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INTERNATIONAL FALLOUT: HOW THE IRA IN THE US AND JCA AND REVISION OF THE EU PHARMACEUTICAL STRATEGY IN EUROPE WILL HAVE GLOBAL CONSEQUENCES

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INTRODUCING THE PANEL

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IRA

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JCA

TealeHealth, UK

Sam Mettam
MA MSc

Industry perspective

Jazz Pharmaceuticals, UK

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PANEL AGENDA
MAY 5-8, 2024

Introductory remarks
David Alderson

Inflation Reduction Act (IRA) in the US
Diana Brixner

Joint Clinical Assessment (JCA) and EU legislation
Chris Teale

What is a pharmaceutical company's view?
Sam Mettam

Moderated discussion
David Alderson

INTERACTIVE POLLING QUESTIONS

All polling questions will be embedded into the presentations. For each poll, a polling slide will be presented. When the polling stops, the results will appear on your presentation and on the screen

Example QR code; do not scan

Please scan the QR code and enter your multiple-choice answers

You will have 20 seconds to input your answer

CHANGES ARE BEING IMPLEMENTED IN A COMPLEX ECO SYSTEM – CONNECTED, GLOBAL, AND LONG TERM IN NATURE

This session will seek to explore and highlight:

The global consequences of the Inflation Reduction Act (IRA) and Joint Clinical Assessment (JCA) and revision of the EU Pharmaceutical Legislation – with respect to healthcare systems and R&D

- Impact of reducing national health system funding?
- Impact on industry innovation / R&D funding?
- Possible unintended consequences?
- Product and lifecycle strategy?
- Stakeholder engagement and inclusion?

LAUDABLE AIMS OF THE CHANGES – BUT PLENTY OF PUSH BACK

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PhRMA RESEARCH • PROGRESS • HOPE

Alliance for Regenerative Medicine

efpia

Vaccines Europe

EUCOPE

Roche

EuropaBio

Likely to fundamentally change the economics of the pharma industry and disincentivize the industry from placing big bets on diseases with large unmet burdens. - PhMRA survey

[These] policies come between families and their care - Patient advocacy organisations

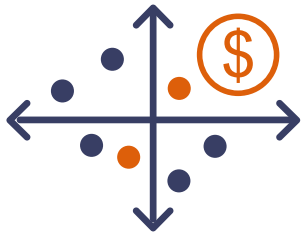
Grave concern with the IRA [and] its attack on medical innovation- PhRMA board members

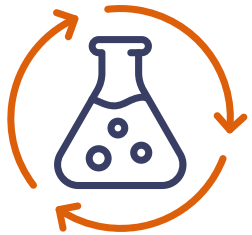
[JCA] arguably falls short of the right to be heard laid down in Art. 41 (2) of the Charter of Fundamental Rights - Roche

