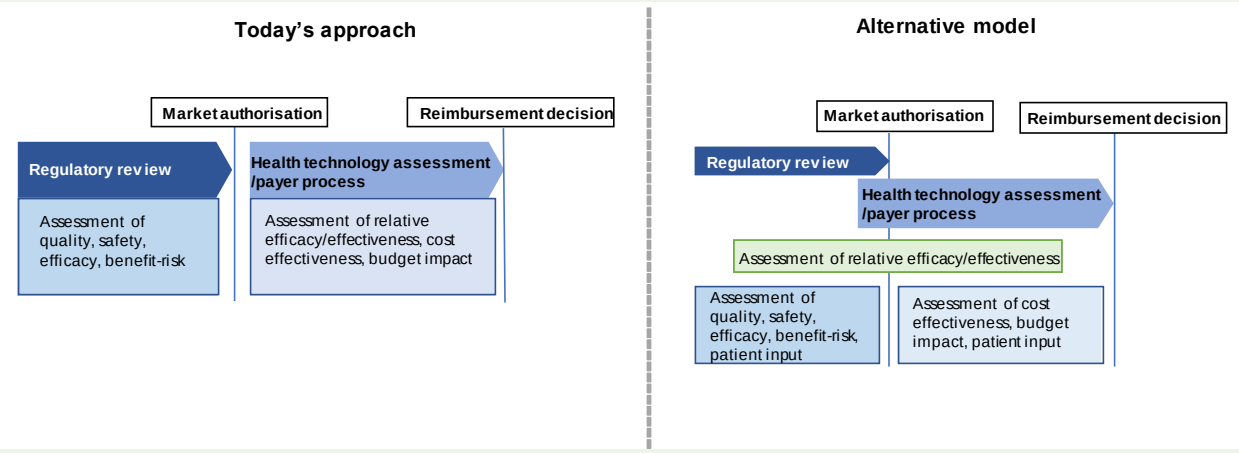
REGULATORY AND HTA DECISION MAKING AND ACCESS TO MEDICINES:

THE CONSEQUENCES OF SEQUENCE



Adapted from Eichler H-G, Bloechl-Daum B, Abadie E et al. *Nature Rev Drug Discov.* 2010;9:277-291.

Summary of the key findings from the Stakeholder Survey

- Sequential regulatory and HTA assessment is the main route through which new medicines are made available.
- Although a parallel review mechanism is available in certain countries, a survey of agencies indicated that its use is dependent on company choice.
- In this survey, 29% of patients and 33% regulatory respondents were aware of any discussion around possible changes of review sequence, compared with 71% of HTA agencies who indicated that they were aware of the potential for a change.
- More than half (57%) of patient respondents were aware of opportunities to use the legal system or a "judicialisation" process to enable access to medicines.
- Both patient and agency respondents indicated a negative perception regarding the judicialisation process: 40% of patients felt that the system is misused and causes greater inequity to treatment options, and 60% of agencies felt that judicialisation has a negative impact on the healthcare system's ability to provide equitable access to medicines.
- Both patients and agencies believe regulatory review should be conducted first (>40% responses) followed by HTA review. However, agency respondents thought the most likely sequence by 2025 will be a parallel review process.

Contents

Report prepared by

Tina Wang
HTA Programme Manager, Centre for Innovation in Regulatory Science
Email: twang@cirsci.org

Neil McAuslane
Director, Centre for Innovation in Regulatory Science
Email: nmcauslane@cirsci.org

Magda Bujar
Project Manager, Centre for Innovation in Regulatory Science
Email: mbujar@cirsci.org

Jesmine Cai
Senior Analyst, Centre for Innovation in Regulatory Science
Email: jcai@cirsci.org

Lawrence Liberti
Executive Director, Centre for Innovation in Regulatory Science
Email: lliberti@cirsci.org

Centre for Innovation in Regulatory Science
Friars House, 160 Blackfriars Road
London SE1 8EZ UK
Email: cirs@cirsci.org
Website: www.cirsci.org

CIRS - The Centre for Innovation in Regulatory Science Limited - is a neutral, independently managed UK-based subsidiary company, forming part of Clarivate Analytics (UK) Limited. CIRS' mission is to maintain a leadership role in identifying and applying scientific principles for the purpose of advancing regulatory and HTA policies and processes. CIRS provides an international forum for industry, regulators, HTA and other healthcare stakeholders to meet, debate and develop regulatory and reimbursement policy through the innovative application of regulatory science and to facilitate access to medical products through these activities. This is CIRS' purpose. CIRS is operated solely for the promotion of its purpose. The organisation has its own dedicated management and advisory boards, and its funding is derived from membership dues, related activities, special projects and grants.

BACKGROUND

Introduction

Historically, every jurisdiction with some form of regulatory agency capacity has undertaken the review of medicines as a first step in the market access process. This step is intended to verify the quality, safety and efficacy of a product and to establish that its benefits outweigh its harms within the context of the proposed indication. The subsequent evaluative step has been a health technology assessment (HTA) or a payer decision regarding the comparative effectiveness and cost-effectivness of the product, resulting in an access decision. While in many developed nations/healthcare systems this approach has worked well for some time, in others these systems appear to provide challenges to equitable medicine access. Another important consideration, especially in regions such as Latin America, is the "judicialisation" of health and the legal demands this has created on the health system.

As a reaction to the economic challenges of funding medicine access via national healthcare systems with finite allocated budgets, there have been moves to utilise HTA assessment to prioritise medicine access within the healthcare system. One approach would be that once a positive HTA recommendation has been made to determine the indication for which the new therapy is relevant and should be included in the national formulary, this would be followed by a rigorous regulatory review of quality, safety and efficacy.

The idea of conducting HTA assessments concurrent with regulatory reviews or used as a means of priority setting, therefore, has been actively discussed.

To gain a more detailed understanding of the evolution of the relationship between regulatory and HTA decision-making processes, CIRS undertook a research project to investigate "How might the sequence of regulatory and HTA decision making influence patient access to new medicines?" This study focused on the effect of sequence on medicines and not other treatment technologies.

