Regulators, Payers and Industry Convergence or Divergence?

Emeritus Professor Lloyd Sansom AO
University of South Australia
And
Department of Health, Australia
Conflicts in context of presentation

- Advisor to Pharmaceutical Benefits Division, Department of Health
- Member, Therapeutic Goods Administration Advisory Board
- Chair, SA Medication Advisory Committee
- Chair, Medication Reference Group, Safety and Quality Commission
- Member, HTAi Policy Forum
Regulators and Payers

- The major aim of assessment for registration is to provide consumers with safe and effective drugs.
- The major aim of health technology assessment for subsidy is to promote equity of access and to ensure that the cost effectiveness of a drug represents “value for money” taking into account opportunity costs.
What is Health Technology Assessment?

“HTA involves the medical, social, ethical and economic implications of the development, diffusion and use of a health technology. HTA has been positioned as a ‘bridge between scientific evidence and the needs of policymakers”
The interaction for decision makers

- Health Benefits to patients
- Non health benefits to patients
- Benefits to carers and family
- Benefits to society/health/social care system
Changes with Time

- 1990s: The focus was on registration (predominately by FDA) and was generally the only barrier to establishing a market. Access generally followed registration either paid for by individuals or third party payers.
- The clinical development program was directed by the requirements for registration.
- Some countries were introducing cost effectiveness requirements.
Changes with time

- 2000-2010. The escalating costs of health care, including pharmaceuticals saw many more countries introducing cost effectiveness requirements. This approach required comparative efficacy and cost data and the consideration of “value”. Managing uncertainty in the context of a value became a necessity for payers, particularly with the increasing price of pharmaceuticals.

- However the clinical development programs continued to be focused on registration and payers were left with dealing with inadequate data for their purpose.
Changes with time-present

- The cost of pharmaceuticals has risen to an extent that without subsidy new agents generally will not have a market.
- The demand from consumer for earlier access has increased particularly for those diseases with high unmet clinical need (not defined?).
- Many companies still are structured on a “registration first focus” and are not thinking about requirements of payers as part of their development programs.
The Development Pathway

Target:
- Target discovery and validation

PoC:
- PoC clinical trials

Approval:
- Clinical development

Exploratory phase:
- Apply biomarkers, modelling and simulation, and advanced statistical methodology
- Demonstrate PoC and establish dose selection

Confirmatory phase:
- Apply innovative tools and clinical trial designs such as adaptive or seamless studies
- Identify target patient population, confirm optimal dose and dosing regimen and establish the benefit/risk ratio

Nature Reviews | Drug Discovery
“Pharmaceutical regulators and healthcare reimbursement authorities operate in different intellectual paradigms and adopt very different decision rules. As a result, drugs that have been licensed are often not available to all patients who could benefit because reimbursement authorities judge that the cost of therapies is greater than the health produced”
“If the FDA has been given the power to make decisions that have such huge ramifications, it must be accountable for the cost-benefit ratio of these decisions. In this case, a study showed there was no survival benefit yet the costs will be billions of dollars per year. Is there any wonder why our health care expenditures are expected to double to over $4 trillion within 10 years”
Registration versus Subsidy

“…so there is an increasing obligation for the developers of new treatments to provide evidence on a broader range of questions and outcomes in addition to the efficacy and safety data required by licensing authorities”

Freemantle et al. Pharmacoeconomics 2005;23(8);747-754
Data requirements

• The data requirements of payers and regulators are often quite different and the industry has been tardy at recognising the specific data needs of payers leaving payers with attempting to make decisions in the absence of adequate data and with high uncertainty.

• Clinical trials designs that address the requirements of the regulators and payers are essential. The Green Park Initiative was an attempt to do this for trials in Alzheimer’s Disease.

• The failure to address this issue in a collaborative manner will lead to greater costs and longer delay to subsidised access by patients.
Clinical Trial Data relevance to Regulators and Payers

• Were quality of life measurements taken during the trial? For some drugs Q of L is the most relevant patient outcome but often no such measurement is made in pivotal clinical trials for registration eg a recent submission for intermittent claudication and 6 minute walk distance measurement without any measure of quality of life. – WHY!!