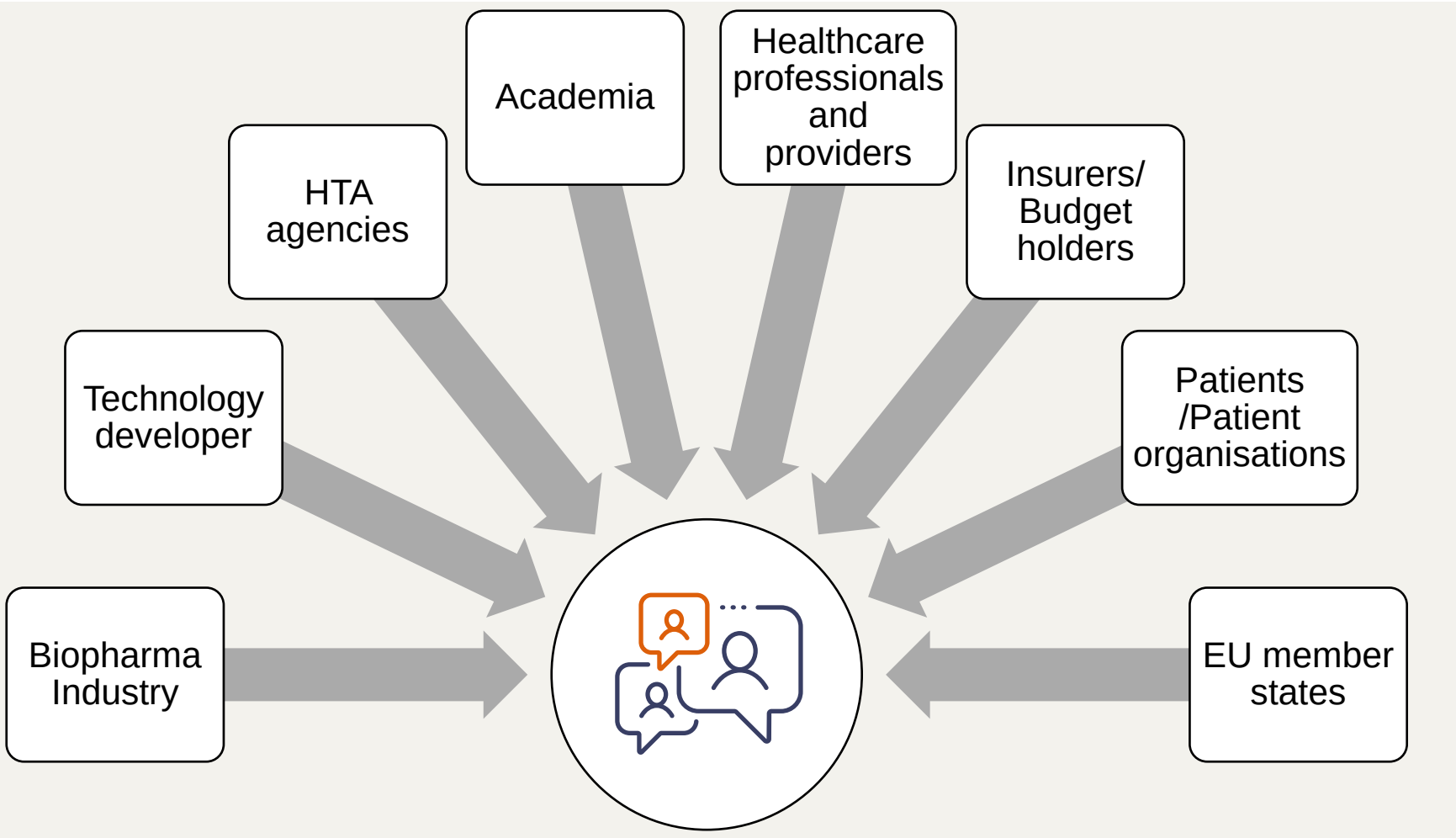
The draft rules in their current format will create an unworkable framework for JCAs - ARM, EFPIA, EUCOPE, EuropaBio, Vaccines Europe

[JCA]will fail to deliver on its aim of ensuring better access for patients to innovative health technologies- ARM, EFPIA, EUCOPE, EuropaBio, Vaccines Europe

MULTIPLE PERSPECTIVES TO CONSIDER IN A COMPLEX ECO SYSTEM







INTERNATIONAL FALLOUT – HOW THE INFLATION REDUCTION ACT (IRA) IN US AND JOINT CLINICAL ASSESSMENT (JCA) AND REVISION OF THE EU PHARMACEUTICAL STRATEGY IN EUROPE MAY HAVE GLOBAL IMPACT.

Diana Brixner, PhD

Professor, Pharmacotherapy Department

Founder Pharmacotherapy Outcomes Research Center

University of Utah

May 8th, 2024

ISPOR Atlanta

UNIVERSITY OF UTAH COLLEGE OF PHARMACY

The IRA here and abroad - direct negotiation

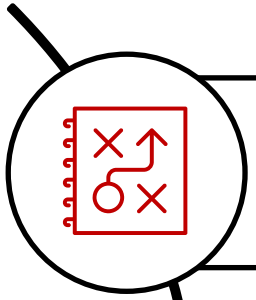
The Inflation Reduction Act (IRA) allows the federal government (Medicare) to negotiate US drug prices for the first time, directly with biopharma and biotech companies

1. The IRA grants Medicare the authority to **negotiate drug prices directly** with biopharma and biotech companies.
2. Eligible drugs must be among **the top in terms of Medicare expenditure**, lack generic or biosimilar equivalents, and have been **on the market for a specified number of years** (7 for small molecules, 11 for biologics).
3. The **first ten drugs subject to negotiation** were announced in late August; negotiation is ongoing, with new prices taking effect in January 2026.
4. While it **applies solely to the Medicare population**, it could indirectly impact other populations in the US and globally

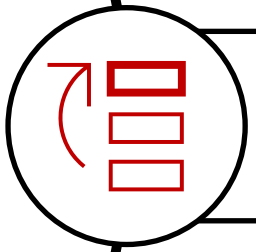
The US system may evolve based on comparison with established price negotiation processes in other countries

https://www.akingump.com/en/insights/alerts/the-impact-of-the-inflation-reduction-act-of-2022-on-pharmaceutical-innovation-patent-litigation-and-market-entry
US; United States

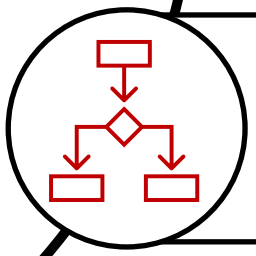
Clinical development and R&D strategies



Biopharma companies will need to **evolve their R&D strategies** and development capabilities.
Blockbuster drugs will come with down the road consequences



Considerations include **portfolio prioritization across countries**, clinical development, financial planning, and real-world evidence.