Two-part study design

- A literature review of the published literature and grey literature was conducted to understand regulatory and HTA decision-making sequences, to inform hypothetical effects of potential changes, and to examine the implications and consequences for healthcare stakeholders.
- A survey was also undertaken across patient representatives and agencies (regulatory and HTA) to explore perceptions and understandings regarding the current and potential evolution of review sequences and relationships between regulatory, HTA and payer assessments on access.

For the purposes of this study, the following definitions were used:

Regulatory agencies: Agencies that review a dossier for a new medicine and provide a marketing authorisation based on quality, safety and efficacy.

Health technology assessment (HTA) agencies: Agencies that conduct a cluster of assessment and measurement techniques that aim to assess the relative value of a new medicine and that commonly involve some form of economic measurement, or measures of social well-being; typically going beyond assessing measures of clinical effectiveness found in the conventional clinical trials.

Judicialisation: A legal process whereby a patient may request, through the courts, access to an approved medicine not included in a national formulary or paid for by a government health programme, but which the payer will be required to make available to the patient, paid for through the national budget.

Payer organisations: Entities other than the patient that finance or reimburse the cost of health services. These may include the government, private insurers, other third-party payers or health plan sponsors.

About this Briefing

This R&D Briefing summarises the background of the study and key findings from the literature review and stakeholder surveys, with examples to demonstrate the countries with different sequences in regulatory, HTA and coverage processes for new medicines.

REGULATORY-HTA DECISION-MAKING SCENARIOS

Based on the results of a literature review, we identified four scenarios for regulatory and HTA decision making sequence: two existing pathways (scenarios I and II), and two hypothetical pathways based on the debate surrounding potential changes (scenarios III and IV). Patient input will become increasingly important across all four of the scenarios.

Scenario I

Regulatory and HTA decision making occur in sequence

Regulatory review (safety, quality, efficacy) → **HTA review** (clinical and/or cost effectiveness, other factors) → **Reimbursement decision**

In this scenario, regulatory review is conducted first to determine the benefit-risk profile of a new medicine, followed by the HTA review to assess the value of the medicine for a reimbursement decision. The regulatory-HTA sequence is seen at a national level in many countries, and also at a super-national level in Europe where a centralised regulatory decision made by the European Medicines Agency is followed by jurisdictional HTA recommendations by member states. However, this traditional pathway now has been challenged in terms of its sustainability and efficiency for bringing new medicines to patients in a timely manner.

Scenario II

Regulatory and HTA decision making occur in parallel

Regulatory review (safety, quality, efficacy)

HTA review (clinical and/or cost effectiveness, other factors) → **Reimbursement decision**

In this scenario, the regulatory review is initiated first. Pharmaceutical companies submit evidence to the regulatory agency that prove the efficacy, safety, and quality of the product. However, in contrast to scenario I, during the regulatory review process companies submit dossiers to the HTA body so that the two steps can occur in parallel. Following the regulatory approval, an HTA recommendation will be made. This sequence is established with the aim of shortening the overall time for the two-step decision-making process and promoting timely access to new medicines. This sequence is available in Australia and Canada as well as Thailand and South Korea.

Scenario III

HTA evaluation is integrated as a component of regulatory review

Regulatory + HTA review (assessment of safety, quality, relative-efficacy and/or cost-effectiveness) → **Reimbursement decision**

In this scenario, regulatory decision making is not only based on efficacy, safety and quality criteria, but also includes an element of HTA evaluation. A regulatory approval will be granted based on a positive assessment result, followed by a reimbursement recommendation from the HTA appraisal process, with the final reimbursement decision to be made by payer. Currently, there is no formal system in any country using this model.

Scenario IV

HTA evaluation is conducted prior to the regulatory review

HTA review (cost-effectiveness, budget impact, affordability) → **Regulatory review** (safety, quality, efficacy) → **Reimbursement decision**

In this scenario, HTA assessment would be conducted first to examine the economic implications based on cost-effectiveness, affordability, and/or budget impact criteria. Following a positive HTA recommendation, the regulator will assess the efficacy, safety and quality of a new medicine and grant marketing authorisation accordingly. Currently, there is no formal system in any country using this model.

ANALYSIS OF FOUR SEQUENCE SCENARIOS

Table 1: A comparison of four sequence scenarios based on literature research*

Scenario	I Sequential	II Parallel	III Integrated	IV Reversed
Countries	Majority of countries	• Australia • Canada • Thailand • South Korea	No formal system in place	No formal system in place
Rationale for this sequence	Traditional sequence that has evolved naturally	Parallel review to shorten overall review time	Paradigm of evolution of relative efficacy assessment to be conducted by regulator	Designed to address the more efficient use of HTA processes and to work within highly cost-constrained economies
Challenges of this sequence	• Access may be delayed • Potential unequal access level • Duplication of work between regulatory and HTA bodies • Debate of efficacy /relative efficacy issue	• Possible waste of HTA resource • Impact company pricing strategy • Duplication of regulatory/HTA work	• May be limited by the legal framework • Challenge of aligning the review methodologies	• HTA capacity may be rate limiting • Block access through private markets • Does not prevent Judicialisation actions
Key points from literature research	• Sequential decision making process may create a time delay from regulatory approval to market access • Access delay can be attributed to the time needed by companies to prepare submissions under the relevant local HTA processes, the time taken for the HTA agency to review submissions and make recommendations • A number of initiatives have been undertaken to improve the interaction between the regulatory agency, HTA bodies and industry, which may lead to a potential new paradigm to make new medicines reach patients expeditiously	• Ability to shorten overall time for market access • However, this model may lead to waste of HTA resource if a negative regulatory decision was granted • The time to launch is not only associated with review time by regulatory agency and HTA bodies, but is also linked to the company's strategy. It requires the company to demonstrate robust data to support reimbursement decisions and address locally relevant HTA needs at nearly the same time as the regulatory submission	• HTA requirements are integrated within regulatory processes with experts for regulatory review and HTA assessment brought together • The review de-links the economic consideration from HTA assessment and focuses on clinical evaluation of relative efficacy of a new product during regulatory review, followed by reimbursement decision to be made with economic considerations such as budget impact and affordability that will meet regional / national needs • This model has been considered to reduce the regulatory/HTA duplication of work	• Where judicialised access decisions can be made, there are concerns that the court has acted as a decision maker in the area of drug reimbursement • Therefore, there is ongoing debate that HTA should be sequenced first and only products with positive HTA recommendations would be accepted for regulatory review and the criteria for economic evaluation will act as a filter for new medicines to be approved for marketing. • Advocates suggest that there is no reason to subject a product to a comprehensive regulatory review if there is little chance of the product being included in a national formulary • Access by private pay would not be available

