022, nine countries (Denmark, Norway, Sweden, Iceland, The Netherlands, Belgium, Portugal and Canada) formed a transcontinental market access working group and discussed potential solutions to ensure sustainable and equitable access to effective medicines, particularly in smaller markets.[13] The organizations have agreed that, going forward, they will focus on ways to manage insufficient data on the effect of new, expensive medicines, to help secure stable and effective access to new medicines.

> More scrutinized assessments have been imposed due to the financial problems derived from the pandemic. Cost-effectiveness analysis has been applied to more health technologies.
>
> **Spain Payer**
> **Public Academic Research**

Strategic Implications

The new JCA regulation is expected to have a significant impact on the future of EU HTA submissions as it is expected to allow for timely access decisions by pooling the HTA resources and expertise across markets; however, it remains to be seen how this pan-European assessment will be adapted and applied to each national HTA assessment, as procedures greatly differ between EU member states. Manufacturers may benefit from early engagement with emerging markets where HTA bodies are still developing, establishing strong relationships from a product-agnostic perspective through institutional support.

[7] Hollingworth, S., Fenny, A. P., Yu, S.-Y., Ruiz, F., & Chalkidou, K. (2021, July 7). Health Technology Assessment in Sub-Saharan Africa: A descriptive analysis and narrative synthesis - cost effectiveness and resource allocation. BioMed Central. Retrieved January 6, 2023, from https://resource-allocation.biomedcentral.com/articles/10.1186/s12962-021-00293-5

[8] Sharma, M., Teerawattananon, Y., Dabak, S. V., Isaranuwatchai, W., Pearce, F., Pilasant, S., ... & Htoo, T. S. (2021). A landscape analysis of health technology assessment capacity in the Association of South-East Asian Nations region. Health research policy and systems, 19(1), 1-13

[9] INAHTA welcomes Niho Slovak Republic as a member! INAHTA. (2022, June 7). Retrieved January 6, 2023, from https://www.inahta.org/2022/06/inahta-welcomes-niho-slovak-republic-as-a-member/

[10] INAHTA welcomes ANS Brazil as a member! INAHTA. (2022, February 22). Retrieved January 6, 2023, from https://www.inahta.org/2021/12/inahta-welcomes-ans-brazil-as-a-full-member/

[11] INAHTA members list. INAHTA. (2022, October 21). Retrieved January 7, 2023, from https://www.inahta.org/members/members_list/

[12] Comissão Nacional de Incorporação de Tecnologias no Sistema único de saúde. CONITEC. (n.d.). Retrieved January 6, 2023, from http://conitec.gov.br/images/Consultas/Relatorios/2022/20220620_Relatorio_Oficina_Limiares_2022.pdf)

[13] 9 Countries Form Transcontinental Market Access Working Group. NAVLIN DAILY. (2022, November 29). Retrieved January 7, 2023, from https://www.navlindaily.com/article/14862/9-countries-form-transcontinental-market-access-working-group

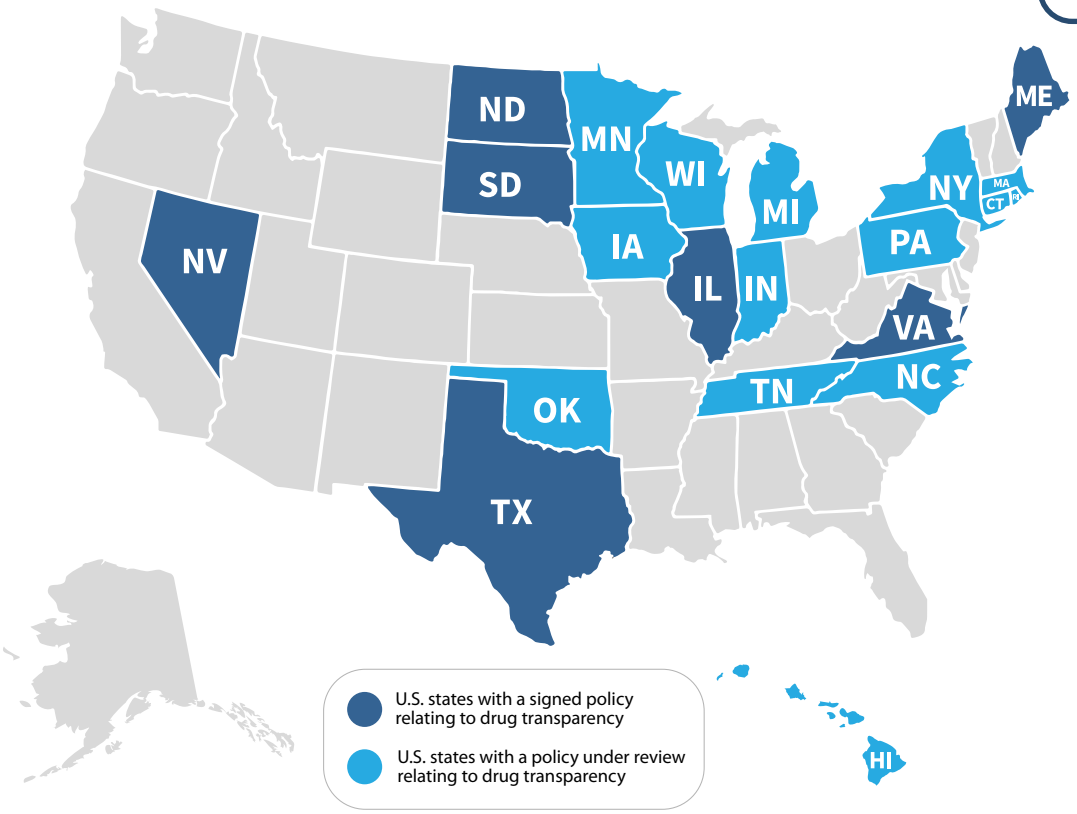
Increasing Price Transparency Regulation

