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.
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-effectiveness 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.
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>
<thead>
<tr>
<th>Scenario</th>
<th>I Sequential</th>
<th>II Parallel</th>
<th>III Integrated</th>
<th>IV Reversed</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Countries</strong></td>
<td>Majority of countries</td>
<td>Australia, Canada, Thailand, South Korea</td>
<td>No formal system in place</td>
<td>No formal system in place</td>
</tr>
<tr>
<td><strong>Rationale for this sequence</strong></td>
<td>Traditional sequence that has evolved naturally</td>
<td>Parallel review to shorten overall review time</td>
<td>Paradigm of evolution of relative efficacy assessment to be conducted by regulator</td>
<td>Designed to address the more efficient use of HTA processes and to work within highly cost-constrained economies</td>
</tr>
<tr>
<td><strong>Challenges of this sequence</strong></td>
<td>• Access may be delayed • Potential unequal access level • Duplication of work between regulatory and HTA bodies • Debate of efficacy/relative efficacy issue</td>
<td>• Possible waste of HTA resource • Impact company pricing strategy • Duplication of regulatory/HTA work</td>
<td>• May be limited by the legal framework • Challenge of aligning the review methodologies</td>
<td>• HTA capacity may be rate limiting • Block access through private markets • Does not prevent Judicialisation actions</td>
</tr>
<tr>
<td><strong>Key points from literature research</strong></td>
<td>• 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</td>
<td>• 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</td>
<td>• HTA requirements are integrated within regulatory processes with experts for regulatory review and HTA assessment brought together • The review delinks 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</td>
<td>• 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</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Stakeholder survey</th>
<th>Regulatory agencies</th>
<th>HTA agencies</th>
<th>Patient representative groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survey sent to</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>39 contacts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Responses received</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(% response rate)</td>
<td>13</td>
<td>8</td>
<td>18</td>
</tr>
<tr>
<td>Agencies from</td>
<td>7 (54%)</td>
<td>7 (88%)</td>
<td>7 (39%)</td>
</tr>
<tr>
<td>Australia</td>
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<tr>
<td>Brazil</td>
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<td>Singapore</td>
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<td>Sweden</td>
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<tr>
<td>European Union</td>
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<tr>
<td>Agencies from</td>
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<td>Australia</td>
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<td>Scotland</td>
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<td>Sweden</td>
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<tr>
<td>Taiwan</td>
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<td></td>
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<tr>
<td>Patient groups from</td>
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<tr>
<td>Canada</td>
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<td>Denmark</td>
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<td>Greece</td>
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<td>The Netherlands</td>
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<tr>
<td>Spain</td>
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<td></td>
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<tr>
<td>Romania</td>
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</tbody>
</table>

**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.
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- 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?

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regulatory review first, followed by HTA review</td>
<td>57%</td>
</tr>
<tr>
<td>HTA review first, followed by regulatory review</td>
<td>29%</td>
</tr>
<tr>
<td>Regulatory review first, but no HTA review</td>
<td>14%</td>
</tr>
<tr>
<td>Parallel process of regulatory and HTA review</td>
<td>0%</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Awareness</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>29%</td>
</tr>
<tr>
<td>No</td>
<td>57%</td>
</tr>
<tr>
<td>Do not know</td>
<td>14%</td>
</tr>
</tbody>
</table>

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

- **HTA involvement rations/restricts me and my doctor from possible medicines that could be used to treat my disease:** 33%
- **HTA ensures that a medicine in my country provides the best value and equitable access of effective medicines to patients:** 17%
- **Other - HTA, depending on the case can enable or restrict access/equity:** 17%
- **Other - Role of HTA not transparent:** 17%
- **Have no opinion:** 17%

#### 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?

<table>
<thead>
<tr>
<th>Awareness</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>57%</td>
</tr>
<tr>
<td>No</td>
<td>43%</td>
</tr>
</tbody>
</table>

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

- The judiciary system is misused and causes greater inequity across treatment options: 40%
- The legal system is a useful mechanism as it enables patients access to medicines which should be made available and ensures equity of treatments: 20%
- Other - it represents a different channel to be heard if HTA ruling is unfavourable: 20%
- Other - the judiciary is too slow to be used: 20%
**Figure 7: In your jurisdiction, which option most adequately describes the regulatory and reimbursement system?**

