Regulatory agencies: not only gatekeepers, but also enablers of innovation?

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Traffic regulation: informed by evolving technology (?)
Pharmaceutical Regulation

EMAs mission:

The mission of the European Medicines Agency (EMA) is to foster scientific excellence in the evaluation and supervision of medicines, for the benefit of public and animal health in the European Union (EU).
Pharmaceutical Regulation

Gatekeeper & Enabler

Public/published opinion?

Excessive conservatism

Excessive optimism

**Product-level**: product-specific decisions

**Meta-level**: openness to evolutions of science, standards, and society
In this talk...

• Balancing benefits and potential harms
• Balancing (un)certainty and time of access
• Enabling the evolution of...
  • ... the concept of “drug”
  • ... evidence / clinical study designs
  • ... information needs
• Conclusions
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Beneficence

Benefit to public health

Non-malefence

Avoidance of drug-related harm

Max. Risk Tolerance (high likelihood of type I errors)

Max. Risk Aversion (high likelihood of type II error)
Examples

**Tolcapone**: marketing authorisation (MA) in EU for Parkinson’s disease 1997; fatal hepatotoxicity cases → MA suspended 1998; patients pleaded for right to gain access and accept responsibility; MA suspension lifted in 2004

**Natalizumab**: MA in US for multiple sclerosis 2004; case reports of progr. multifocal leucoencephalopathy → voluntarily withdrawn from market; reintroduced in 2006 at request of patients

**Alosetron**: MA in US for irritable bowel disease 2000; cases of (fatal) ischemic colitis → voluntarily withdrawn from market; reintroduced (with restrictions) in 2002 at request of patients
Lessons learned:

• Emphasise benefit-risk, not risk (and steer clear of “first do no harm”)

• Bring the patients’ voice on board (and mind the gap between patients and consumer advocates)

• Open the black box (full transparency: clinical trial data, decision making process, CoI, ...)

• Explain the trade-offs and rationale of decisions
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Types of uncertainties

<table>
<thead>
<tr>
<th>Known unknowns</th>
<th>vs</th>
<th>Unknown unknowns</th>
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<tbody>
<tr>
<td>(Teratogenicity post-Thalidomide)</td>
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<td>(Teratogenicity pre-Thalidomide)</td>
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<table>
<thead>
<tr>
<th>Scientific</th>
<th>vs</th>
<th>Behavioural</th>
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<tr>
<td>(No long-term data)</td>
<td></td>
<td>(How will the product be used on-market?)</td>
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Benefit to public health

Avoidance of uncertainty

Time; accumulation of knowledge
Uncertainty in regulatory decisions (1/2)

Lessons learned

- **All** regulatory decisions are taken under conditions of unavoidable uncertainty

- Regulators need to:
  - Ask “How much uncertainty is acceptable” (at time of approval)
  - Proactively communicate uncertainty
  - Ensure fast reduction of uncertainties → **life span approach to knowledge generation**
Uncertainty in regulatory decisions (2/2)
Lessons learned

• All stakeholders need to accept:
  • Majority of research questions can never be answered at time of marketing authorisation → need for life span approach to knowledge generation
  • Majority of research questions can never be answered by way of randomised controlled trial (remember statins: “we have >130,000 patients randomised in outcome trials“!) → need for additional data sources and analytic methodologies
Early vs. routine approval

Conditional marketing authorisation (CMA): “.. may be granted ... where the benefit of immediate availability outweighs the risk of less comprehensive data than normally required, ..”

→ implies acceptance of more uncertainty

Does “ acceptance of higher uncertainty” with CMA translate into poorer outcomes?

Judging by results...
Conditional marketing authorisation; outcomes

38 CMAs granted in EU (since 2006):
18/38 still in “conditional” state
19/38 converted to full MA (after a mean of ~4 years)
1/38 withdrawn from market

Possible Interpretation?

• Chance finding, next cohort may not look so good?
• “Regulators are reluctant to change their own assessments”?
• “European regulators are too risk averse, threshold for accepting higher uncertainty is too high”?
• “Regulators are really good at picking the winners”?
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Evolution of the concept of “drug”

Reproducibility of product $\rightarrow$ predictability of action
Product quality – Evidentiary standards (CMC, GLP, GMP**, ...)
### Cell/Gene therapies – “product personalisation”