** The bibliography of the literature search is attached as an Annex to this Briefing*

A KEY STAKEHOLDER PERCEPTION SURVEY

A survey was conducted by CIRS across the following stakeholders to explore perceptions and understanding of the current and potential value posed by various review sequences in their jurisdiction.

For the patient group survey, the questions aimed to capture understanding and perceptions regarding
- Current regulatory/HTA/payer review sequences
- The impact of these sequences on patient access

For the regulatory and HTA agency survey, the questions aimed to capture understanding and perceptions regarding
- The impact of regulatory and HTA/payer reviews sequences on patient access and drivers for future changes
- Possible scenarios for future regulatory and HTA/payer review sequences and the implication and barriers to these scenarios

Figure 1: Response rate of key stakeholder survey

	Stakeholder survey		
	Regulatory agencies	**HTA agencies**	**Patient representative groups**
Survey sent to 39 contacts	**13**	**8**	**18**
Responses received (% response rate)	**7 (54%)** Agencies from Australia Brazil Canada Israel Singapore Sweden European Union	**7 (88%)** Agencies from Australia Brazil Canada England Scotland Sweden Taiwan	**7 (39%)** Patient groups from Canada Denmark Greece The Netherlands Spain Romania

•Summary of the key findings from the stakeholder survey

- Sequential regulatory and HTA assessment is the main route through which new medicines are made available.
- Although a parallel review mechanism is available in certain countries, a survey of agencies indicated that its use is dependent on company choice.
- In this survey, 29% of patients and 33% regulatory respondents were aware of any discussion around possible changes of review sequence, compared with 71% of HTA agencies who indicated that they were aware of the potential for a change.
- More than half (57%) of patient respondents were aware of opportunities to use the legal system or a "judicialisation" process to enable access to medicines.
- Both patient and agency respondents indicated a negative perception regarding the judicialisation process: 40% of patients felt that the system is misused and causes greater inequity to treatment options, and 60% of agencies felt that judicialisation has a negative impact on the healthcare system's ability to provide equitable access to medicines.
- Both patients and agencies believe regulatory review should be conducted first (>40% responses) followed by HTA review. However, agency respondents thought the most likely sequence by 2025 will be a parallel review process.

CURRENT REGULATORY AND HTA SEQUENCE

Patient perspectives

Understanding of the current regulatory and HTA review process

Figure 2: In your country, to your knowledge which is the sequence of activities that occurs, before a medicine can be made available to patients?

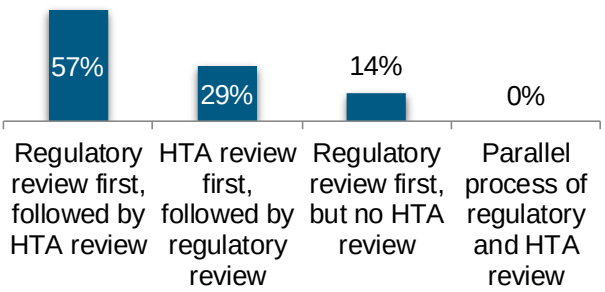


Figure 3: Are you aware of any discussions in your country around possible changes to the review and reimbursement process for new medicines?

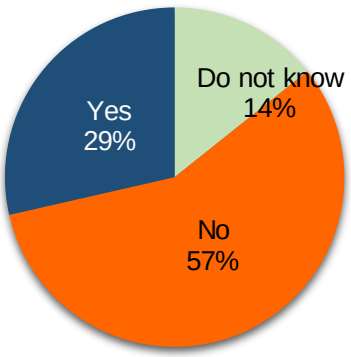
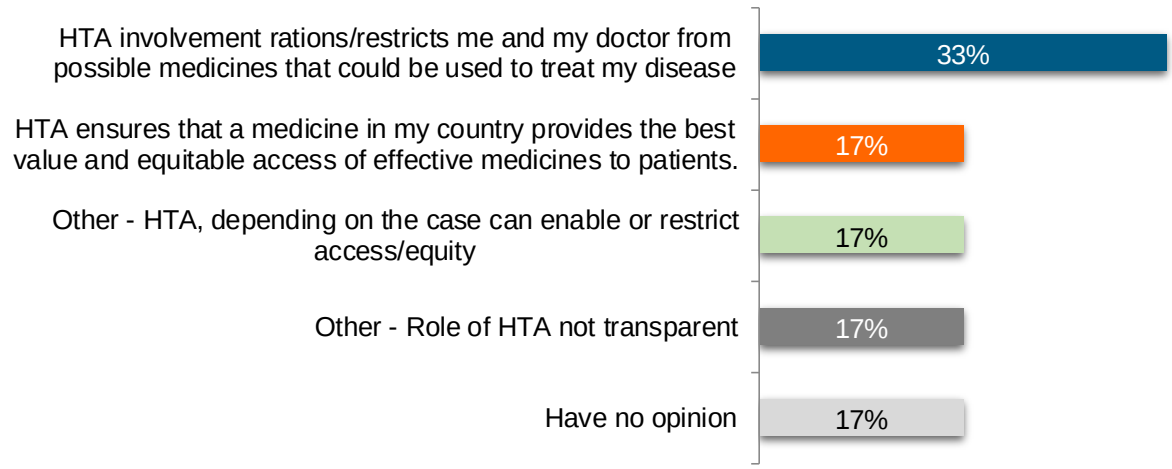


Figure 4: If HTA occurs in your country, please mark the statement you think best reflects the situation.