Greater net-price transparency is an ongoing goal of legislators and payers, but 2022 saw some of the strongest implementations and rhetoric deployed to date.

United States

In the U.S., there was action at both the federal level via the Centers for Medicare & Medicaid Services (CMS) hospital transparency and wastage rules as well as in individual states - with five states adding laws in 2022, for a total of nineteen overall. The details of these programs vary significantly across states, imposing a burdensome patchwork of disclosure requirements on manufacturers. The most common model is that of a Prescription Drug Accountability Board – a body which monitors price changes and makes inquiries into products with particularly high increases between years.

U.S. States With Drug Pricing Policies That Are Under Review or Already Signed Into Law



Payer Perspectives

How impactful was the trend of increasing price transparency regulation in 2022?

Rating:
1 = Hardly any impact
5 = A dominating force

U.S. Payer Perception of Impact:

3.7/5

Ex-U.S. Payer Perception of Impact:

3/5

Further Notes:

Across recent years, states' interest in moderating drug prices has been focused on regulating pharmacy benefit managers (PBMs) and their practices. Notably, New York (NY) recently passed legislation which mandates PBMs obtain licensing from the State Department of Financial Services

Recent legislation in Virginia (VA) requires managed care organizations to include provisions in their contracts with PBMs that prohibit "spread pricing"; when the PBM pays pharmacies less for prescription drugs than it charges health plans. The PBM then pockets the difference.

Internationally, the World Health Organization (WHO) increased the urgency of its call for price transparency via the Oslo Medicines initiative, releasing documents explaining the benefits to policymakers and encouraging policy innovation in the space.[14,15]

Europe

This trend is at an earlier phase in the EU from a regulatory perspective, though longstanding informal sharing of new prices between payers may already exist. In 2022, the European Parliament formally recommended increasing the transparency of net prices as a part of their broader Beat Cancer Plan strategy.[16] In local markets there is more heterogeneity in practice – for example, while Italy has imposed requirements for reimbursement submissions to include discounts or managed entry agreements in other EU countries, Germany has reduced restrictions around transparency in the biosimilars area to enable greater confidentiality in these products' net prices.[17] Germany further reassessed its combinations legislation, but determined that rather than reduce transparency restrictions, combinations will be subject to the Act on the Reform of the Market for Medicinal Products (AMNOG) rules alongside a new combination markdown. This new required markdown for combinations is stated to be 20% of the company's sales price unless a benefit assessment of "significant benefit" is achieved through the AMNOG assessment for the combination.

The claim that this trend is at an earlier stage in the EU is further supported by our survey results, as ex-U.S. payers (specifically EU payers) expressed greater difficulty in manufacturer price negotiations. Notably, differences in difficulty are not comparative to previous years and may reflect cultural differences between U.S. and ex-U.S. respondents. The higher difficulty expressed by ex-U.S. respondents may also be linked to the launch of Joint Clinical Assessmentsin the EU in 2022 (see the HTA section in this white paper).

Payer Perspectives

How would you assess the difficulty of determining the appropriate management approach for the products you reviewed in 2022?

Rating:
1 = Very straightforward
10 = Highly challenging

U.S. Payer Perception of Impact:

4.7/10

Ex-U.S. Payer Perception of Impact:

7.1/10

JCAs were introduced in the EU as a way to offer a unifying health technology assessment to EU member states in an effort to centralize the assessment process to promote equitable access for middle and lower income European markets. The higher difficulty for ex-U.S. payers may be capturing some of the difficulties EU payers and manufacturers were experiencing that led to the introduction of joint clinical assessments.

