Improving synergy between HTA bodies and regulatory agencies

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Is the silo-based model for medicine evaluation broken?

- Between March 2000 and March 2018, just 56% of drugs approved by EMA were recommended by NICE for reimbursement\(^1\)
- <50% of new cancer medications assessed during 2013-2017 across 20 countries, received positive reimbursement recommendations\(^2\)


Study objective

To provide insights into opportunities and outcomes of synergy initiatives between HTA and regulatory agencies
Methods

- **Systematic review**
  - *Medline, EMBASE, and the International Pharmaceutical Abstracts database were searched until 21 October 2019*
  - *We also searched for grey literature (working papers, commissioned reports, policy documents) via google scholar and several national and multinational institutional websites*

- **Cross-sectional survey**
  - *Online-based from January to April 2020*
  - *HTA bodies and regulatory agencies in Europe only*
  - *The same set of questions seeking insight into HTA-regulatory interactions*
  - *Six (6) key questions*
    - ✓ *Formal link of collaborating?*
    - ✓ *Types and examples of collaboration*
    - ✓ *Key outcomes and challenges*
Results

Total search hits (n=30,110)

Duplicates removed (n=4355)

Records after Duplicates removed (n=25755)

Removed after title and abstract screening (n=25651)

Full text articles screened (n=104)

Excluded after full-text review (n=88)

Identified via reference (n=6)

Articles included (n=22)

Key resources identified from grey literature (n=38)

Key resources included (n=60)
Results

Survey

• The online survey received responses from 22 HTA bodies (21 countries) and 6 regulatory agencies (5 countries)

• Response rates were 18% (6/34) and 61% (22/36) for regulatory agencies and HTA bodies, respectively.

• Of the regulatory agencies, one was from Western Europe, two from Northern Europe, two from Central and Eastern Europe, and a representative from the EMA.

• Among the HTA bodies, nine were from Western Europe, seven from Central and Eastern Europe, four from Northern Europe, and two from Southern Europe
# Understanding HTA-regulatory focus

<table>
<thead>
<tr>
<th>Regulatory approval</th>
<th>HTA assessment (to inform reimbursement decisions)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Legal mandate</strong></td>
<td>Usually defined within national public health legislation</td>
</tr>
<tr>
<td></td>
<td>HTA may be undertaken by a group within and accountable to a payer</td>
</tr>
<tr>
<td><strong>Primary role</strong></td>
<td>Provide market authorization within the mandated jurisdiction based on an assessment of safety, quality, efficacy, and risk–benefit profile</td>
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<tr>
<td></td>
<td>Support for clinical and coverage decisions based on assessment of relative effectiveness, costs and, in some, system affordability, value for money, and values within the system</td>
</tr>
<tr>
<td><strong>Decision</strong></td>
<td>Evaluates whether the clinical benefits for patients outweigh the risks? Should this technology be available?</td>
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<tr>
<td></td>
<td>Assess whether the product offers useful, appropriate (and affordable) benefits for all or a select subgroup of patients compared to what is most commonly used in the disease area?</td>
</tr>
<tr>
<td><strong>Assessment focus</strong></td>
<td>Efficacy, safety, quality (e.g., GMP)</td>
</tr>
<tr>
<td></td>
<td>Effectiveness, safety, quality of life, economics, budgetary impact, social, ethical, legal, organizational</td>
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</tbody>
</table>
| **Strength of Evidence** | Pre-launch: Efficacy and safety from RCTs (usually placebo-controlled)  
Post-launch: Relative efficacy or effectiveness may be considered when reviewing product’s ongoing risk– benefit profile |
|                     | Pragmatic RCT*, observational studies, decision-analytic techniques (modelling) |

## Characteristics of studies they prioritize

<table>
<thead>
<tr>
<th>Validity</th>
<th>Internal validity</th>
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<tbody>
<tr>
<td>Comparator</td>
<td>Placebo</td>
</tr>
<tr>
<td>Endpoints</td>
<td>Laboratory findings and surrogate endpoints</td>
</tr>
<tr>
<td>Time horizon</td>
<td>Trial duration</td>
</tr>
<tr>
<td></td>
<td>Lifetime or at minimum the time needed to capture all risks and benefits of therapy</td>
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</tbody>
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*Pre-launch: Efficacy and safety from RCTs (usually placebo-controlled)  
Post-launch: Relative efficacy or effectiveness may be considered when reviewing product’s ongoing risk– benefit profile  
Pragmatic RCT*, observational studies, decision-analytic techniques (modelling)
What is harmonization?

