Balancing market access to new drugs with the need for benefit/risk data

OECD, Berlin, September 2010

Hans-Georg Eichler
Agenda

• The role of a drug regulatory agency
• Balancing early access with the need for comprehensive data
• From one-off licensing to “live licence”
• The way forward?
The drug regulator’s role...

..to protect public health against unsafe or ineffective drugs against the consequences of untreated disease

This role translates into a mandate to support the development of beneficial drugs
The drug regulator’s walk on the tightrope

Protect public health …

… against negative consequences from unsafe or ineffective medicines

When in doubt, be negative, “we need more information”

Worry about false-positive decision

“What Type-1 error”

What are the consequences?

… against negative consequences from failing to meet unmet medical need

When in doubt, be positive, “it might be a patient's only hope”

Worry about false-negative decision

“What Type-2 error”

What are the consequences?
The drug regulator’s walk on the tightrope

Protect public health …

… against negative consequences from unsafe or ineffective medicines

When in doubt, be negative, “we need more information”

Experts Say that FDA Cannot Ensure Drug Safety

What are the consequences?

… against negative consequences from failing to meet unmet medical need

When in doubt, be positive, “it might be a patient's only hope”

Worry about false-negative decision

no penalty for being negative!

How will (dis-)incentives influence regulators’ behaviour?
The regulator’s dilemma

- **Industry**: Require favourable conditions for innovation
- **Payers/prescribers/HTA organizations**: Request comparative efficacy/effectiveness data
- **Patient groups**: Demand early access to potentially life-saving drugs (for example, Abigail Alliance)
- **Media/scientific community**: Demand stricter safety assessment after series of market withdrawals
- **Unmet medical need**: For example, epidemiology of obesity, diabetes
- **Excess medicalization**: For example, obesity, metabolic syndrome, mood disorders

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**Time to marketing authorization**

- **Shorter timelines**: Higher level of uncertainty
- **More studies/patients**: Delayed market access

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The regulator’s dilemma

“…it has been said that the FDA has just two speeds of [drug] approval – too fast and too slow.”

Hamburg MA & Sharfstein JM. NEJM 360;24: 2493-5; 2009
“C’mon, c’mon — it’s either one or the other.”
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Information needs for Licensing?
Addressing the regulator’s dilemma

Example:
A – Need for early access
B – Emphasis on safety
The drug-development productivity gap

The success rate in clinical development has dropped over the past 10 years.

* The development time data point for 2007 includes data from 2006 and 2007 only.

Source: CMR International & IMS Health
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• From one-off licensing to “live licence”
• The way forward?
From one-off licensing…

- MA
- Warning, DHPC
- Withdrawal backlash

Level of understanding of benefit-risk

Drug Development Phase

PhV, other sources
…to live-licence approach

- Earlier (conditional?) MA
- Amended MA/SmPC, Communicate
- Amended MA/SmPC, Communicate

Level of understanding of benefit-risk

Drug Development Phase

PM-studies, PhV

Effectiveness Research

Time
Evolution of Remicade (EU): Safety

- **T24 stopped**
- **CD: 2nd to 3rd line therapy**
- **FDA panel Lymphoma**
- **DDL Lymphoma**
- **Delayed Hypersensitivity**
- **TB education**
- **CHF DDL**
- **TB DDL**
- **TB/infections alert card**
- **PSUR interstitial pneumonitis/fibrosis**
- **PSUR 6 & 7 vasculitis**
- **PSUR 9 heart failure**
- **Dinv Letter hematological AE**
- **Pneumonia**
- **Severe infections**
- **PSUR3 pancytopenia listeriosis**
- **PSUR 5 myelitis, anemia, hepato cellular damage**
- **PSUR 8 agranulocytosis, pancreatitis**
- **Malignancies**
- **Hepatotoxicity**
- **General DDL**
- **Alcoholic Hepatitis study stopped**
- **Dinv letter transaminases**
- **DDL Hepatotoxicity**
- **SP commitment to CD and RA registry**
...to live-licence approach

- Earlier (conditional?) MA
  - Amended MA/SmPC, Communicate
  - Withdrawal, Communicate

Level of understanding of benefit-risk

Drug Development Phase

PM-studies, PhV

Outcomes Research

Time →
Example: Background incidence for MI (UK, men 30-69y): 6/1000. To detect a 1 in 1000 incidence of drug-induced MI requires study of >160,000 patients (1-sided alpha = .05, beta = .20)

Post-marketing drug withdrawals will not be a thing of the past…
do not necessarily indicate failure of the regulatory process…
need to be accepted with any model of drug approval –early or late…

The only alternative is not to approve anything
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- The way forward?
The way forward? (1)

Enhance methodology of benefit-risk assessment

• “Assessing 21st century drugs with 19th century methods”

• Goals:
  – Qualitative $\rightarrow$ Quantitative
  – Implicit criteria $\rightarrow$ Explicit criteria
  – Incorporate patients’ valuations of beneficial/adverse outcomes
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The way forward? (2)

- Licensing: Benefits and Risks
- Relative Efficacy Assessment
- HTA: Cost and Health consequences

HLPF report: “distinction between [...] relative effectiveness of medicinal products and health-economic assessments.”

“The REA (CER) paradigm”
The way forward? (3)

The harder you look, the more you find
The spiral of risk awareness

New safety findings

“Rotavirus vaccines for infants contain porcine virus DNA”!!

Request for more safety data

Pharmaco-epi studies

Meta-analysis

Larger safety database

Suicidality
(SSRI’s, Anti-epileptics, Statins, Tamiflu…)

Cardiovascular risk
(Vioxx, Avandia, Viagra…)

What next?
The way forward? (3)

Evolve post-marketing research activities

- Pharmacovigilance
  - Risk management
  - Benefit-risk management
  - Effectiveness management
  - Relative effectiveness management
The way forward? (4)

Communicate benefits *and* risks

Challenges:
- Provide proper explanations
- Provide quantitative estimates of benefits
- Be fully transparent – including value judgements
The way forward? (5)

From “Big Bang” to small steps

Staggered approval (EMA),
Progressive Licensing (Health Canada),
Progressive Authorisation Scheme (NEWDIGS)
– start narrow, grow from there
– gradual entry into market
– collaboration between industry, regulators, and payers
The way forward? (5)

Different models under discussion:

• start with small patient population (e.g. high responders) $\rightarrow$ limit utilisation $\rightarrow$ more studies with wider population $\rightarrow$ ...

• “Initial Authorisation”, $\rightarrow$ controlled distribution with active surveillance $\rightarrow$ “Full Authorisation”

Major challenge for sponsors (slow market penetration) and payers (high price for low evidence? CED)

Blurring of distinction between pre- and post-licensing stages
Thank you