Use of the judicialisation process

Figure 5: Are you aware in your country if you are able to use the legal system or a judicialisation process to enable access to medicines?

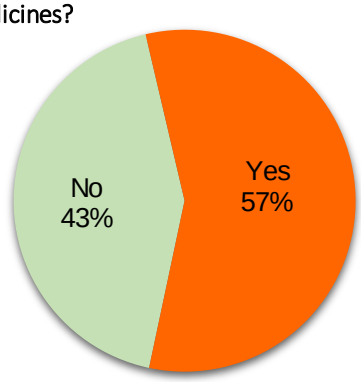
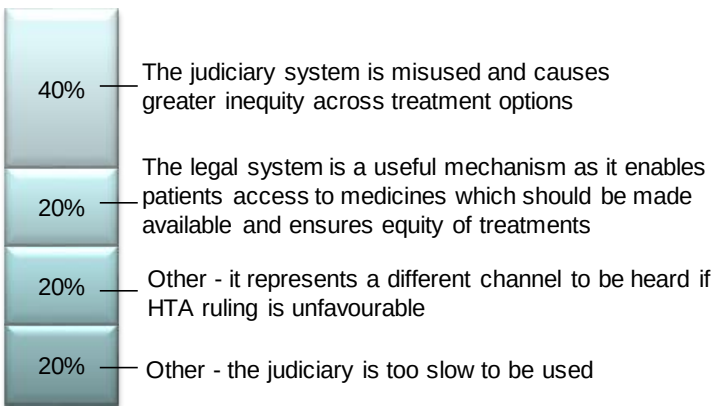


Figure 6: Which of these statements best represents your opinion/perception?

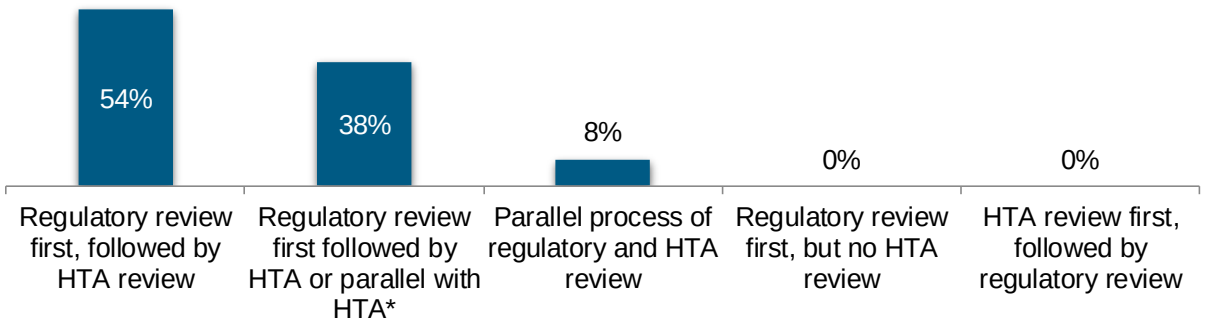


CURRENT REGULATORY AND HTA SEQUENCE

Agency perspectives

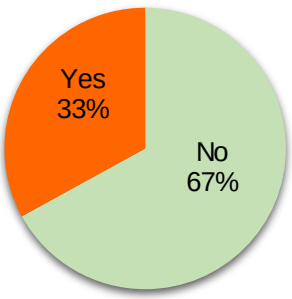
Understanding the current regulatory and HTA review process

Figure 7: In your jurisdiction, which option most adequately describes the regulatory and reimbursement system?

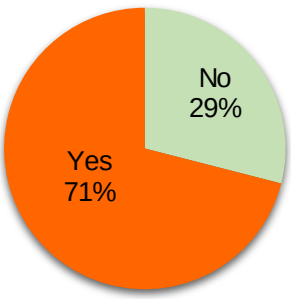


** Both sequential and parallel are available and it depends on the sponsors to decide the submission route*

Figure 8: In your jurisdiction, has there been any discussion regarding a potential change from this current regulatory and HTA/payer sequence to a new approach?



Regulatory agency response n=6



HTA agency response n=7

Use of judicialisation process

Figure 9: In your jurisdiction, what role does judicialisation play as a route to access new medicines not covered by a national healthcare plan? (n=12)

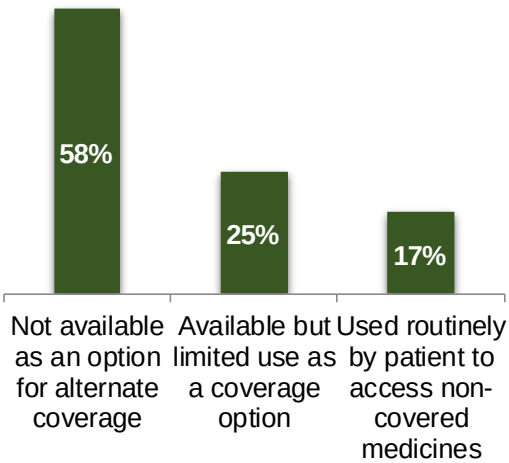
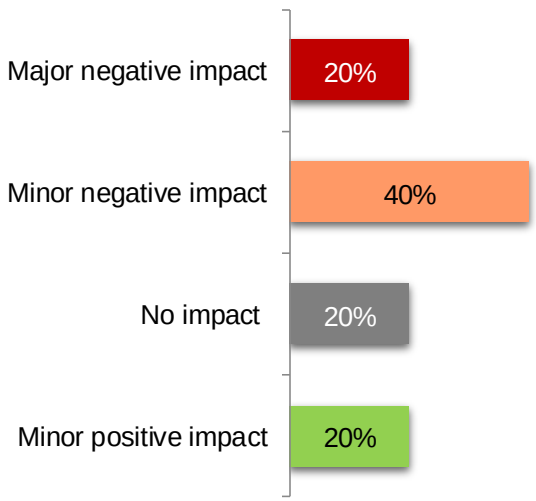