Japan

Japan also pushed for even greater price transparency in 2022 via a change to the Monthly Labor Survey (MHLW) Cost Accounting pricing method for drugs with no existing price benchmark. Under this method, products without an appropriate comparator for pricing are priced via a premium to costs associated with manufacturing, research and development and other factors. While a premium over costs is awarded, the size of that premium depends on how forthcoming manufacturers are with their cost information. While formerly this premium modifier was 0.2, in cases of disclosure rates below 50%, it has now been reduced to 0.

In other words, manufacturers that fail to achieve the 50% disclosure rate will receive no premium at all in their price. Although this law aims to strongly incentivize pricing transparency in alignment with Japan's already high pricing transparency expectations, it remains to be seen whether this particular incentive will be sufficient in inciting significant change to pricing transparency in Japan. Manufacturers should come prepared to provide ex-Japan to Japan transfer prices if unable to deliver satisfactory transparency to validate submitted prices.

Further Reading

Japan's Latest Drug Pricing Policy Updates: Key Changes and Expected Impact

Read Now >

Strategic Implications

To the extent that these regulations publicize private discounting variation across states and payers, they will likely serve to strengthen the negotiating position of payers to push for the discounts they see offered in other markets.

[14] World Health Organization. (n.d.). Promoting price transparency - WHO Guideline on Country Pharmaceutical Pricing Policies. Retrieved January 6, 2023, from https://apps.who.int/iris/bitstream/handle/10665/341898/9789240024632-eng.pdf?sequence=1

[15] World Health Organization. (n.d.). The Oslo Medicines Initiative. World Health Organization. Retrieved January 6, 2023, from https://www.who.int/europe/initiatives/the-oslo-medicines-initiative

[16] MEPs call for a more effective EU strategy to beat cancer: News: European parliament. MEPs call for a more effective EU strategy to beat cancer | News | European Parliament. (2022, February 16). Retrieved January 6, 2023, from https://www.europarl.europa.eu/news/en/press-room/20220210IPR23006/meps-call-for-a-more-effective-eu-strategy-to-beat-cancer

[17] Partnersadmin. (2021, October 3). Will AIFA's net price disclosure requirement be a game-changer for Orphan Drug Access? " partners4access. Partners4Access. Retrieved January 6, 2023, from https://partners4access.com/blogs/will-aifas-net-price-disclosure-requirement-be-a-game-changer-for-orphan-drug-access/

Persisting Appraisal Challenges Associated With Cell and Gene Therapy Expansion

The entry of new cell and gene therapies, as well as the expansions of existing therapies, is altering the pricing and reimbursement landscape for cell and gene products.

2022 has witnessed both the approval of new therapies (e.g., Carvkyti, a CAR-T cell therapy by Legend biotech and Johnson & Johnson was approved for multiple myeloma on February 18th, 2022) and the launch of existing therapies into new indications (e.g., FDA's approval of Kite Pharma's Yescarta as a second line therapy for patients who have relapsed just once from Large B-Cell Lymphoma (DLBCL)). In 2022, the total number of globally approved gene therapies reached 22, the total number of RNA therapies approved reached 21, and the total number of non-genetically modified cell therapies reached 59.[18,19]

Gene Therapies
ABECMA®
BREYANZI®
CARVYKTI®
COLLATEGENE®
DELYTACT®
GENDICINE®
IMLYGIC®
KYMRIAH®
LIBMELDY®
LUXTURNA®
NEOVASCULGEN®
ONCORINE®
RELMA-CEL®
REXIN-G®
ROCTAVIAN®
SKYSONA®
STRIMVELIS®
TECARTUS®
UPSTAZA®
YESCARTA®
ZOLGENSMA®
ZYNTEGLO®

RNA Therapies
AMONDYS 45®
AMPLIGEN®
AMVUTTRA®
ARCoV®
COMIRNATY®
EXONDYS 51®
GENNOVA COVID-19 VACCINE
GIVLAARI®
KYNAMRO®
LEQVIO®
MODERNA COVID-19 VACCINE
NULIBRY®
ONPATTRO®
ORIGINAL/OMICRON VACCINE
OXLUMO®
PFIZER & BIONTECH'S OMICRON BA.4/BA.5-ADAPTED BIVALENT BOOSTER
SPINRAZA®
TEGSEDI®
VILTEPSO®
VYONDYS 53®
WAYLIVRA®

Payer Perspectives

How impactful do you perceive the trend of cell and gene therapy expansion in 2022?