• Should ethics committees allow such trials without Q of L measurement

• It could have been done in the same trial
2013 survey of biotech companies

- “Despite near-universal recognition of the importance of demonstrating value many biotech companies do not think these trends will appreciably affect their business in the near future”

- “are you entering into negotiations with the data they want—or the data you have?”

- “payers aren’t paying for science –they are paying for value”

Trial versus Clinical Setting

APPLICABILITY

- The participants and circumstances of use in a trial may not be the same as the proposed population for treatment (and might therefore have different expected risk). The results have to be applied to the proposed population and expected risk, e.g., the severity of the disease in the patients in the trial, prior exposure to other therapies, etc.
The length of follow-up of participants in the trial may be less than the expected duration of treatment. Results may need to be extrapolated to the proposed duration of treatment (e.g., 6-week trial of an antidepressant, extrapolation of survival beyond the duration of the trial).
• The outcomes measured in the trial might not be the patient-relevant outcomes of treatment. Results generated in this way need to be **TRANSFORMED** to take account of patient-relevant final outcomes (eg QALY)
Therefore the results of trials need to be applied, extrapolated and transformed (collectively referred to as ‘translated’) into a decision analysis appropriate for the proposed clinical use.

The question remains as to the extent to which the translation is uncertain. It is this uncertainty which drives the utility of post marketing/listing monitoring.
Economic evaluation—how do you determine ‘value-for-money?’

**Cost Minimisation**—used when drugs have the same outcome. Ensure that the new drug is no worse than comparator (ie therapeutic equivalence).

**Cost effectiveness**—clinical advantage measured in natural unit (eg life-years gained or points of BP reduction) ie cost per unit of effect
Economic evaluation

- **Cost utility analysis**: health outcomes rated by preference strength (e.g., healthy years or quality adjusted life years - QALY). Output is cost per unit of preference state.

- **Modelled economic evaluation**: estimation of remote outcomes, final outcome, cost offsets.
Incremental Cost-Effectiveness Plane

- **Intervention:** less effective, more costly
  - Location: Point B

- **Intervention:** more effective, more costly
  - Location: Point A

- **Intervention:** less effective, less costly
  - Location: Point C

- **Intervention:** more effective, less costly
  - Location: Point D
<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (relative to comparator)</th>
<th>Outcome (relative to comparator)</th>
<th>Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (NE quadrant)</td>
<td>Positive</td>
<td>Positive</td>
<td>???</td>
</tr>
<tr>
<td>B (NW quadrant)</td>
<td>Positive</td>
<td>Negative</td>
<td>B is dominated</td>
</tr>
<tr>
<td>C (SW quadrant)</td>
<td>Negative</td>
<td>Negative</td>
<td>???</td>
</tr>
<tr>
<td>D (SE quadrant)</td>
<td>Negative</td>
<td>Positive</td>
<td>Comparator is dominated</td>
</tr>
</tbody>
</table>
In the Australian system there is NO FIXED threshold. The PBAC makes a judgment based on the ICER, the level of uncertainty and other factors.
Relevant factors

**Readily Quantifiable**

- comparative health gain
- affordability
- financial implications for PBS
- financial implications for Govt health budget
- comparative cost effectiveness
Relevant factors

Less Readily Quantifiable

- severity of condition treated
- presence of effective alternatives
- ability to target therapy to those likely to benefit most
- uncertainty
- equity
- Govt health priorities and other relevant factors including social values
What is an acceptable ICER?

