Regulatory Science Workforce Needs to Maintain a Robust Global Therapeutics Pipeline

Xavier Luria, M.D.
Head of Safety and Efficacy of Medicines
European Medicines Agency (EMA)

Strengthening a Workforce for Innovative Regulatory Science in Therapeutics Development: An Institute of Medicine Workshop, National Academy of Sciences, Washington, September 2011

The views presented here are personal, not those of the EMA
Therapeutic Pipeline

World Preview 2016 (from Evaluate Pharma: Beyond the Patent Cliff, 2011)
Agenda

- Classical regulatory approach
  vs what?
  Beyond approval?
- Efficacy vs. effectiveness
- Regulators vs Payers/HTA
- End-points
- Conclusions
Agenda

• Classical regulatory approach
  vs what?
  Beyond approval?

• Efficacy vs. effectiveness
• Regulators vs Payers/HTA
• End-points
• Conclusions
EU Harmonisation: Impacting over time

Initiative → Agreement to go ahead → Done → Impacting → When do you see the consequences?

Time
What are the requirements to put a drug on the market?

EU pharmaceutical law

- The balance of benefits and risks should be positive for any marketing authorisation
  - No notion of “effectiveness”, “relative effectiveness”, “cost-effectiveness” in EU legislation

- Refusal of a marketing authorisation if quality, safety or efficacy not sufficiently demonstrated based on objective criteria
What makes a good regulatory decision?

- Take the “right” decision - and do it in a rational, predictable way (avoid Type I and Type II errors)
- Justify/explain the decision
- Communicate the decision (+justification + explanation) to external stakeholders
- Provide more detail than just “yes/no” (qualitative ➔ quantitative)
The regulators’ dilemma

“C’mon, c’mon — it’s either one or the other.”
Types of Approval

- Adequate Data
- Exceptional Circumstances
- Normal Circumstances
- Follow Up Measures

Time to Approval

100%
Road map to 2015

The European Medicines Agency’s contribution to science, medicines and health
EMA Road map to 2015

[...] a key issue for regulators will be whether a more 'staggered' approval (or progressive licensing) concept should be envisaged for situations not covered by conditional marketing authorisations [..., e.g.], characterised by a better-defined or more restricted population of good responders, followed by a broadening of the population post-authorisation when more 'real-life' data are available.

The Agency would like to launch a debate with all stakeholders on the appropriateness of introducing such a concept, including a consideration of appropriate incentives to support new medicines development.

[...] progressive licensing should not lead to a reduced level of evidence for first-time marketing authorisation.
Different names, same ideas

- EMA: staggered approval
- FDA: progressive reduction of uncertainty
- Health Canada: progressive authorization
- HSA Singapore: test bed for adaptive regulation
- Payers (HTAi): managed entry
- MIT/NEWDIGS: progressive licensing project
Evolution of drug regulation

Knowledge, investment

Time

1980’s

2010’s

2020’s?

licensing
A better model for evolution?

- Current model of licensing
- Progressive Authorization

[Graph showing the relationship between time and knowledge investment]
Progressive Authorisation scenarios – “design factors”

- Broaden Treatment-eligible population
- Reduce Uncertainty around endpoint
- Enable new-new combo development
- Ensure effectiveness
- Address rare AEs
Progressive Authorisation (PA), next step in drug licensing?

PA is a prospectively planned, adaptive approach to regulation of drugs. Through iterative phases of information gathering followed by regulatory evaluation and action, PA seeks to align regulatory market access of a new drug with emerging information on benefits and risks.

PA seeks to maximize the positive impact of new drugs on public health by balancing timely access for patients with the need to provide appropriate information on benefits and risks.
Obstacles to Progressive Authorisation

- Concerns over lowered standards
- Doable under current statute?
- Getting commitment to conduct "stage n+1 studies"?
- Are follow-on studies doable after "loss of equipoise"?
- Alignment between regulators – payers – prescribers?
- Different reward structure required to incentivise drug development enterprise?

Is there an alternative to considering broad application of more adaptive ways of drug licensing?
Agenda

• Classical regulatory approach vs what? Beyond approval?

• Efficacy vs. effectiveness

• Regulators vs Payers/HTA

• End-points

• Conclusions
It is increasingly difficult to bring new drugs to market...

... but it will be even harder to keep them on the market

Drugs (and regulators) become victims of the Efficacy-Effectiveness gap
Positive Benefit/Risk

Negative

Clinical Trial Scenario

Authorised Label Scenario

Outside-label Scenario

Efficacy-Effectiveness Gap

Cumulative % of treated patients experiencing benefits and risks

100%

0%

Benefits

Risks

High Variability

Low

Regulatory Science, EMA (XLO9/11)
Agenda

- Classical regulatory approach vs what?
  Beyond approval?
- Efficacy vs. effectiveness
- **Regulators vs Payers/HTA**
- End-points
- Conclusions
The EU dilemma
The regional divide

Regulators
- **1** standard for drug approval
- **1** application, **1** assessment
- **1** decision valid in 27 EU + 3 EFTA countries

HTA/payers
- **30+** different HTA methodologies and interpretations
- **30+** independent decisions about whether the medicine should be paid for
What distinguishes regulators from HTA/payers?