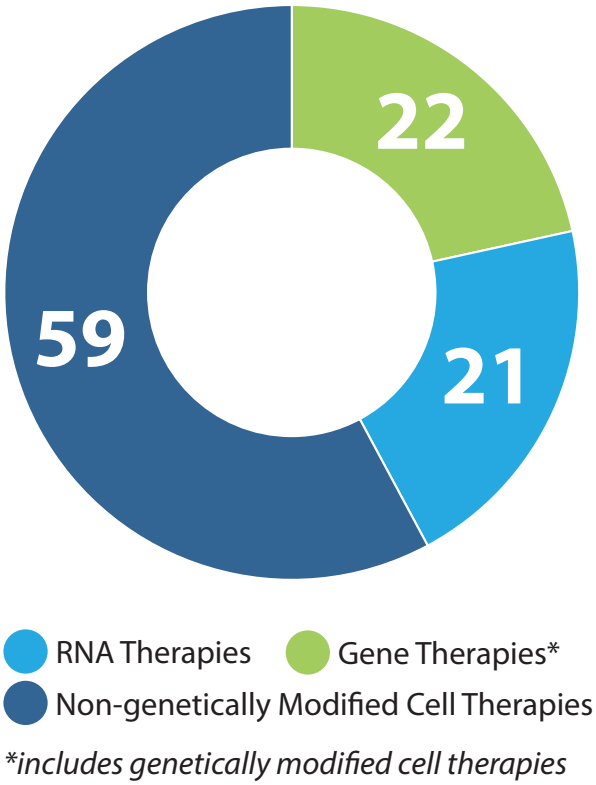
Rating:
1 = Hardly any impact
5 = A dominating force

U.S. Payer Perception of Impact:

4.5/5

Ex-U.S. Payer Perception of Impact:

4.3/5



**includes genetically modified cell therapies*

Among the most impactful approvals in 2022 includes CSL Behring's Hemgenix (etranacogene dezaparvovec-drlb) by the FDA in late November. Hemgenix is the first gene therapy which treats adults with hemophilia B. Traditionally, hemophilia B is treated with routine intravenous infusions of Factor IX replacement products to promote clotting and prevent bleeding episodes. As a one-time gene therapy, Hemgenix provides a valuable opportunity for reducing the burden of the disease in contrast.

Similar to Hemgenix, Bluebird's Zynteglo (beti-cel) is another recently approved therapy which provides the opportunity of eliminating the burden of disease associated with traditional treatment methods. Zynteglo was approved by the FDA in mid-August and is a one-time gene therapy designed for the treatment of the genetic cause of beta-thalassemia in both adult and pediatric patients. Prior to Zynteglo's entrance, patients of this rare genetic disease typically required regular red blood cell transfusions and iron chelation which often leads to health complications.

However, with an estimated price point of USD 3.5 million, Hemgenix is anticipated to be the most expensive drug on a single use basis in the U.S. ahead of Zynteglo's estimated price point of USD 2.8 million. Together, these drugs set a new benchmark by which other gene therapies in development might be compared. This increasing pricing trend is already evident by the price point of Hemgenix coming months after Zynteglo's approval.

Some U.S. payers note Zynteglo as the most significant clinical breakthrough this year, with payers claiming that the cell and gene space is home to the most important clinical breakthroughs of 2022.

Despite positivity around their clinical significance, no payers named Zynteglo or cell and gene therapies as the products launched with the best clinical value relative to cost. This demonstrates that cell and gene therapies, although seen as significant clinical breakthroughs, may not be perceived by payers to be the best value due to their high price tags and limited available data at time of launch. It is important to note that Hemgenix had not been approved at the time the survey was conducted.

Whereas the potential health gains of cell and gene therapies are undeniable, they often raise concerns among HTA bodies due to their high costs and uncertain value propositions. Multiple reports have pointed out that conventional HTA assessments are not suited for cell and gene therapies, as

the substantial uncertainties in these therapies' clinical outcomes and their long-term nature complicate the appraisal process. Similarly, value for these therapies may be difficult to capture given that these curative therapies may have a life-long impact, which is difficult to capture in budget impact models where therapies' impact is typically assessed over a 5-year window. Thus, some of the main challenges associated with assessing these innovative therapies have been identified as:

- **Challenges with capturing economic costs:** Cell and gene therapies target rare, high unmet need diseases that make estimating the cost of a disease difficult.
- **Challenges with benefit estimation:** The clinical benefits of cell and gene therapies are challenging to estimate given the nature of their pivotal clinical trial design. It is typical, for example, for clinical trials of cell and gene therapies to only have an experimental arm alongside stringent eligibility criteria that further leads to limited enrollment size. Moreover, limited comparative evidence resulting from these factors on top of the aforementioned difficulties around capturing the durability of effects add to the challenges of benefit estimation.

Payer Perspectives

One significant trend payers have noted includes the emergence of more value-based contracts being negotiated to address concerns around benefit estimation.