The IRA's provisions may **influence companies' decisions** on drug development and investment due to negotiation by drug, not indication, there may be reduced incentives to invest in subsequent indications.
Multiple indications may tip the scale to CMS negotiations

https://www.bcg.com/publications/2023/navigating-inflation-reduction-act-impact-on-drug-pricing-innovation
https://www.npcnow.org/sites/default/files/2023-06/IRA%20Subsequent%20Indications_AH%20poster%20%281%29.pdf

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US IRA – extended implications

The IRA's impact extends beyond companies to payers, patients, and providers. In the US, Commercial payers could push for lower prices, affecting non-Medicare populations.

The US IRA is often compared to European drug price controls.
The two are not directly equivalent, although they may influence each other.

European countries have various mechanisms for controlling drug prices, including reference pricing, health technology assessments, and negotiated agreements.

The IRA's provisions differ significantly from these European approaches.

https://www.bcg.com/publications/2023/navigating-inflation-reduction-act-impact-on-drug-pricing-innovation

US IRA - Impact on new treatments

- PhRMA stated 78% of its member companies are expecting to cancel some of their early-state development projects

- Decreased investment in drug innovation has been seen in Europe as a result of pharmaceutical price controls
- Due to a more restrictive HTA review process via NICE, only 59 vs. 85% of new medications launched between 2012 and 2021 were available in the UK compared to the US. Breakthrough therapies for cystic fibrosis were not available for several years in the UK
- Trends in decreasing investment are seen in other countries, including Germany, France, and Italy
- 7 of 25 novel, approved gene therapies in Europe have been removed due to a lack of evidence (availability, accessibility, acceptability), uptake and adoption

NHS, National Health Service; PhRMA, Pharmaceutical Research and Manufacturers of America

IRA Characteristics Mapped to EU Consequences

US IRA components	EU impact
Eligible drugs must be high-cost, lack generic or biosimilar equivalents, and have been on the market for a specified duration.	In Europe there is less penetration of small molecule generics but increased uptake of biosimilars and products are often launched after the US
Lower revenues from the US market to support innovation and for R&D	Lower resources for drug development in other countries
Inflation rebates and required manufacturer discounts may affect pharmaceutical manufacturers' revenue streams	Such additional drug price reductions may also be considered by EU country policy makers.
While the IRA directly applies to Medicare patients, effects will extend to other payers possibly Affecting Medicaid "best price" and commercial payer negotiations	These price reductions may also serve as a reference prices for EU markets, influencing pricing strategies beyond the US

Conclusions

1. **European Considerations:** European drug developers and pricing experts should closely monitor the IRA's implementation and consider potential adjustments to their strategies.
2. Collaborations, clinical development, and pricing decisions may need to adapt to the changing landscape.

https://www.bcg.com/publications/2023/navigating-inflation-reduction-act-impact-on-drug-pricing-innovation

Interactive Questions and Answer Choices

How would you balance clinical development and innovation for a product which will undergo IRA price negotiation >10 years post launch?

1. Prioritize biologic development due to longer time to potential CMS price negotiation
2. Consider investing in injectable/specialty/Part B drugs to avoid negotiation
3. Produce high volume small molecule products and maximize sales at a higher price in the first 7 years
4. Focus on exempt orphan drug development
5. Partner with academia and small companies for innovation

THE APPROACHING STORM IN EUROPE

REVISION OF THE EU PHARMACEUTICAL STRATEGY AND PAN-EU HTA REGULATION / JOINT CLINICAL ASSESSMENT (JCA)

Chris Teale
Managing Director
TealeHealth Ltd
United Kingdom

ISPOR Atlanta 8th May 2024

What is planned in Europe?

TealeHealth

Revision of EU Pharmaceutical Strategy

Objectives

Increase attractiveness of EU for (R&D) investment
Promote better more equitable healthcare for citizens
Reduce time to access
Other*

Mechanism

Adjust duration of exclusivity, dependent on
- level of unmet medical need,
- comparative trials against standard of care,
- significant share of R&D taking place in the EU

Increase access transparency.

