Bridging the gap: Regulatory and HTA

Facing the Challenges: Equity, Sustainability and Access
30 November 2018

Presented by Michael Berntgen
Head of Product Development Scientific Support Department
Facing the challenge: from EU regulatory approval to national HTA/P&R decisions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>EU MA Approval</th>
<th>Time for HTA/P&amp;R after MA (month)</th>
</tr>
</thead>
<tbody>
<tr>
<td>bosutinib (Bosulif)</td>
<td>chronic myeloid leukaemia</td>
<td>03/2013</td>
<td>7  7  11  18</td>
</tr>
<tr>
<td>vismodegib (Erivedge)*</td>
<td>basal cell carcinoma</td>
<td>07/2013</td>
<td>n/a  7  5  20</td>
</tr>
<tr>
<td>cabozantinib (Cometriq)*</td>
<td>medullary thyroid cancer</td>
<td>03/2014</td>
<td>n/a  10  8  n/a</td>
</tr>
</tbody>
</table>

*first in class; MA = marketing authorisation; P&R = price and reimbursement

Synergy through alignment of evidence generation plans

**Starting point:** Regulators and HTAs
- answer different questions
- have different requirements in terms of evidence

**Aim:** decision makers come together early to discuss
- the planned development including populations / comparators / design of trial / endpoints
- the requirements for post-licensing evidence generation

**Expectation:** Optimised evidence generation plan ➔ Improve access for patients

“Clinical benefit” is universal ➔ once established it can be contextualised
Early engagement on development: why (and how)?

EMA works with HTA bodies since 2010 and with payers since 2017

Parallel Consultation as central platform to discuss evidence generation

- Agree what evidence from clinical trials is needed to meet the needs of both regulators and HTAs
- Help to better understand the applicant’s development plan and the basis for authorisation by CHMP
- Tripartite scientific advice (EMA-HTA-Payers) yet to start

Focus on facilitating the development of innovative medicines that serve patients’ needs and are accessible for patients
The impact of cross-decision maker engagement in evidence generation planning - First analyses

**Topic 1: Level of alignment**

- Level of agreement (position of HTA bodies vs. regulators; review of clinical trial features based on 31 scientific advice procedures):
  - full agreement
  - partial agreement
  - disagreement.

Tafuri et al., British J Clin Pharm, Volume 82, Issue 4, 965-973

**Topic 2: Uptake in development**

Tafuri et al., British J Clin Pharm, doi: 10.1111/bcp.13524
Post-licensing evidence generation (PLEG) – the next domain of collaboration on evidence planning

Qualification of registries for post-licensing data generation:

- European Cystic Fibrosis Society Patient Registry (ECFSPR) ➔ parallel qualification with HTAs
- European Society for Blood & Marrow Transplantation (EBMT) Registry [relevant for CAR-T therapies] ➔ HTAs involved in the supporting workshop

Publicly available outputs!
Guiding evidence generation to establish clinical benefit

- Knowledge
- Information
- Evidence
- Planning
- Implementation
- Decision

Guidelines on development
New endpoints for drug development
Learnings from decision making
Guidelines make learnings and knowledge available

The revision of the Multiple Sclerosis guideline in 2015 considered

• Numerous product-specific scientific advices
• Two methodological advices
• Learnings from the review of several marketing authorisation applications
• Outcome of a public workshop in 2013
• Published position on regulatory and scientific challenges *

* Balabanov et al., MS Journal (20), 128201287 (2014)
The challenge in practice: Recent experience with ocrelizumab

Regulatory approval for treatment of adult patients with

- relapsing forms of multiple sclerosis (RMS) with active disease
- early primary progressive multiple sclerosis (PPMS) in terms of disease duration and level of disability

### G-BA (DE)
- Active RMS → minor added benefit compared to Interferon beta-1a/b or glatiramat
- Highly active RMS → added benefit not proven compared to alemtuzumab, fingolimod, natalizumab or baseline therapy
- PPMS → indication of minor added benefit compared to SoC

### NICE (UK)
- RMS → slows disease progression compared with some treatments but not others; uncertainty of slowing disease progression in highly active and rapidly evolving severe disease; recommended only after alemtuzumab (due to costs)
- PPMS → in progress (current position [Sep 18]: not cost-effective)

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1 G-BA decision of 2 August 2018 (AM-RL-XII_Ocrelizumab)
2 NICE guidance TA533 (RMS) and ongoing NICE appraisal ID938 (PPMS)
Establishment of new endpoints for drug development

Qualification of Stride Velocity 95th Centile measured by a wearable device as outcome measurement in Duchenne muscular dystrophy (DMD) ➔ acceptability as secondary endpoint for regulatory decision making

- Patient-relevant ✓
- Use of digital data ✓

Draft guidance for public consultation (closed on 30 November 2018) ➔ input from all stakeholders incl. HTA/payers invited

Other examples: PUCA index; Dopamine transporter imaging to identify early PD patients
Learnings from sequential decision making

For Relative Effectiveness Assessment by EUnetHTA, EMA and EUnetHTA established a framework to share information (final regulatory output) and facilitate mutual understanding:

- 3 products completed so far (4th in preparation)
- Learnings for optimising regulatory output to increase understanding of B/R assessment for use by HTAs

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### Regorafenib for hepatocellular carcinoma

<table>
<thead>
<tr>
<th>EMA/CHMP EPAR¹</th>
<th>EUnetHTA REA²</th>
</tr>
</thead>
<tbody>
<tr>
<td>- RESORCE trail, OS gain (2.8 months) considered of clinical benefit</td>
<td>- RESORCE trail, OS gain (2.8 months) considered a modest gain</td>
</tr>
<tr>
<td>- Uncertainties: sorafenib intolerant patients; patients with ECOG PS&gt;1 and/or Child Pugh B addressed through SmPC changes</td>
<td>- Insufficient evidence on impact on HRQoL (&quot;regrettable&quot; for end-stage patients)</td>
</tr>
<tr>
<td></td>
<td>- Evidence gaps: sorafenib intolerant patients and patients with ECOG PS&gt;1 and/or Child Pugh B further research data collection necessary</td>
</tr>
</tbody>
</table>

¹ EMA/CHMP EPAR EMEA/H/C/002573/11/0020
² EUnetHTA REA Project ID: PTJA02

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Priority areas of the EMA/EUnetHTA work plan 2017-2020

• Early dialogue / scientific advice
• “Late dialogues” / peri-licensing advice
• Methodological approaches for study designs
• Unmet medical need and therapeutic innovation
• Significant benefit vs. added therapeutic value
• Identification of the treatment eligible population
• Information exchange regulators ↔ HTA bodies
• Patient and clinician engagement
• Population or intervention-specific areas
How can players along the technology lifecycle work together to support the introduction of innovative health technologies

- Collaboration on topic identification and prioritisation by various players
- Early flag of innovation that would benefit from closer engagement across decision makers

E.g. readiness for subsequent decision making in a timely manner, respecting different remits

E.g. parallel consultation (scientific advice) involving various decision-makers to ensure evidence generation meets different needs

E.g. preparedness of patient registries to collect relevant information in a robust manner

**Collaboration between decision makers can enable better preparedness of the healthcare systems for development and introduction of innovation with true clinical benefit.**
Thank you for your attention

Further information

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