- **Regulatory review first, followed by HTA review**: 54%
- **Regulatory review first followed by HTA or parallel with HTA**: 38%
- **Parallel process of regulatory and HTA review**: 8%
- **Regulatory review first, but no HTA review**: 0%
- **HTA review first, followed by regulatory review**: 0%

*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?**

- **No**: 67%
- **Yes**: 33%

*Regulatory agency response n=6*  
*HTA agency response n=7*

**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)**

- **Not available as an option for alternate coverage**: 58%
- **Available but limited use as a coverage option**: 25%
- **Used routinely by patient to access non-covered medicines**: 17%

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

- **Major negative impact**: 20%
- **Minor negative impact**: 40%
- **No impact**: 20%
- **Minor positive impact**: 20%
### 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**

<table>
<thead>
<tr>
<th>Regulatory agency response</th>
<th>HTA agency response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country A</td>
<td></td>
</tr>
<tr>
<td>Country B</td>
<td></td>
</tr>
<tr>
<td>Country C</td>
<td></td>
</tr>
<tr>
<td>Country D</td>
<td></td>
</tr>
</tbody>
</table>

**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**

<table>
<thead>
<tr>
<th>Regulatory agency response</th>
<th>HTA agency response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country A</td>
<td></td>
</tr>
<tr>
<td>Country B</td>
<td></td>
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<tr>
<td>Country C</td>
<td></td>
</tr>
<tr>
<td>Country D</td>
<td></td>
</tr>
</tbody>
</table>

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**

<table>
<thead>
<tr>
<th>Regulatory agency response</th>
<th>HTA agency response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country A</td>
<td></td>
</tr>
<tr>
<td>Country B</td>
<td></td>
</tr>
<tr>
<td>Country C</td>
<td></td>
</tr>
</tbody>
</table>

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)

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parallel process of regulatory and HTA review</td>
<td>46%</td>
</tr>
<tr>
<td>Regulatory review first, followed by HTA review</td>
<td>39%</td>
</tr>
<tr>
<td>Other - an integrated system with different possible sequences</td>
<td>15%</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regulatory review first, followed by HTA review</td>
<td>43%</td>
</tr>
<tr>
<td>Parallel process of regulatory and HTA review</td>
<td>36%</td>
</tr>
<tr>
<td>Other - an integrated system with different possible sequences</td>
<td>14%</td>
</tr>
<tr>
<td>HTA review first, followed by regulatory review</td>
<td>7%</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Driver</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parallel process of regulatory and HTA review/Other - an integrated system with different possible sequences</td>
<td>• Push for increased collaboration, particularly at EU level&lt;br&gt;• Increased convergence/alignment for data generation and discussion pre- and post-licensing&lt;br&gt;• Need for better resource utilisation and sustainable health care system to allow equal and affordable access to cost-effective medicines&lt;br&gt;• 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</td>
</tr>
<tr>
<td>Regulatory review first, followed by HTA review</td>
<td>• No change – status quo will prevail&lt;br&gt;• Insufficient time as structural changes take many years&lt;br&gt;• HTA scope includes review of other data (real-world clinical/cost effectiveness) compared with regulator&lt;br&gt;• Some change compared with current mode due to:&lt;br&gt;  o Political pressure that will force HTA bodies to collaborate with each other and with regulators compared to today&lt;br&gt;  o Shortening of the time lag between market approval compared with current situation by “moving” the conduct of HTA earlier</td>
</tr>
</tbody>
</table>

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)

- Regulatory approval should always be first in my country so that a medicine can be available irrespective of whether or not it is reimbursed by a national system (40%)
- There should only be one agency that evaluates both regulatory and HTA and one decision on whether medicines should be available in our country (20%)
- Other - Regulatory approval is too liberal for national (public) reimbursement (20%)
- Other - The HTA assessment should have a real role, should be really taken into account by the decision makers of the reimbursement – especially for life-saving new drugs (20%)
- Only medicines deemed a value to the healthcare system following an HTA appraisal should go through regulatory approval (0%)
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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