Figure 10: Please rate the degree of the impact of "judicialisation" on your healthcare system's ability to provide medicines (n=5)



CURRENT REGULATORY AND HTA SEQUENCE

Comparison of responses from stakeholders in the same jurisdiction

Understanding the current regulatory and HTA review process

Figure 11: Comparison of respondents' views on the current regulatory and HTA review process

	Regulatory agency response	HTA agency response
Country A		
Country B		
Country C		
Country D		

Type of review sequence:

- Regulatory review first, followed by HTA review
- Parallel process of regulatory and HTA review
- Regulatory review first followed by HTA/parallel with HTA

Figure 12: Comparison of views on the potential changes

	Regulatory agency response	HTA agency response
Country A		
Country B		
Country C		
Country D		

In your jurisdiction, has there been any discussion regarding a potential change from this current regulatory and HTA/payer sequence to a new approach?

- Yes
- No

Use of the judicialisation process

Figure 13: Comparison of respondents' views on the judicialisation process

	Regulatory agency response	HTA agency response
Country A		
Country B		
Country C		

In your jurisdiction, what role does judicialisation play as a route to access new medicines not covered by a national healthcare plan?

- Used routinely by patients to access non-covered medicines
- Available but limited use as a coverage option
- Not available as a option for alternate coverage

FUTURE REGULATORY AND HTA SCENARIOS

Future scenarios by 2025 – Agency responses

Figure 14: Which scenario do you think is likely to reflect the situation by 2025 in your jurisdiction? Agency responses (n=13)

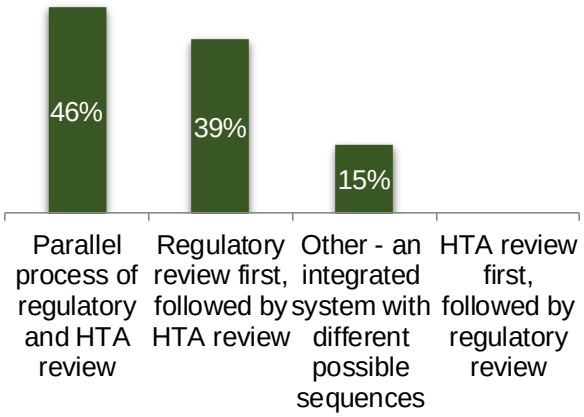


Figure 15: Which is the ideal scenario that you would like to see happen? Agency responses (n=14)

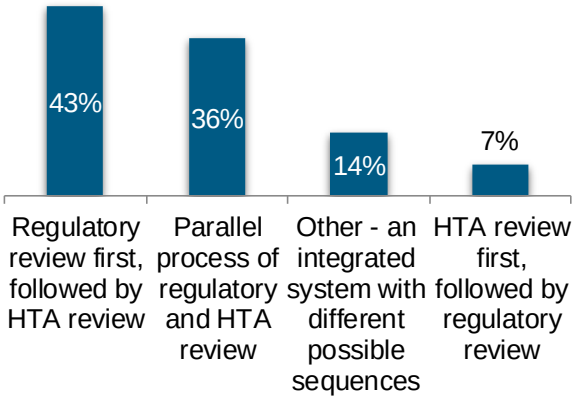
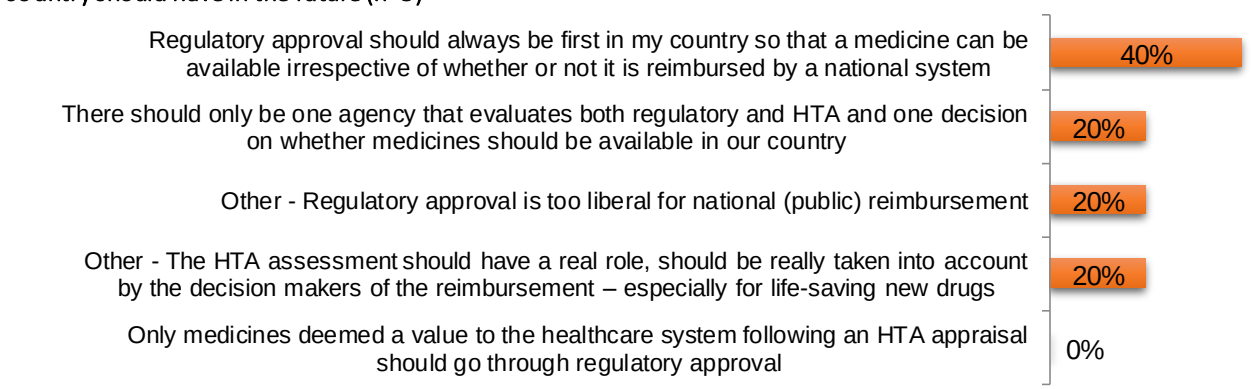


Figure 16: What is the main driver for scenarios to happen by 2025?– Response from agencies

Scenario	Driver
Parallel process of regulatory and HTA review/Other - an integrated system with different possible sequences	• Push for increased collaboration, particularly at EU level • Increased convergence/alignment for data generation and discussion pre- and post-licensing • Need for better resource utilisation and sustainable health care system to allow equal and affordable access to cost-effective medicines • Political pressure from increasingly knowledgeable patients as well as others stakeholders such as payers and clinicians to ensure drugs with the greatest benefit are available earlier
Regulatory review first, followed by HTA review	• No change –status quo will prevail • Insufficient time as structural changes take many years • HTA scope includes review of other data (real -world clinical/cost effectiveness) compared with regulator • Some change compared with current mode due to: ◦ Political pressure that will force HTA bodies to collaborate with each other and with regulators compared to today ◦ Shortening of the time lag between market approval compared with current situation by "moving" the conduct of HTA earlier