<table>
<thead>
<tr>
<th>Regulators</th>
<th>HTA/payers</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Evaluate each drug on its own merit (benefit-risk)</td>
<td>• Maximise health with a finite budget ➔ allocation decision</td>
</tr>
<tr>
<td>Drug A Yes or No?</td>
<td>Drug A or Drug B?</td>
</tr>
<tr>
<td>Health Technologies</td>
<td>• Drugs <em>(therapeutic, preventive)</em></td>
</tr>
<tr>
<td>---------------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>• Benefit Risk</td>
<td></td>
</tr>
<tr>
<td><em>(Marketing Authorisation)</em></td>
<td></td>
</tr>
<tr>
<td>• Relative Efficacy Assessment <em>(CAV)</em></td>
<td></td>
</tr>
<tr>
<td>• Rel. Effectiveness</td>
<td></td>
</tr>
<tr>
<td>• Health Technology Assessment <em>(incl. cost consequences)</em></td>
<td></td>
</tr>
<tr>
<td>• Coverage decision <em>(incl. appraisal, soc. preferences)</em></td>
<td></td>
</tr>
<tr>
<td>• Utilisation <em>(on-/off-label, med. errors)</em></td>
<td></td>
</tr>
</tbody>
</table>

Horizontal and vertical inconsistencies among Member States
<table>
<thead>
<tr>
<th>Health Technologies</th>
<th>FDA</th>
<th>PCORI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Benefit Risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Marketing Authorisation)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Relative Efficacy Assessment (CAV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Rel. Effectiveness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Health Technology Assessment (incl. cost consequences)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Coverage decision (incl. appraisal, soc. preferences)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Utilisation (on-/off-label, med. errors)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Horizontal and vertical inconsistency between private and public sector, different states

*: Patient-Centered Outcomes Research Institute
Areas of possible interaction between regulators and HTA

**Ongoing**

- Help relative effectiveness assessment (EPAR)
- Pilot on parallel scientific advice

**Opportunities**

- Joint scientific advice
- Alignment on post-marketing research activities
- Scientific guidelines
  - Relative efficacy/effectiveness methods
- Early access, conditional access
Press Release 16 February 2010

European Medicines Agency and EUnetHTA Joint Action start collaboration on European Public Assessment Report (EPAR) contribution to relative effectiveness assessments
Road map to 2015

The European Medicines Agency’s contribution to science, medicines and health
The Agency will engage with HTA bodies ... to avoid as far as possible the appearance of two different medicine-development programmes... in terms of alignment of regulators' and HTA bodies' evidence requirements, through joint approaches to scientific advice, mutual input on clinical guidelines...
Regulators versus payers (II)

A number of differences have been pointed out when comparing the licensing process with relative-effectiveness and cost/benefit assessment processes, in terms of the choice of clinical endpoints, efficacy versus effectiveness, and relative efficacy versus placebo-controlled studies.
Agenda

- Classical regulatory approach
  vs what?
  Beyond approval?
- Efficacy vs. effectiveness
- Regulators vs Payers/HTA
- **End-points**
- Conclusions
EMA Road map to 2015

strategic goals with an impact on “endpoints”:

- Engage in dialogue with payers/HTAs
- Take on board the patients’ voice
- Improve benefit-risk methodology
Patients’ utilities, a new type of “endpoint”? 

- Reinforce the benefit/risk-balance assessment model. ... increasing clarity and transparency and inclusion of quantitative elements (?) 

- Patient empowerment and patients' participation in healthcare decisions.... this should lead to patients’ utilities being taken into account in a more systematic way for the benefit/ risk assessment.
Benefit-Risk Methodologies EMA Project (>2007)

Work Packages:

1: Describe current practice of B-R assessment ✅

2: Assess applicability of current tools for regulatory B-R assessment ✅

3: Develop and field test tools and processes to demonstrate their usefulness ✅

4: Synthesize information from the field test and develop a B-R tool box for everyday use.

5: Develop a training package for regulatory assessors
IMI is an ambitious public-private partnership

2 Billion EURO

1 Billion Euro
Public Partnership

1 Billion Euro
Private Partnership
European Network of Centres of Pharmacoepidemiology and Pharmacovigilance

Focus on: building infrastructure, developing rules of engagement
Agenda

• Classical regulatory approach vs what?
  Beyond approval?
• Efficacy vs. effectiveness
• Regulators vs Payers/HTA
• End-points

• Conclusions
Conclusions

Easier to predict what will likely NOT happen

- Euro-NICE
- EMA (CHMP) to do RE-assessment
- Go fast to a new scenario where the efficacy/effectiveness gap is filled

Easier to identify (some) new crucial elements

- Patients involvement
- Benefit Risk assessment Evolution (likely no REvolution) ...
Conclusions

... 

- Progressive Authorisation
- End-points evolution
- Guidelines redefined
- Increasing role of academia in the regulators and industry dialogues (...at the end of the day, we mostly talk about products!)

*Those who have knowledge don't predict. Those who predict don't have knowledge.*

Lao Tse, 6th century B.C.