- NICE uses a fixed threshold (BP20K/BP50K)
- PBAC does not use a fixed threshold
- An ICER does not represent the value of a life
- A benchmark figure has been suggested to be GDP/capita
- Social values and uncertainty are the major factors in decision making
4 Paradigms

- **Efficacy** - extent of benefit over harm under *ideal* conditions
- **Effectiveness** - extent of benefit over harm under *real world* conditions
- **Comparative Efficacy** - extent of benefit over harm under *ideal* conditions compared to an appropriate comparator
- **Comparative Effectiveness** - extent of benefit over harm under *real world* conditions compared to an appropriate comparator
Efficacy v’s Effectiveness

- At the time of the decision, regulators and payers have been dealing with data which address efficacy and comparative efficacy in an attempt to minimise confounding of real world data.
- Post marketing data has in the past been primarily focused on signals for toxicity rather than evidence of effectiveness or comparative effectiveness.
- To require two clinical development pathways for registration and subsidy is not the answer as this will add costs and delays.
- So how can we be smarter?
Earlier Access

- While the need to minimise the time taken for decisions by regulators and payers has been acknowledged by improving the efficiency of the processes and by the introduction of the availability of managed entry programs and *Coverage with Evidence Development (CED)*, there is little evidence that this has made a significant difference in the timelines.
Earlier Access

- More recent developments by both the FDA (Accelerated approval) and the EMA has introduced the concept of *Registration with Evidence Development* or Adaptive Licensing.
- The critical question is whether the efforts to collect “the evidence” should be a collaboration between payers and regulators and whether the evidence collected will reduce the initial uncertainty.
TEAMWORK?
Adaptive licensing, sometimes called staggered approval or progressive licensing, is a prospectively planned process, starting with the early authorization of a medicine in a restricted patient population, followed by iterative phases of evidence gathering and adaptations of the marketing authorization to expand access to the medicine to broader patient populations.
Adaptive Licensing EMA

“With the adaptive licensing pilot project we intend to explore with real medicines in development a progressive licensing approach that would allow timely access for patients to new medicines that address serious conditions with unmet medical needs,” explains Hans-Georg Eichler, the Agency’s Senior Medical Officer. “The approach seeks to maximize the positive impact of new medicines on public health by balancing timely access for patients with the need to provide adequate evolving information on their benefits and risks.”
Adaptive Licensing  Eichler et al 2012

Diagram a:
- Time (years) on the x-axis
- Number of patients treated on the y-axis
- License
- Patients treated, no active surveillance
- Patients in observational studies, registries, etc.
- Patients in RCTs (or other interventional studies)

Diagram b:
- Time (years) on the x-axis
- Number of patients treated on the y-axis
- Initial license
- "Full" license
Adaptive Licensing

Initial approval: Experimental effect-size and confidence interval inform terms of a prospective registry

Subsequent approval: Provides conditions for "full license"

- Cumulative estimated effect size
- Cumulative confidence interval
- Threshold effect size for continued approval (chosen near limit of lower confidence interval)
- Predicted effectiveness

Experimental | Observational | Licensing
Adaptive Licensing

Registration

Regulator

Payer

Safety  Efficacy  Quality  Cost-effectiveness  Affordability

uncertain but "high" clinical need

Adaptive Licensing

Greater/less uncertainty?
Other issues with CED/Adaptive Licensing

Patient relevant outcomes eg survival may be influenced by the introduction of newer technologies during the adaptive-licensing period. Patients cannot be stopped from switching to alternate therapies, if available. The desired endpoint is therefore contaminated and may not address the issue of uncertain effectiveness.
Other issues with CED/Adaptive Licensing

- The EMA announcement suggests that this adaptive approach can be used to collect data to support applications for broader patient populations. This has a very significant impact on the payer as the cost effectiveness may be different in different populations and will have a significant impact on the risk management by price at the time of entry-this issue needs to be urgently discussed between the stakeholders.
Other issues with CED/Adaptive Licensing

- The starting price must take into account the degree of uncertainty, and formal arrangements which including binding arrangements on the possible disinvestment (and the management of patients who wish to continue the drug) or price movements as result of the data collected must be agreed to all parties a priori.
Data Requirements