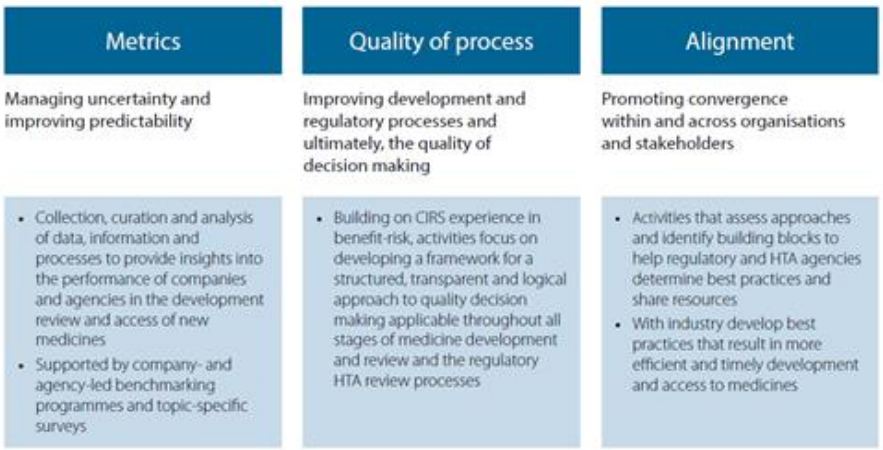
Future scenario by 2025 - Patient responses

Figure 17: Please choose the statement that describes what your view is with regard to the system you believe your country should have in the future (n=5)



ABOUT CIRS

CIRS overlapping themes



Through its research, Workshops and other activities, CIRS focuses on the themes of metrics, quality of process and alignment.

The CIRS programme of activities includes:

International Workshops: Meetings for members are convened at which invited participant interactions are optimised to facilitate networking, constructive discussion, recommendations and actions.

CIRS research projects: Specialised research and surveys are carried out among leading pharmaceutical companies and regulatory and HTA agencies with expert analyses and interpretation of the findings.

Identification of and advocacy for best international practices: Using findings from our Workshops and research projects CIRS interacts with companies, regulators, HTA agencies and other international organisations to promulgate efficiencies in global medicine development.

Publications and presentations: Reports are prepared from Workshops and projects. Dissemination of findings and recommendations through the R&D Briefing series, conference presentations, papers in peer-reviewed journals and the CIRS website are key aspects of the CIRS educational communication mission.

This independent research study was conducted by CIRS as part of its ongoing initiatives to understand pharmaceutical development and regulatory activities around the world. Support for this analysis was funded in part by a grant from The Pharmaceutical Research and Manufacturers of America (PhRMA).

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Centre for Innovation in Regulatory Science
Friars House, 160 Blackfriars Road, London
United Kingdom
SE1 8EZ
Email: cirs@cirsci.org
Website: www.cirsci.org