Pan-EU HTA Regulation

Objectives

Improve availability of innovative health technologies
Ensure efficient use of resources
Strengthen the quality of HTAs
Reduce effort duplication for national HTA / industry

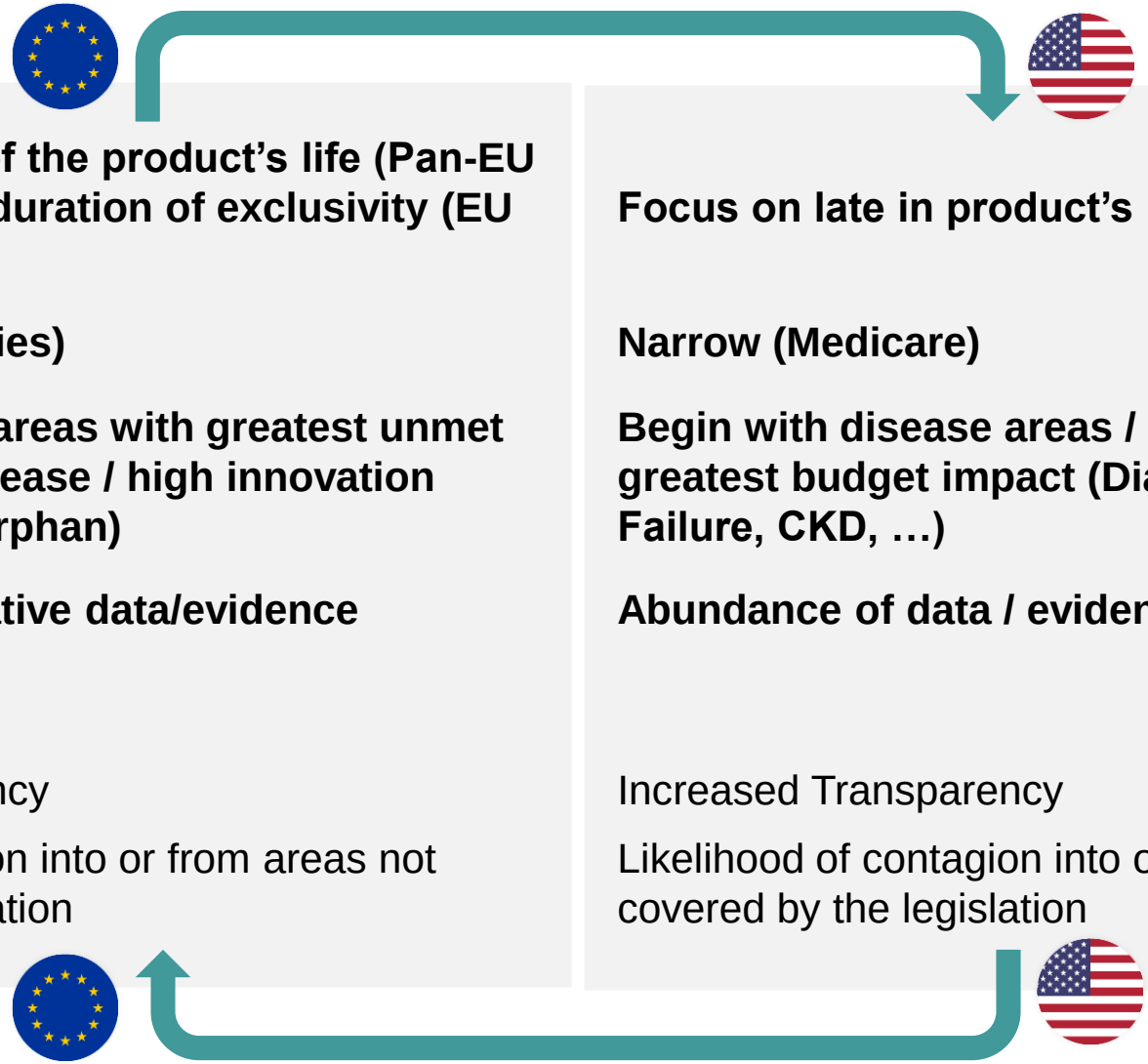
Mechanism

Joint Clinical Assessment (JCA)
Population, Intervention, Comparator, Outcomes (PICO) Framework

Value judgements, pricing and reimbursement decisions, and time to access will remain within the remit of the 27 Member States **, where they will depend on local affordability, priorities, and societal preferences.

* Includes Antimicrobial Resistance (AMR) and transferable exclusivity vouchers (TEV) , Definition of Unmet Medical Need (UMN), Orphan drugs
** Article 6 Treaty of Rome - EU countries hold primary responsibility for organizing and delivering health services and medical care.

How does the approach in Europe compare to the USA?