Strategic Implications

The expansion of cell and gene therapy calls for unconventional HTA assessments with specialized routes for these innovative therapies.

[18] Center for Biologics Evaluation and Research. (n.d.). Approved Cellular and Gene Therapy Products. U.S. Food and Drug Administration. Retrieved January 8, 2023, from https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products

[19] Gene, Cell, & RNA Therapy Landscape. American Society of Gene and Cell Therapy-Q3 2022 Quarterly Data Report. (n.d.). Retrieved January 8, 2023, from https://asgct.org/publications/news/october-2022/informa-citeline-q3-landscape-report

Changing Early and Orphan Access Opportunities

New policies have been introduced globally to manage the high budget impact of therapies with early and orphan access designations.

In response to the numerous new products achieving early access or entering orphan designations in recent years, payers across the globe have implemented new policies with the aim of managing the large budget impact of these therapies. There is heterogeneity in the nature of these policies, but they will all have significant pricing and market access implications for any products entering orphan indications or hoping for early access.

Payer Perspectives

How impactful do you view changes to early and orphan access opportunities to be in 2022?

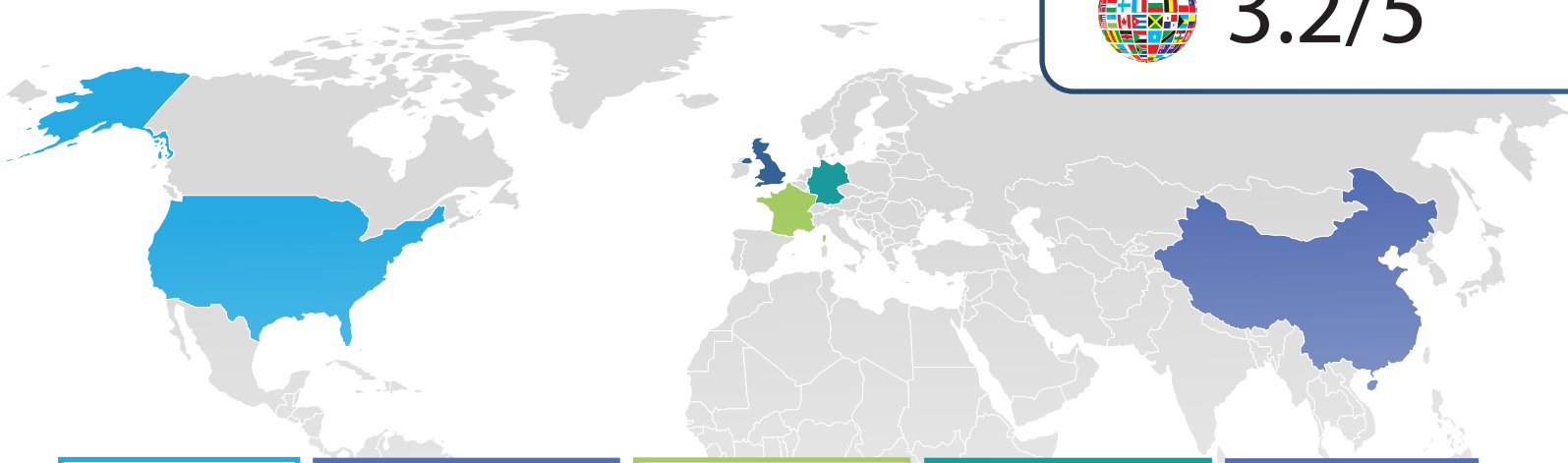
Rating:
1 = Hardly any impact
5 = A dominating force

U.S. Payer Perception of Impact:

3/5

Ex-U.S. Payer Perception of Impact:

3.2/5



United States

Manufacturers whose products are associated with a value-based purchasing arrangement in all states were granted the ability in July 2022 to report varying "best price points" for outpatient drugs to the Medicaid Drug Rebate Program.

United Kingdom

As part of the government's Rare Disease Action Plan, the Department of Health and Social Care has made GBP 340 million available through the Innovative Medicines Fund to purchase and fast-track access to cutting-edge non-oncology treatments while further real-world evidence is collected to inform final NICE decision on clinical and cost effectiveness.

Germany

A number of new measures aimed at overall budget control are in consideration, including removing the "Non-quantifiable Added Benefit" rating for orphan drugs, lowering the sales threshold for orphan drugs from EUR 50 million to EUR 30 million, and limiting free-pricing period to six months to name a few.

France

In the past, reimbursement to medicines have been conducted after price negotiations with Comité Economique des Produits de Santé (CEPS); however, this new policy will allow for direct reimbursement to medicines receiving an ASMR I-IV following evaluation by the Transparency Committee.