CIRS Centre for Innovation in Regulatory Science

ANNEX: LITERATURE REVIEW BIBLIOGRAPHY

- Allen, N., F. Pichler, T. Wang, S. Patel and S. Salek (2013). "Development of archetypes for non-ranking classification and comparison of European National Health Technology Assessment systems." Health Policy **113**(3): 305-312.
- Augustovski, F., C. Iglesias, A. Manca, M. Drummond, A. Rubinstein and S. G. Marti (2009). "Barriers to generalizability of health economic evaluations in Latin America and the Caribbean region." Pharmacoeconomics **27**(11): 919-929.
- Banta, D. (2002). "Economic development key to healthier world." JAMA **287**(24): 3195-3197.
- Banta, D. (2003). "The development of health technology assessment." Health Policy **63**(2): 121-132.
- Banta, D. (2009). "Health technology assessment in Latin America and the Caribbean." Int J Technol Assess Health Care **25 Suppl 1**: 253-254.
- Banta, D. and R. T. Almeida (2009). "The development of health technology assessment in Brazil." Int J Technol Assess Health Care **25 Suppl 1**: 255-259.
- Banta, D., F. B. Kristensen and E. Jonsson (2009). "A history of health technology assessment at the European level." Int J Technol Assess Health Care **25 Suppl 1**: 68-73.
- Bryan, S., S. Sofaer, T. Siegelberg and M. Gold (2009). "Has the time come for cost-effectiveness analysis in US health care?" Health Econ Policy Law **4**(Pt 4): 425-443.
- Cerri, K. H., M. Knapp and J. L. Fernandez (2014). "Decision making by NICE: examining the influences of evidence, process and context." Health Econ Policy Law **9**(2): 119-141.
- Ciani, O. and C. Jommi (2014). "The role of health technology assessment bodies in shaping drug development." Drug Des Devel Ther **8**: 2273-2281.
- Cleemput, I., M. Franken, M. Koopmanschap and M. le Polain (2012). "European drug reimbursement systems' legitimacy: five-country comparison and policy tool." Int J Technol Assess Health Care **28**(4): 358-366.
- Clement, F. M., A. Harris, J. J. Li, K. Yong, K. M. Lee and B. J. Manns (2009). "Using effectiveness and cost-effectiveness to make drug coverage decisions: a comparison of Britain, Australia, and Canada." JAMA **302**(13): 1437-1443.
- Cuche, M., R. Beckerman, C. A. Chowdhury and M. A. van Weelden (2014). "Early dialogue with health technology assessment bodies: A European perspective." Int J Technol Assess Health Care **30**(06): 571-578.
- Drummond M (2008). "Key principles for the improved conduct of health technology assessments for resource allocation decisions." Int J Technol Assess Health Care **24:3**: 244-258.
- Drummond, M., P. Neumann, B. Jonsson, B. Luce, J. S. Schwartz, U. Siebert, S. D. Sullivan and I. G. H. Adv (2012). "Can We Reliably Benchmark Health Technology Assessment Organizations?" Intl J Technol Assess Health Care **28**(2): 159-165.
- Ehmann, F., M. Papaluca Amati, T. Salmonson, M. Posch, S. Vamvakas, R. Hemmings, H. G. Eichler and C. K. Schneider (2013). "Gatekeepers and enablers: how drug regulators respond to a challenging and changing environment by moving toward a proactive attitude." Clin Pharmacol Ther **93**(5): 425-432.
- Eichler, H.-G., B. Bloechl-Daum, E. Abadie, D. Barnett, F. König and S. Pearson (2010). "Relative efficacy of drugs: an emerging issue between regulatory agencies and third-party payers." Nature Rev Drug Discov **9**(4): 277-291.
- Eichler, H. G., H. Hurts, K. Broich and G. Rasi (2016). "Drug Regulation and Pricing--Can Regulators Influence Affordability?" N Engl J Med **374**(19): 1807-1809.
- Franken, M., M. le Polain, I. Cleemput and M. Koopmanschap (2012). "Similarities and differences between five European drug reimbursement systems." Int J Technol Assess Health Care **28**(4): 349-357.
- Frønsdal K, P. F., Mardhani-Bayne L, Henshall C, Røttingen JA, Mørland B, Klemp M. (2012). "Interaction initiatives between regulatory, health technology assessment and coverage bodies, and industry." Int J Technol Assess Health Care: 374-381.
- Garattini, L. and S. Ghislandi (2007). "Should we really worry about "launch delays" of new drugs in OECD countries?" Eur J Health Econ **8**(1): 1-3.
- Hailey, D. (2009). "The history of health technology assessment in Australia." Int J Technol Assess Health Care **25 Suppl 1**: 61-67.
- Haynes, B. (1999). "Can it work? Does it work? Is it worth it? The testing of healthcare interventions is evolving." BMJ **319**(7211): 652-653.
- Healy, E. M. and K. I. Kaitin (1999). "The European Agency for the Evaluation of Medicinal Products' centralized procedure for product approval: Current status." Drug Info J **33**(4): 969-978.
- Henshall, C. (2012). "Describe Decision-Making Systems, Assess Health Technology Assessment Reports." Int J Technol Assess Health Care **28**(2): 168-168.
- Hirako, M., N. McAuslane, S. Salek, C. Anderson and S. Walker (2007). "A comparison of the drug review process at five international regulatory agencies." Drug Info J **41**(3): 291-308.
- Hofer, M. P., C. Jakobsson, N. Zafiropoulos, S. Vamvakas, T. Vetter, J. Regnstrom and R. J. Hemmings (2015). "Regulatory watch: Impact of scientific advice from the European Medicines Agency." Nat Rev Drug Discov **14**(5): 302-303.
- Jonsson, B. (2015). "Bringing in health technology assessment and cost-effectiveness considerations at an early stage of drug development." Mol Oncol **9**(5): 1025-1033.
- Kataria, B. C., D. S. Mehta and S. B. Chhaiya (2013). "Drug lag for cardiovascular drug approvals in India compared with the US and EU approvals." Indian Heart J **65**(1): 24-29.
- Kendall, T., L. McGoey and E. Jackson (2009). "If NICE was in the USA." Lancet **374**(9686): 272-273.
- Kim, C. Y. (2009). "Health technology assessment in South Korea." Int J Technol Assess Health Care **25 Suppl 1**: 219-223.