Focus on the start of the product's life (Pan-EU HTA / JCA) and the duration of exclusivity (EU Pharma Strategy)	**Focus on late in product's life (IRA)**
Broad (all 27 countries)	**Narrow (Medicare)**
Begin with disease areas with greatest unmet need / burden of disease / high innovation (Oncology, ATMP, Orphan)	**Begin with disease areas / products with greatest budget impact (Diabetes, Heart Failure, CKD, …)**
Scarcity of comparative data/evidence	**Abundance of data / evidence**
Increased Transparency	Increased Transparency
Likelihood of contagion into or from areas not covered by the legislation	Likelihood of contagion into or from areas not covered by the legislation

Revision of EU Pharmaceutical Strategy*

Focus on Duration of Exclusivity

Regulatory data protection (RDP) period reduced from 8 to 7.5 years

Up to one additional year of RDP

- 12 months for an indication with **unmet medical need**
- 6 months for conducting **comparative trials** against standard of care
- 6 months if a significant share of **R&D in the EU**

Market protection unchanged at 2 years

An extra year for a new indication that provides **significant clinical benefits vs existing therapies.**

Orphan market exclusivity of 9 years, with a two-year extension for addressing **high unmet need**

"The marketing authorisation holder shall **apply** for pricing and reimbursement and **negotiate**….. the company must ensure appropriate and **continued supply** to cover the needs of patients."

To measure access to medicines across the EU, evidence-based, **measurable indicators** will be developed…

A **report** assessing access to medicines and barriers to improving access in each Member State will be published…the Commission shall create a dedicated **website** with easily accessible **information** on access indicators… intended for the public and relevant stakeholders."

Less focus on Faster Access**

* Position adopted by European Parliament 10 April 2024

** Although the stated objectives of the strategy include "reduce time to access to innovative medicines" EU has no direct influence on time to access at member state level. An earlier proposal to add 2 years of regulatory data protection (RDP) dependent on a new medicine being available in all 27 EU Member States within 2 years of getting marketing authorisation has been dropped.

Joint Clinical Assessment (JCA)

What is it?

- "…JCA constitutes a scientific analysis of the **relative effects of the health technology** on the health outcomes against chosen parameters based on the assessment scope. The analysis will include consideration on the **degree of certainty** of the relative effects, taking into account the **strengths and limitations of the available evidence**" *

- **From 2025, oncology products and ATMPs** (cell & gene therapies) will be subject to JCA, orphan designation products by 2028, and all central authorised medicinal products by 2030.

How will it be done?

- A scoping process defines the framework for assessment - the **PICOs (Population, Intervention, Comparator, Outcomes)** - and the data requirements from the manufacturer.

- A PICO survey will be sent to **all 27 EU countries** to gather information about their needs in terms of the PICO parameters.

- The quantity of PICOs returned could be very high, based on different needs in different countries, resulting in the need for **consolidation of the PICOs** by the JCA assessors.

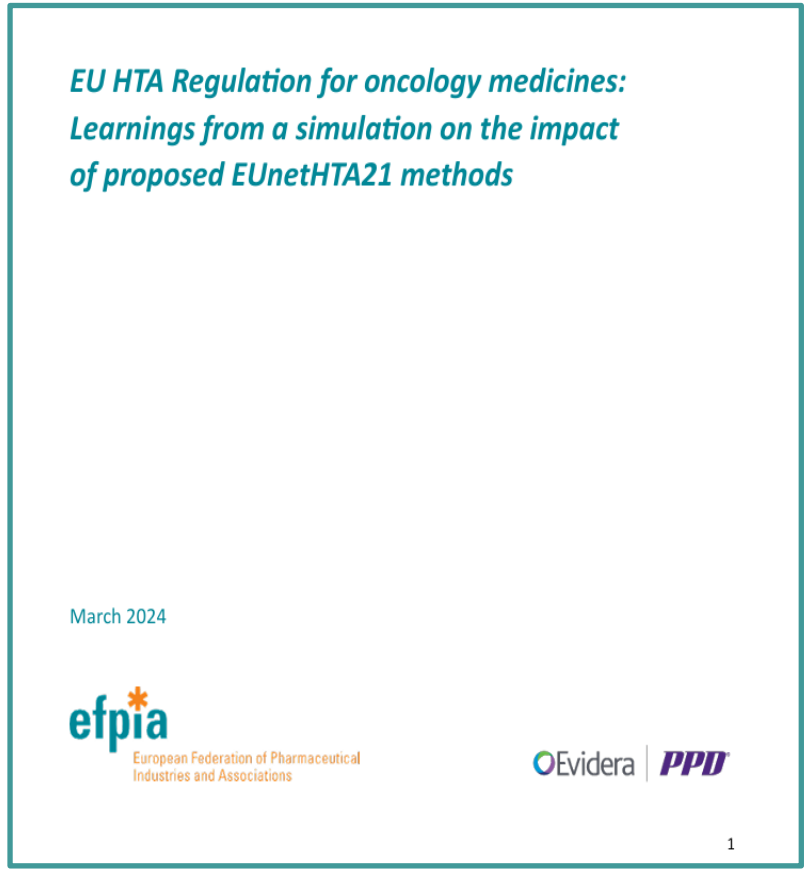
- This should result in a **limited number of PICOs** which form the basis of the JCA dossier?