- The type of evidence acceptable to payers and regulators has been and continues to be the subject of debate.
- The hierarchy of evidence concept is supported by some and not others.
- Each type of evidence has its limitations and techniques to address these limitations are often available but used haphazardly e.g. propensity scores in the analysis of observational data.
- Regulators, Payers and Industry need to dialogue these issues.
HTA, data and hierarchy of evidence

- ‘If you find that a study was not randomized, we’d suggest that you stop reading it and go on to the next article”

Sacket et al Evidence-based medicine; how to practice and teach EBM. Churchill Livingstone 1997
Randomised controlled trials (RCTs), long regarded as the “gold standard” of evidence have been put on an undeserved pedestal. Their appearance at the top of “hierarchies” of evidence is inappropriate; and hierarchies themselves are illusory tools for assessing evidence.

Hierarchies attempt to replace judgement with an over-simplistic, pseudo-quantitative assessment of the quality of the available evidence.
Sir Michael Rawlins Harveian Oration

• “arguments about the relative importance of different kinds of evidence are an unnecessary distraction. What is needed instead is for ‘investigators to continue to develop and improve their methodologies; for decision makers to avoid adopting entrenched positions about the nature of evidence; and for both to accept that the interpretation of evidence requires judgement”
“As currently conducted, RCTs are inefficient and have become more complex, time consuming and expensive”

“The traditional frequentist school has provided a solid foundation for medical statistics. But the artificial division of results into”significant” or “not-significant” is better suited for one-time dichotomous decisions such as regulatory approval, and is not the best model for comparing interventions as evidence accumulates over time, as occurs in a dynamic health system
Evidence Development

- There is an urgent need for an international dialogue between regulators, payers and industry to ensure that attempts to improve the timely access to necessary medicines by post marketing/subsidy processes are coordinated in such a way that the objectives will be met ie a convergence of vision rather than divergence of approach.
Methodological Issues of common interest

- When regulators and payers make different decisions regarding which is the most appropriate methodology to analyse data, industry has a legitimate reason to complain. We must be able to at least have a transparent process of justifying why different requirements may exist.
Examples of common methodological issues

- Indirect comparisons
- Early cross over in trials
- Surrogate outcomes and their relationship to patient-relevant outcomes
- Efficacy versus effectiveness-how do we managed confounding in real-world data?
- Use of international registries for ultra-orphan diseases
- Value of a new technology and its impact on risk-benefit analysis and funding decisions
- Should quality of life always be considered by regulators and payers-if so how?
- How will adaptive or Bayesian clinical trial designs be managed
Indirect Comparisons

- The payer is generally required to undertake comparative efficacy analysis of a new technology with its comparator which is generally an active intervention. Many clinical trials submitted to regulator are placebo controlled trials which are not informative to comparative efficacy although some regulators are now requesting active comparator trials under some circumstances.
Indirect Comparisons

- The Payer often has to use an indirect comparison between trials involving a common comparator to establish comparative efficacy. This offers challenges of applicability of the data etc but the alternative is a requirement for RCTs involving active comparators. These trials will be longer, bigger and more expensive due to the smaller incremental difference between 2 active agents.

- Indirect comparisons and network analysis will continue to be used by both regulators and payers—but do we know who the analyse them and its their approach consistent?
Early Crossover

- This is a particular issue in oncology
- Ethics committees often require the option for early crossover
- Early cross over may compromise the ability to answer the hypothesis. There is likely to be significant selection bias introduced by early crossover
Early Crossover

- The use of Inverse Probability Weighting or Structure Failure time methodologies have been examined—are they appropriate, what is their reliability and stability? The use of these and other methods is still uncertain and their appropriate place is yet to be determined. This is an issue for both regulators and payers.
Confounding and Surrogates

- Post Marketing data-observational data - how confounded? Can we manage confounding? Is there an agreement between regulators, payers and industry of what is the appropriate way to manage confounding?