ANNEX: LITERATURE REVIEW BIBLIOGRAPHY

- Kleijnen, S., M. Fathallah, M. W. van der Linden, P. Vancraeynest, B. Dahmani, A. Timoney, A. De Boer, H. G. Leufkens and W. G. Goettsch (2015). "Can a Joint Assessment Provide Relevant Information for National/Local Relative Effectiveness Assessments? An In-Depth Comparison of Pazopanib Assessments." Value Health **18**(5): 663-672.
- Kristensen F, N. C. (2008). Health technology assessment and health policy-making in Europe. European Observatory of Health Systems and Policies.
- Kristensen, F. B., J. Chamova and N. W. Hansen (2006). "Toward a sustainable European Network for Health Technology Assessment. The EUnetHTA project." Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz **49**(3): 283-285.
- Lasagna, L. (1989). "Congress, the FDA, and new drug development: before and after 1962." Perspect Biol Med **32**(3): 322-343.
- Liberti, L., P. Stolk, N. McAuslane, A. Somauroo, A. M. Breckenridge and H. G. Leufkens (2015). "Adaptive licensing and facilitated regulatory pathways: A survey of stakeholder perceptions." Clin Pharmacol Ther **98**(5): 477-479.
- Lipska, I., J. Hoekman, N. McAuslane, H. Leufkens and A. M. Hovels (2015). "Does conditional approval for new oncology drugs in Europe lead to differences in health technology assessment decisions?" Clin Pharmacol Ther **98**(5): 489-491.
- Macaulay, R. and P. Hempshall (2015). "A necessary convergence? US payers adopting EU Behaviors." Value Health **18**(3): A75.
- Mason, A., M. Drummond, S. Ramsey, J. Campbell and D. Raisch (2010). "Comparison of anticancer drug coverage decisions in the United States and United Kingdom: does the evidence support the rhetoric?" J Clin Oncol **28**(20): 3234-3238.
- Mathes, T., E. Jacobs, J. C. Morfeld and D. Pieper (2013). "Methods of international health technology assessment agencies for economic evaluations--a comparative analysis." BMC Health Serv Res **13**: 371.
- Mauskopf, J., J. Walter, J. Birt, L. Bowman, C. Copley-Merriman and M. Drummond (2011). "Differences among formulary submission guidelines: implications for health technology assessment." Int J Technol Assess Health Care **27**(3): 261-270.
- Menon, D. and T. Stafinski (2009). "Health technology assessment in Canada: 20 years strong?" Value Health **12 Suppl 2**: S14-19.
- Menon, D. and L. A. Topfer (2000). "Health technology assessment in Canada. A decade in review." Int J Technol Assess Health Care **16**(3): 896-902.
- Moseley, G. B., 3rd (2005). "The prospects for medical technology in the next decade." Stud Health Technol Inform **118**: 15-31.
- Nicod, E. and P. Kanavos (2012). "Commonalities and differences in HTA outcomes: a comparative analysis of five countries and implications for coverage decisions." Health Policy **108**(2-3): 167-177.
- Nielsen, C. P., S. W. Lauritsen, F. B. Kristensen, M. L. Bistrup, A. Cecchetti and E. Turk (2009). "Involving stakeholders and developing a policy for stakeholder involvement in the European network for health technology assessment, EUnetHTA." Int J Technol Assess Health Care **25 Suppl 2**: 84-91.
- Panteli, D., H. Eckhardt, A. Nolting, R. Busse and M. Kulig (2015). "From market access to patient access: overview of evidence-based approaches for the reimbursement and pricing of pharmaceuticals in 36 European countries." Health Res Policy Syst **13**: 39.
- Pignatti, F., B. Aronsson, N. Gate, S. Vamvakas, G. Wade, I. Moulon and P. Le Courtois (2002). "The review of drug applications submitted to the European Medicines Evaluation Agency: frequently raised objections, and outcome." Eur J Clin Pharmacol **58**(9): 573-580.
- Psaty, B. M., E. M. Meslin and A. Breckenridge (2012). "A lifecycle approach to the evaluation of FDA approval methods and regulatory actions: opportunities provided by a new IOM report." JAMA **307**(23): 2491-2492.
- Rawlins, M. D. (2009). "The decade of NICE." Lancet **374**(9686): 351-352.
- Rawlins, M. D. (2012). "Crossing the fourth hurdle." Br J Clin Pharmacol **73**(6): 855-860.
- Regnstrom, J., F. Koenig, B. Aronsson, T. Reimer, K. Svendsen, S. Tsigkos, B. Flamion, H. G. Eichler and S. Vamvakas (2010). "Factors associated with success of market authorisation applications for pharmaceutical drugs submitted to the European Medicines Agency." Eur J Clin Pharmacol **66**(1): 39-48.
- Rogowski, W. H., S. C. Hartz and J. H. John (2008). "Clearing up the hazy road from bench to bedside: a framework for integrating the fourth hurdle into translational medicine." BMC Health Serv Res **8**: 194.
- Ross, J. S., K. Dzara and N. S. Downing (2015). "Efficacy and safety concerns are important reasons why the FDA requires multiple reviews before approval of new drugs." Health Aff (Millwood) **34**(4): 681-688.
- Schulthess, D., M. Chlebus, R. Bergstrm and K. V. Baelen (2014). "Medicine adaptive pathways to patients (MAPPs): using regulatory innovation to defeat Eroom's law." Chin Clin Oncol **3**(2): 21.
- Schumock, G. T. and A. S. Pickard (2009). "Comparative effectiveness research: Relevance and applications to pharmacy." Am J Health Syst Pharm **66**(14): 1278-1286.
- Schweitzer, S. O., M. E. Schweitzer and M. Sourty-Le Guellec (1996). "Is there a U.S. drug lag? The timing of new pharmaceutical approvals in the G-7 countries and Switzerland." Med Care Res Rev **53**(2): 162-178.
- Sinha, G. (2010). "Japan works to shorten "drug lag," boost trials of new drugs." J Natl Cancer Inst **102**(3): 148-151.
- Sivalal, S. (2009). "Health technology assessment in the Asia Pacific region." Int J Technol Assess Health Care **25 Suppl 1**: 196-201.
- Sorenson, C. and K. Chalkidou (2012). "Reflections on the evolution of health technology assessment in Europe." Health Econ Policy Law **7**(1): 25-45.
- Sorenson, C., H. Naci, J. Cylus and E. Mossialos (2011). "Evidence of comparative efficacy should have a formal role in European drug approvals." BMJ **343**: d4849.

ANNEX: LITERATURE REVIEW BIBLIOGRAPHY

- Spinner, D. S., J. Birt, J. W. Walter, L. Bowman, J. Mauskopf, M. F. Drummond and C. Copley-Merriman (2013). "Do different clinical evidence bases lead to discordant health-technology assessment decisions? An in-depth case series across three jurisdictions." Clinicoecon Outcomes Res **5**: 69-85.
- Stevens, A., R. Milne and A. Burls (2003). "Health technology assessment: history and demand." J Public Health Med **25**(2): 98-101.
- Sullivan, S. D., J. Watkins, B. Sweet and S. D. Ramsey (2009). "Health technology assessment in health-care decisions in the United States." Value Health **12 Suppl 2**: S39-44.
- Tsoi, B., L. Masucci, K. Campbell, M. Drummond, D. O'Reilly and R. Goeree (2013). "Harmonization of reimbursement and regulatory approval processes: a systematic review of international experiences." Expert Rev Pharmacoecon Outcomes Res **13**(4): 497-511.
- Uchiyama, M. (1993). "[Regulatory science forum--its background and goal]." Eisei Shikenjo Hokoku (111): 140-141.
- van Luijn, J. C. F., F. W. J. Gribnau and H. G. M. Leufkens (2007). "Availability of comparative trials for the assessment of new medicines in the European Union at the moment of market authorization." Brit J Clin Pharmacol **63**(2): 159-162.
- Wileman, H. and A. Mishra (2010). "Drug lag and key regulatory barriers in the emerging markets." Perspect Clin Res **1**(2): 51-56.
- Wonder, M., M. E. Backhouse and E. Hornby (2013). "Early scientific advice obtained simultaneously from regulators and payers: findings from a pilot study in Australia." Value Health **16**(6): 1067-1073.
- Wood, A. J. J. (1999). "The safety of new medicines - The importance of asking the right questions." JAMA **281**(18): 1753-1754.