- Harmonization is broadly considered to encompass the streamlining of regulatory and reimbursement processes

- It is also deemed process-oriented and centered on reducing the time between regulatory and reimbursement decisions, and minimizing duplication of work

- From the survey, most regulatory agencies (4/6; 67%) and half (11/22, 50%) of the HTA bodies reported having a formal link for ‘collaborating’ with the other
Key avenues for HTA-regulatory collaboration

- Early tripartite dialogues
- Alignment of evidentiary requirements
- Post-authorization data generation
- Adaptive licensing pathways
- Parallel reviews
Alignment of evidentiary needs

• Commonality of safety and efficacy assessment
• Increasing interest in relative efficacy and comparative effectiveness research (CER)
• Contextual issues
  ❖ Study design
  ❖ Endpoint
  ❖ Comparator

• Perhaps differences are exaggerated??

There was a large overlap in inclusion of trials in regulatory and HTA assessments, although the focus on specific outcomes slightly differed.
Alignment of evidentiary needs

A = Acceptable primary end point; B = Inclusion of active comparator arm in the trial; C = Use of patient reported outcomes; D = use of health-related quality of life measures; E = Choice and use of surrogate measures; F = Criteria considered in choice of comparator: therapeutic; G = Use of subgroup analyses; H = Inclusion and choice of secondary efficacy parameters; I = Definition of unmet medical need; J = Use of biomarkers to monitor patient outcomes; sourced from Wang et al. 2018
Promoting early tripartite dialogues

• Regulatory early dialogue has been in place for many years

• During 2008 -2012, 85% of applications that received and followed early EMA scientific advice were ultimately granted marketing authorization compared to only 41% that did not

• Early dialogue with HTA relatively new

• Tripartite dialogues offer opportunity to define divergent data needs and align evidentiary requirements for developers

• Several tripartite dialogues exist both at national (UK, Sweden, Australia) or multi-country levels (EMA, Tapestry network, green park collaboration)
Promoting early tripartite dialogues

• EMA-HTA parallel scientific advice, 2010
• 63 PSAs completed by 2015

Note: based on first 11 procedures
Promoting early tripartite dialogues

• 518 answers provided by regulators and HTA assessors in 31 PSAs revealed that full agreements, partial agreements, disagreements were reached in 61%, 23% and 16% of responses

• Several compromises in product development have been noted

• Tafuri and colleagues found that developers implemented comparators to address needs of HTA and regulators in 60% (12/21) studies

• Developers more inclined to satisfy regulatory advice

• No mechanism for addressing divergence
Parallel submission

<table>
<thead>
<tr>
<th>Region/country</th>
<th>Stakeholders</th>
<th>Name of program</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>TGA (Regulator) PBAC (HTA/payer)</td>
<td>Parallel submission/review</td>
</tr>
<tr>
<td>Canada</td>
<td>Health Canada (Regulator) CADTH (HTA/payer)</td>
<td>Parallel submission/review</td>
</tr>
<tr>
<td>Netherlands</td>
<td>MEB (regulator) ZIN (HTA/payer)</td>
<td>Parallel submission/review (Pilot)</td>
</tr>
<tr>
<td>US</td>
<td>FDA (regulator) CMS (HTA/payer)</td>
<td>Parallel submission/review</td>
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Could parallel submission explain the shorter time between regulatory approval to HTA decision in certain countries?
• Australia (n=46; median=44 days) compared to Canada (n=38; median=269 days), France  (n=57; median=230 days), England (n=27; median=314 days), Germany (n=51; median=139 days), Poland (n=32; median=444 days), Scotland (n=47; median=260 days), and Sweden (n=48; median=184 days)

Adaptive licensing pathways

A

Widening of the indication Scenario
(Final target indication in blue and red)

1st approval in subpopulation → 2nd approval

Adaptive Approach

1st approval

Traditional Route

Time

B

Prospectively planned Reduction of uncertainty Scenario

Knowledge required for full approval

The sponsor could follow one of two strategies

1st approval → 2nd approval

Adaptive Approach

1st approval

Traditional Route

Time

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Post-authorisation data generation

• Post-authorisation efficacy studies
• Post-authorisation safety studies
• Development of methodological guidance
• Use of real-world data
  ✓ Establishment of patient registries
Barriers and challenges

Structural

Humanistic

Resources
Key limitations

• Survey experience limited to Europe

• Most PSA dialogues are confidential, so document review may not fully capture processes

• Further dialogue planned for October 2020
Conclusions

• Overall, we found that while there are areas of divergence, there has been progress over time in narrowing the gap in evidentiary requirements for HTA and regulatory agencies

• Several mechanisms such as early tripartite dialogues, parallel submissions (reviews), adaptive licensing pathways, and post-authorisation data generation have been explored as avenues for improving collaboration.

• Several pilot initiatives have shown positive effects of these models to reduce the time between regulatory and HTA decisions

• Data on long-term impacts are limited.

• Several barriers including legal, organizational, and resource-related factors were also evident
Thank you!