China

We have observed consistent inclusion of approximately seven rare disease products included in each NRDL update for the past couple of years, potentially enabling us to use this pattern and make some inference about what products might make the cut in 2022 / 2023.

Germany

The federal election in September 2021 ushered in a new coalition government in Germany, which came equipped with a detailed roadmap of healthcare reforms aimed at mitigating the budget difficulties of the COVID-19 pandemic. Although the official implementation of the majority of the changes will not come to fruition until January 2023, we are beginning to see the direction of these changes realized in 2022 following their formal adoption.[20] However, the official implementation of the majority of these adopted changes will not come to fruition until January 2023. With the additional challenges of the Russian invasion of Ukraine and energy crisis, it is likely that these reforms will gain new importance to the government's budget control plan.

- A variety of measures are considered, but most relevant to orphan products is the proposed possible reform of the benefit rating of "Non-quantifiable Added Benefit" in the G-BA review process. Since reforms in 2011, orphan products approved by the EMA have been assumed to have an added benefit and forego the formal review process (until they exceed a sales threshold of EUR 50 million in Germany). This change would remove the advantage for orphan products, subjecting them to full assessments before launch. The government cites a report which found that, of the orphan products which did eventually undergo full assessment, 54% were found to have "No Added Benefit". A related reform adopted by Bundestag (German Federal Parliament) lowers the sales threshold from EUR 50 million to EUR 30 million, with only the first indication being eligible for automatic additional benefit status, and is set to be implemented in 2023.
- Finally, Germany's current regulations allow for free pricing of all approved products for their first year on the market, including orphan drugs, followed by a negotiation with the government. Under the proposed change, this period would be halved to just six months of free pricing.

Further Reading

The German Financial Stabilization of Statutory Health Insurance System Act: Expected Impact and Implications for Manufacturers

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> "The economic situation [in Germany] is featured by a sharp turn-around, making tighter economic barriers to market access, and even additional cost containment measures [are] almost inevitable for the time to come. This may clash especially with more high-cost therapies (e.g., newer generations of CAR-T therapies) reaching the market or emerging on the horizon."
>
> **Germany Payer**
> **Public Academic Research Institution**

France

In June 2021, France introduced a large package of healthcare reforms, the "Healthcare Innovation 2030" plan, with the twin goal of improving the country's healthcare system and enhancing the output of the domestic industry.[21,22] One major reform affects the early access of new products, offering access before pricing negotiation.

In the past, reimbursement for medicines has been conducted after price negotiations with Comité Economique des Produits de Santé (CEPS); however, this new policy will allow for direct reimbursement to medicines receiving an ASMR I-IV following evaluation by the Transparency Committee (TC). Under this updated provision, price negotiations will be conducted after launch for products that receive an ASMR of I-IV. While the reform indicates that the manufacturer will have one year from launch to negotiate a price, there are still uncertainties around expected paybacks in case the price at launch is lower than the negotiated price (which was required of products undergoing Autorisation Temporaire d'Utilisation or ATUs in the past). If a product receives an ASMR of V (i.e., no therapeutic improvement), the product will go through the original process where the product's price will be set to be lower than that of existing comparator treatments by CEPS.

Additionally, this reform also broadens the access to the liste en sus, which is a funding system including high-cost innovative drugs that are too expensive to be included within the DRG-based payment system (Tarification à l'activité or T2A) system of French hospitals. Originally, only therapies that received an ASMR of I-III were eligible for inclusion unless a therapy receiving an ASMR IV or V had a direct comparator that was already included in the list; however, **this updated policy extends access to the liste en sus to all therapies receiving an ASMR of IV.**

United Kingdom

England has long used the Cancer Drugs Fund to facilitate early access to innovative treatments for cancer patients. Building on the success of that program, in June 2022 the government launched the broader Innovative Medicines Fund, backed by an initial GBP 340 million.[23] These funds will be available for the NHS to purchase potentially transformative products before a final decision approval has been reached with the English HTA, NICE. To be eligible for these funds, products have been approved by the Medicines and Healthcare products Regulatory Agency (MHRA) for safety and efficacy first.

Further Reading

France Pilots Opportunity to Increase Speed to Reimbursement for Select Innovative Products

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China

In recent years, during China's annual update of their National Reimbursement Drug List (NRDL), they have consistently included approximately seven products for rare diseases. This pattern may enable prediction of which products they will add in their next update, as it narrows the scope of how many are likely to be incorporated.