 * Official Journal of the EU, 2021, Regulation (EU) 2021/2282.

Research highlighted JCA challenges for oncology products*

JCA Simulation: challenges

- Simulation of JCA for 3 recent cancer drugs resulted in **16, 22, and 57 PICOs** – reduced to **7, 6, and 23 PICOs on consolidation**
- All 3 technologies would require **indirect treatment comparisons or network meta-analyses**
- Importance of **observational data** highlighted – RWE informed **comparative effectiveness** analysis in two of the products
- All presented challenges in meeting EUnetHTA 21's proposals for data acceptability and comparisons
- For 1 drug, the comparator was no longer standard of care by the time of the marketing authorisation application
- Overall survival is often immature. This increases need for assessors to **consider all (multiple) endpoints**



* https://www.efpia.eu/news-events/the-efpia-view/statements-press-releases/guidance-needed-to-ensure-eu-joint-clinical-assessment-improves-patient-access-to-innovative-cancer-treatments/

A perfect storm appears to be approaching, with significant consequences if left unchecked

JCA issues

Unmanageable number of PICOs?

Sparsity of comparative data in first assessments?

Complex methodologies for oncology and ATMPs?

Minimal involvement of submitting companies?

Unrealistic timelines?

Value judgement lying outside scope?

Insufficient expert resources at National level to undertake both JCA and HTA?

insufficiently incorporated in National HTA processes?

National price setting disconnected from JCA and Pan-EU HTA?

EFPIA view* (9 April 2024)

"….. unworkable framework for JCA, duplication of work. …..**serious concerns over workability ……**

risks the aim of joint EU HTA of ensuring better access ….. timelines are unworkable and **too short to allow companies to provide quality input**"

A personal view

Increased time to market access and **price dilution**- including **"no launch**" or **product / company withdrawal**

- Shortage of resources at member state level
- Growth of Inter/intra-national reference pricing and cross-border trade
- Inadequate return on investment

- https://www.efpia.eu/news-events/the-efpia-view/statements-press-releases/life-science-industry-concerns-over-the-workability-of-eu-hta-europe-cannot-miss-out-on-the-opportunity-to-speed-up-access-to-innovative-medicines-for-european-patients/

What can we learn from previous storms?

TealeHealth

Achieving faster patient access

The European Price Transparency Directive*

Things rarely work out as planned. The journey takes longer, the route to implementation continually evolves and adapts as roadblocks and barriers are discovered

After more than 30 years, the overarching goal of pricing and reimbursement decision transparency within 180 days has **never been achieved** in all EU member states.

- JCA **INDIRECTLY** influences faster access. **DIRECT** influence comes from national initiatives
- Focus on national initiatives rather than debating shortfalls of JCA
- National solutions may be easier to implement and, via dissemination of “best practice”, deliver greater value faster.
  - *E.g., “Net Zero” ***
- Move towards granting immediate access to patients on European authorisation and adjust following assessment and negotiation.
  - *Average time between market authorisation and patient access in EU27 is 517 days****
- A pragmatic solution delivering <u>both</u> faster patient access and improving the quality, efficiency, effectiveness, and value of JCA.
- A win for <u>all</u> - patients, Pan-EU HTA/JCA, manufacturers, and Europe!
- Obvious, but not easy

* Directive 89/105/EEC on the transparency of measures regulating the prices of medicines for human use and their inclusion in the scope of national health insurance systems

** https://www.cadth.ca/news/new-target-zero-initiative-aims-help-improve-access-new-drugs *** https://www.efpia.eu/media/s4qf1eqo/efpia_patient_wait_indicator_final_report.pdf

What is required to successfully ride the initial* storm?

TealeHealth

Where is further guidance required?

1. **Appropriate methods and relevant sources** for direct and indirect comparisons, when the evidence comes from a single-arm study.
2. Comparing single-arm results to a synthetic comparator while gathering **post-approval real-world evidence** (RWE)
3. **Pragmatic approaches** in relation to **uncertainty** and establishing processes by which **conditional assumptions** can be **rapidly updated** as new data evolves.

What should we expect to see as increasing trends?

1. **Transparency** - Price, Data, Commercial.
2. Multi-Source **Data Integration.**
3. Inter- and Intra-national **Price Referencing**.
4. **Cross border** trade.
5. Importance of **1st to market**

What will countries need to focus on?