<table>
<thead>
<tr>
<th>Development &amp; production level</th>
<th>Evidentiary standards &amp; Quality Assurance</th>
</tr>
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<tbody>
<tr>
<td>1. Common starting platforms (e.g. AAV* vector): pre-competitive development, standardised production</td>
<td>Enable pre-competitive development</td>
</tr>
<tr>
<td>2. Gene-cassette (e.g. for pancreatic cancer): developed &amp; manufactured by individual company</td>
<td>Develop practices for rapid regulatory assessment</td>
</tr>
<tr>
<td>3. Final product (patient-specific composition of genes): “assembled” in real time, at hospital site</td>
<td>Ensure GMP/GLP capability at hospital level</td>
</tr>
</tbody>
</table>

*AAV = Adeno-associated virus
Evolution of evidence / clinical study designs

The randomised controlled trial (RCT):

• The quintessential evidentiary standard ("gold standard") of clinical evidence generation
• Born in 1948 (streptomycin for tuberculosis)
• Matured in the statin-era

Need to enlarge the toolbox of clinical evidence generation
Do we need new data sources and analytic methodologies?

“If we insist on evidence from randomised trials, we will rarely have it, and to the extent we have it, we will have it only for groups of patients who are somewhat similar. ...”

Evolution of evidence / clinical study designs

Drivers of change:

- Ethical concerns
- One-time interventions with long-term outcomes
- Smaller treatment-eligible populations
- Personalised treatment combinations ("combinatorial complexity")

Enablers of change

- Availability of patient-level RCT data
- Availability of real world data (RWD)
What we need is a **learning healthcare system**

... a system in which “science, informatics, incentives, and culture are aligned for continuous improvement and innovation, with best practices seamlessly embedded in the delivery process and **new knowledge captured as an integral by-product of the delivery experience**.

[... Such systems ...] explicitly use technical and social approaches to **learn and improve with every patient who is treated.**”

Source: IoM 2015; http://www.learninghealthcareproject.org/section/background/learning-healthcare-system
New analytic methodologies

A range of (relatively) novel methodologies, analysing RCT and/or RWD have been proposed or refined; examples:

- borrowing of external control group data;
- construction of external control group;
- indirect comparisons for relative efficacy or safety;
- reweighting of RCT results to reflect real life;
- predictive approaches to heterogeneous treatment effects;
- extrapolation of knowledge to an unstudied population;
- replacing RCTs by RWD analysis
- ...
New methodologies: promising but ...

- ... will likely not deliver robust results in all scenarios; not fully validated and accepted
- New data sources without new **accepted** analysis methods (statistical, epidemiological) will not move the needle
- To overcome “methodology aversion”, need to evaluate a new methodology like new drug: **prospectively**, well controlled and according to pre-agreed plan
- Call for action: make use of ‘methodology qualification procedure’ to support acceptance by regulators and other decision-makers
Evolution of information needs

**Regulator’s question:** “do the benefits of this treatment outweigh the risks in a defined population?”

**Downstream decision-maker’s questions?**

<table>
<thead>
<tr>
<th>Industry</th>
<th>Regulators</th>
<th>HTAs</th>
<th>Payers</th>
<th>Clinicians</th>
<th>Patients</th>
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</thead>
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Innovation moves from left to right but

Evidence planning must move from right to left
# Downstream decision-maker’s questions (1/2)

<table>
<thead>
<tr>
<th>Questions or issues</th>
<th>Adaptations by regulators</th>
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<tbody>
<tr>
<td>• Patient relevant endpoints</td>
<td>• Validate/accept patient reported outcomes, data from mobiles, apps...</td>
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<tr>
<td>• Added therapeutic benefit</td>
<td>• Enable indirect comparisons, contextualise benefits/risks</td>
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<tr>
<td>• Appropriate patient (sub-) population(s)</td>
<td>• Describe/quantify benefit in relevant subgroups</td>
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## Downstream decision-maker’s questions (2/2)

<table>
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<th>Questions or issues</th>
<th>Adaptations by regulators</th>
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<tbody>
<tr>
<td>• Affordability</td>
<td>• Increase clarity of label population</td>
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<tr>
<td>• On-market utilisation</td>
<td>• Embrace effectiveness (≠efficacy) assessment</td>
</tr>
<tr>
<td>• Acceptability of uncertainty</td>
<td>• Explicit description of uncertainties (”known unknowns”)</td>
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<tr>
<td>(&quot;balance of probabilities&quot; or</td>
<td></td>
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<tr>
<td>&quot;beyond reasonable doubt&quot;)</td>
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Conclusions

• Regulation is based on policies → are comprised of evidentiary standards → are informed by science

• Regulation (and “the system”) needs to catch up with the fast pace of science

• Good regulatory science is the guarantor of the right balance between gatekeeper and enabler – the voice of reason
Let’s get there safe and fast
Let’s get there safe and fast...

Patients are waiting