The process for orphan drug pricing, however, is not distinct from other formal reimbursement processes in China. For inclusion in the NRDL, marketing authorization holders must engage in negotiations with the National Medical Insurance Bureau. An accelerated marketing authorization pathway (70 days versus the typical 200 days), however, is available for orphan drugs deemed clinically urgent that have been marketed abroad but not in China.[24]

Further Reading

Cracking the Code of the Access Landscape in China: Analysis of the 2021 NRDL Update

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> "From the perspective of the types of medicines to be negotiated, there may be breakthroughs in the budget management of rare disease medicines, but there are currently uncertainties (the results have not yet appeared)."
>
> **China Payer**
> **Ex-National Reimbursement Drug List (NRDL)**

United States

In the U.S., while the Inflation Reduction Act in August 2022 dominated healthcare headlines, another reform that was enacted the month before will also play a role in manufacturer strategy in the coming years.

This change will mean that manufacturers who enter into a value-based purchasing arrangement for a product will be able to report more than one "best price point".

In the current system, manufacturers are required to submit to CMS the lowest price on offer for every product – across any purchasing organization, public or private, and across all dosages and strengths. These prices are then used to inform the Medicaid Drug Rebate Program. Unfortunately, this system is not compatible with value-based agreements, as the complexities of such agreements may result in price points of zero, which could lead to huge impacts if actually fed into the CMS discounting scheme. Under the new arrangement, manufacturers who offer a value-based agreement to all

50 states will be allowed to report multiple "best prices" for each dosage / strength of a product. This will allow them to avoid the challenges caused by the single-price restriction and possible null results. If manufacturers do not offer a value-based agreement in all states, they will still be required to report a single best price.

Healthcare reforms in the U.S. under the Inflation Reduction Act were formally written into law in August. Some key changes to this act include:

- Through a series of discounting rules, the law functions to capture savings from blockbuster medicines that enjoy long-term success in the Medicare market rather than introducing government-manufacturer price-setting negotiations that have become the norm in many global markets.
- Future blockbuster therapies treating diseases with a high share of Medicare patients will face revenue pressure late in the product lifecycle under the new rules, and earlier than they otherwise would have due to loss of exclusivity.
- Reduced long-term revenue potential, combined with constraints around price increases and capped out of pocket spend in Medicare, may lead manufacturers to seek higher prices when launching new products given the price-setting freedom that remains untouched by the new legislation.

On-Demand Webinar

IRA Medicare Inflation Penalties: Implications for Manufacturer Pricing and Contract Strategy Decision Making

Watch Now >

Further Reading

Inflation Reduction Act of 2022: No Room for Negotiation

Read Now >

Strategic Implications

In those markets with significant changes, forecasts of pricing, access and long-term outcomes should be updated to account for these changes. Engage with payers and regulators to understand perspectives on new regulations, and which changes are likely to be successful and possibly therefore adopted by additional markets.

[20] IQWiG. Orphan drugs: privilege of "fictitious" added benefit not justified https://www.iqwig.de/en/presse/press-releases/press-releases-detailpage_58496.html

[21] French Healthcare. Health Innovation Plan 2030: €7.5 billion to return France to its position as leader in healthcare in Europe. https://frenchhealthcare.fr/health-innovation-plan-2030-e7-5-billion-to-return-france-to-its-position-as-leader-in-healthcare-in-europe/

[22] French gouvernement. Innovation in healthcare by 2030. https://www.gouvernement.fr/sites/default/files/contenu/piece-jointe/2022/03/p3_bis-_health_innovation_by_2030_-_background_note.pdf

[23] Morris, L. Life-saving medicines fast-tracked via new £340m NHS fund. https://www.nationalhealthexecutive.com/articles/nhs-patients-receive-life-saving-treatment-innovative-medicines-fund-drugs-pharma

[24] Fangda Partners. Orphan Drugs & Rare Diseases in China. https://pharmaboardroom.com/legal-articles/orphan-drugs-rare-diseases-china/

Additional Highlights of 2022

Lingering Impacts of the COVID-19 Pandemic

COVID-19 and its legacy continue to affect the predictability of budget impact, but payers note that the principles guiding budget impact decisions remain the same. Payers cite oncology, autoimmune and rheumatology as the top three relevant therapeutic areas.

Trinity Life Sciences asked payers to rank the below list of therapeutic areas in terms of their priority to their respective organizations as well as budget impact and organizational focus over the past year. Across both U.S. and ex-U.S. markets, payers cited oncology as the top therapeutic area in 2022. Other top ranking therapeutic areas of the year included cardiology, autoimmune and rheumatology.

> "As the years have passed the uncertainty is going down. This year we could see inclusions, even though the priority on the therapeutic groups and illness priority is still unchanged."
>
> **Mexico Payer**
> **National Healthcare Services Evaluation**

In contrast to budget constraint impacts, however, COVID has been cited to promote a paradigm shift of seeing healthcare and healthcare products as investments rather than costs with some cases of increased funding in healthcare spaces by governments since the pandemic. As such, rather than assessing price tags of treatment alone, payers note a greater scrutiny of other direct (i.e., clinical, health-related quality of life) and indirect benefits (i.e., cost-effectiveness) of treatments.