1. Ensuring Resources and Capabilities required to deliver on timelines of both JCA **and** national HTA / pricing and reimbursement negotiation
2. Adapting appraisal systems to:
   - Leverage JCA
   - Embrace multiple endpoints including surrogates
   - Incorporate multi-source data
   - Include adaptive appraisal and conditional reimbursement

What will companies need to focus on?

1. **Preparation:** Learning from the past, Anticipating the future
2. **Evidence**: Less placebo control, more comparative data
3. **Pricing**: Ensure strong and agile price governance procedures
4. **Access**: Revisit Country Launch Order Sequencing
5. **Capabilities:** Analytic and Negotiation skills

* Initial storm refers to Oncology and ATMPS from 2025 onwards

Given the changes in US and Europe, what is the most likely fallout in Europe over the next 5 years?

Please select one

1. Europe becomes less attractive for investors in Cell & Gene Therapies (ATMPs)
2. Market Access timelines for oncology drugs will increase
3. Quality of JCA will be impacted by timeline and resource limitations
4. All the above

Conclusions

The EU and US legislation cannot be looked at in isolation

Europe is struggling to address the implementation of pan-EU HTA harmonization, increasing the attractiveness of Europe for (R&D) investment, and reducing time to access whilst meeting individual member state affordability challenges, and differences in medical practice and priorities.

US is observing and starting to adapt what works in Europe to fit the government funded part of the US system, with an anticipation there will be contagion into commercial payers and non-Medicare populations.

There will be knock-on effects into Pharma company decisions around geographical and R&D portfolio prioritisations.

IRA & JCA – An interactive session based on an Industry Perspective

Sam Mettam

Global Therapeutic Area Value & HEOR Lead - Oncology

Jazz Pharmaceuticals

Disclaimer

- All ideas and opinions are my own and do not necessarily represent Jazz Pharmaceuticals

Introduction and case study

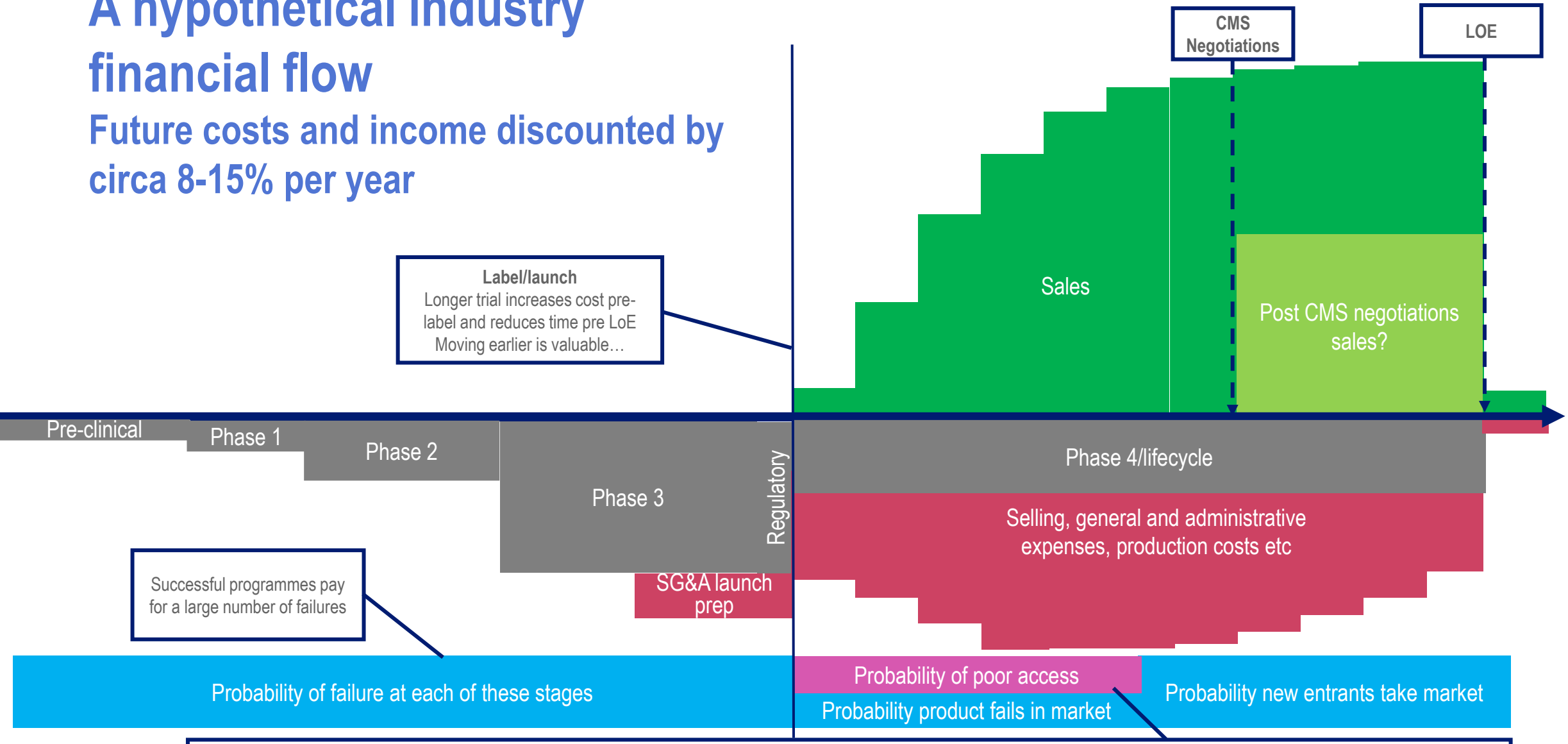
- IRA & JCA will bring substantial changes & uncertainty over the coming years – this will have pragmatic implications for industry
- In this session, we will walk through an interactive scenario that examine decisions industry might take at different points in a product's lifecycle.
- You will vote on actions a company might want to take in each case