- Surrogate endpoints - what needs to be done to validate surrogates for regulators and payers - likely to be different for both agencies
60% of people with diabetes will have a comorbidity that makes management complex (Roughead 2012)
The Future

- We must acknowledge that while we each have our own requirements and need for independence and responsibility, there is a large amount to be gained by a more open and proactive dialogue. This is crucial to ensure that challenges that face us all are better addressed for the sake of the patients.
- Examples such as the Tapestry initiative in Europe and the dialogue between regulators and EuNetHTA in regard to the introduction of Adaptive Licensing are encouraging.
“The greatest enterprise of the mind has always been and always will be the attempted linkage of the sciences and the humanities”

Edward O Wilson
“Consilience. The Unity of Knowledge”

“The ongoing fragmentation of knowledge and the resulting chaos in philosophy are not reflections of the real world but artifacts of scholarship”

“I think it is inevitable that we will accept the adventure, go there, and find out”
Relative Risk v’s Odds ratio
(Eckermann et al 2009; PBAC working party report 2009)

Inconsistent treatment effect with RR in indirect comparisons –

*low death rate example*

<table>
<thead>
<tr>
<th>Indirect comparison with RR</th>
<th>A</th>
<th>C</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death rate</td>
<td>2.0%</td>
<td>4.0%</td>
<td>3.0%</td>
<td>5.5%</td>
</tr>
<tr>
<td>Survival rate</td>
<td>98.0%</td>
<td>96.0%</td>
<td>97.0%</td>
<td>94.5%</td>
</tr>
<tr>
<td>RR (for death)</td>
<td>0.50</td>
<td>0.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>RR death A vs. B</strong></td>
<td>0.92</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR (for survival)</td>
<td>1.02</td>
<td>1.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>RR survival A vs. B</strong></td>
<td>0.99</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Indirect comparison with OR</th>
<th>A</th>
<th>C</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odds Death</td>
<td>0.020</td>
<td>0.042</td>
<td>0.031%</td>
<td>0.058</td>
</tr>
<tr>
<td>Odds Survival</td>
<td>49</td>
<td>24</td>
<td>32</td>
<td>17</td>
</tr>
<tr>
<td>OR (for death)</td>
<td>0.49</td>
<td>0.53</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>OR death A vs. B</strong></td>
<td>0.92</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR (for survival)</td>
<td>2.04</td>
<td>1.88</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>OR survival A vs. B</strong></td>
<td>1.08</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 5: Inconsistent treatment effect with RR in indirect comparisons – high death rate example

<table>
<thead>
<tr>
<th>Indirect comparison with RR</th>
<th>A</th>
<th>C</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death rate</td>
<td>45%</td>
<td>90%</td>
<td>32%</td>
<td>80%</td>
</tr>
<tr>
<td>Survival rate</td>
<td>55%</td>
<td>10%</td>
<td>68%</td>
<td>20%</td>
</tr>
<tr>
<td>RR (for death)</td>
<td>0.50</td>
<td></td>
<td>0.40</td>
<td></td>
</tr>
<tr>
<td>RR death A vs. B</td>
<td></td>
<td>1.25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR (for survival)</td>
<td></td>
<td>5.5</td>
<td>3.4</td>
<td></td>
</tr>
<tr>
<td>RR survival A vs. B</td>
<td></td>
<td></td>
<td>1.92</td>
<td></td>
</tr>
<tr>
<td>(indirect comparison)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect comparison with OR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Odds Death</td>
<td>0.82</td>
<td>9.0</td>
<td>0.47</td>
<td>4.0</td>
</tr>
<tr>
<td>Odds Survival</td>
<td>1.22</td>
<td>0.11</td>
<td>2.13</td>
<td>0.25</td>
</tr>
<tr>
<td>OR (for death)</td>
<td>0.09</td>
<td></td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>OR death A vs. B</td>
<td></td>
<td>0.77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR (for survival)</td>
<td></td>
<td>11</td>
<td>8.5</td>
<td></td>
</tr>
<tr>
<td>OR survival A vs. B</td>
<td></td>
<td></td>
<td>1.29</td>
<td></td>
</tr>
</tbody>
</table>