> "The guiding criterion is therefore no longer only the cost [...], but also and above all, the returns in terms of direct and indirect benefits. This implies a greater focus on direct comparisons, cost-effectiveness data, quality of life data as well as indirect cost facts."
>
> **Italy Payer**
> **National Agency for Regional Health Care**

U.S. Payer Perspectives

How difficult do you believe manufacturer negotiations were for the new products your organization contracted on in 2022?

Rating:
1 = Not difficult at all
10 = Extremely difficult

U.S. Payer Perception of Impact:

5/10

Ranking of Therapeutic Areas by Priority to Payers

Most Budget Impact / Key Organizational Focus Area

- Oncology
- Cardiology
- Autoimmune
- Rheumatology
- Gastroenterology
- Neurology
- Respiratory
- Dermatology
- Urology
- Ophthalmology

Least Budget Impact / Non-Priority Organizational Focus Area

On top of all the aforementioned impacts of the pandemic, further impacts of rising inflation and global supply chain disruptions have been noted as negatively impacting the innovative medicines space. Payers note difficulty predicting drug price increases as well as pharmaceutical production shortages and delays as key challenges to pricing, market access and reimbursement in 2022.

> "The amount of drug shortages and price increases have been challenging to predict and therefore has made this year different than others. We are seeing the emergence of pipeline therapies that were possibly delayed due to the pandemic."
>
> **U.S. PDP Payer**
> **Large National Insurance Plan**

Looking Ahead

Emerging Trend: A Continued Global Move Towards Biosimilars

In 2023 we are beginning to see additional governmental policies emerge in reaction to the larger continued trend of increasing numbers of patents expiring for biological products, and biosimilars consequently emerging. Biosimilars set to enter the market next year includes Amgen's biosimilar Amjevita (adalimumab-atto) for Abbvie's blockbuster rheumatoid arthritis treatment, Humira (adalimumab) in the U.S.

Payers note that biosimilars are beginning to stake claim in the market and are here to stay as familiarity with biosimilars continues to rise. Furthermore, multiple U.S. and ex-U.S. payers note biosimilars as having the best clinical value to cost ratio.

> "[For the first time] this year, biosimilars have arrived to stay. We had an option for Infliximab, which was dispensed for administrative requests and bought by the state, but now the Ministry of Health is inducing it by buying it for national guidelines."
>
> **Brazil Payer**
> **Regional State Health Department**

In September of 2022, the EMA and HMA issued a joint statement endorsing biosimilar interchangeability status.[25] Although decisions regarding substitution at pharmacy-level (the practice of dispensing one medicine instead of another without consulting the prescriber) are still managed by individual Member States, this issued statement signals that biosimilars should be considered clinically equivalent and that they can be used instead of their reference product without the need for additional switching studies. It is important to note, however, that this interchangeability status differs than that in the U.S., which still requires additional data for qualification.

In the U.S., enhanced payments to biosimilars through the Inflation Reduction Act policy temporarily increases the Medicare Part B add-on payment for certain biosimilars from 6% to 8% of the reference product's average sales price (ASP) from October 1st of 2022 through the end of 2027.[26]

[25] Biosimilar Medicines Can Be Interchanged. European Medicines Agency. (2022, October 17). Retrieved January 7, 2023, from https://www.ema.europa.eu/en/news/biosimilar-medicines-can-be-interchanged

[26] Franco, M. A. (2022, August 16). With Inflation Reduction Act Signed, Other Health Policy Issues Ahead for Congress. Holland & Knight. Retrieved January 7, 2023, from https://www.hklaw.com/en/insights/publications/2022/08/inflation-reduction-act-passage-and-health-policy-outlook#:~:text=Enhanced%20Payments%20for%20Biosimilars%3A%20To,through%20the%20end%20of%202027

Conclusion

- As the pricing and market access landscape continues to evolve, monitoring updates to policies and the trends outlined within this white paper should play a key role in informing strategies for bringing new innovative technologies to market.

- In 2023, we expect to see continued reforms across countries such as Germany and Italy and the early consequences of newly implemented policies such as those in the U.S.

- As more patent expirations occur, 2023 may also be a year where biosimilar entry and uptake takes a more permanent foothold across all markets which has implications for future cost-effectiveness standards within the industry.

- The need for thoughtful evidence generation to support strategic pricing, access and reimbursement will continue to increase, as payers affirm its growing importance in their decision-making and manufacturers adopt publication grade RWE to communicate their value story, pre- and post-launch. This trend will be prevalent especially in the U.S. market, with EU and global markets following suit.

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