Case study scenario

- Oncology product in Phase 2
- First indication
- Global commercialisation is required
- **You are the Value & HEOR lead helping to design phase 3**

A hypothetical industry financial flow

Future costs and income discounted by circa 8-15% per year



Payer evidence considerations are very important, but extra cost has to be justified by:

- Reducing probability of poor/no access/poor price; increasing chance of good price or better access; beneficial impacts such as greater physician share

BUT if cost gets too high or programme is delayed too much, eNPV can easily turn negative and programme could be stopped

Scenario: You're part of a cross-functional team who've been asked to dust off the business case and evaluate Phase 3 options for Product X in Cancer A

- 2nd Line Cancer A - population 50,000 US, 100,000 EU5, 30,000 JP
- Small molecule (eligible for IRA CMS negotiations after 7 years; implemented at 9)
- ASCO and ESMO guidelines state options of **Product Z** or Product W (same MoA) in 2L Cancer A.
  - In certain circumstances Product V is recommended (used mostly in 3L)

Product	mPFS (mos)	mOS (mos)	TTD EORTC QLQ C30 (mos)	Gd 3 AEs (%)	US WAC ($k/m)	EU Price (€k/m)	2L Mkt Share (%)
X	11	Immature	7	33	N/A	N/A	N/A
Z	8	22	NR	30	15	5	40
W	8.5	22	6	40	16	5	30
V	6 (RWE)	18 (RWE)	NR	20 (RWE)	2	1	10

Your phase 2 results

Original plan was to compare against **Product Z**

- In addition, there is one future agent (Product U) with a different MOA to product X, W & Z in Phase 3, expected to read out 2 years before Product X (assumed probability of success 50%)

What is your biggest strategic payer concern as you prepare the business case?

1. Impact of IRA in USA
   - E.g. can you generate evidence that will be compelling, what might CMS negotiated price be, what knock on impacts will there be?
2. Impact of JCA on largest European markets
   - E.g. will France, Germany, Italy & Spain use JCA, what will impact of PICO that doesn't match your trial be in FR/DE
3. Ability of JCA to help achieve access faster in smaller European countries
4. Impact of JCA on International Reference Pricing
5. Joint uncertainty of major changes in both US and Europe
6. Something not related to IRA or JCA

Which of these strategies best describe how you would manage this uncertainty?

1. Fastest possible trial & follow up with evidence outside trial/RWE post launch
   - Everything is so uncertain that speed to market may be more important
2. Generate higher quality clinical evidence
   - Most likely to support JCA now and gives higher quality evidence for IRA later
3. You have little influence on trial design anymore because of uncertainty of payer acceptability, so follow up with as much evidence outside trial environment as possible
4. Leaner programme focussed on US only launch and follow up with RWE for IRA negotiations

What is your recommendation on trial design?

- Your aim is to maximize patient benefit whilst making a sensible business decision based on expected Net Present Value
- Assume all trials are second line unless stated

1. **Original two arm trial**: compare to **product Z**
2. **Three arm trial**: compare to **products W and Z**
3. **Four arm trial**: compare to **products W, Z & V**
4. **Physician's choice**: compare to **physician's choice**
5. **Two arm trial with third-line comparator**: compare to **product V**
6. **Placebo-controlled late line trial:** compare to **placebo**

Approaches to evidence generation (inc. clinical programmes) for JCA & IRA

Closing comments

QUESTIONS AND DISCUSSION

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