From regulators to co-developers?

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Who are we? Prescrire

- Prescrire provides reliable and independent information about drugs and therapeutic & diagnostic strategies.
- Our mission: *"To work, in all independence, in favour of quality healthcare, first and foremost in the interest of patients (...)."*
- Monthly journal in French, and in English, as well as an annual supplement on drug interactions in French and several online training modules.
- Prescrire is a fully accredited continuing education organisation.
- Established in 1981, with its main office in Paris, France.
- Member of the International Society of Drug Bulletins.

Today…

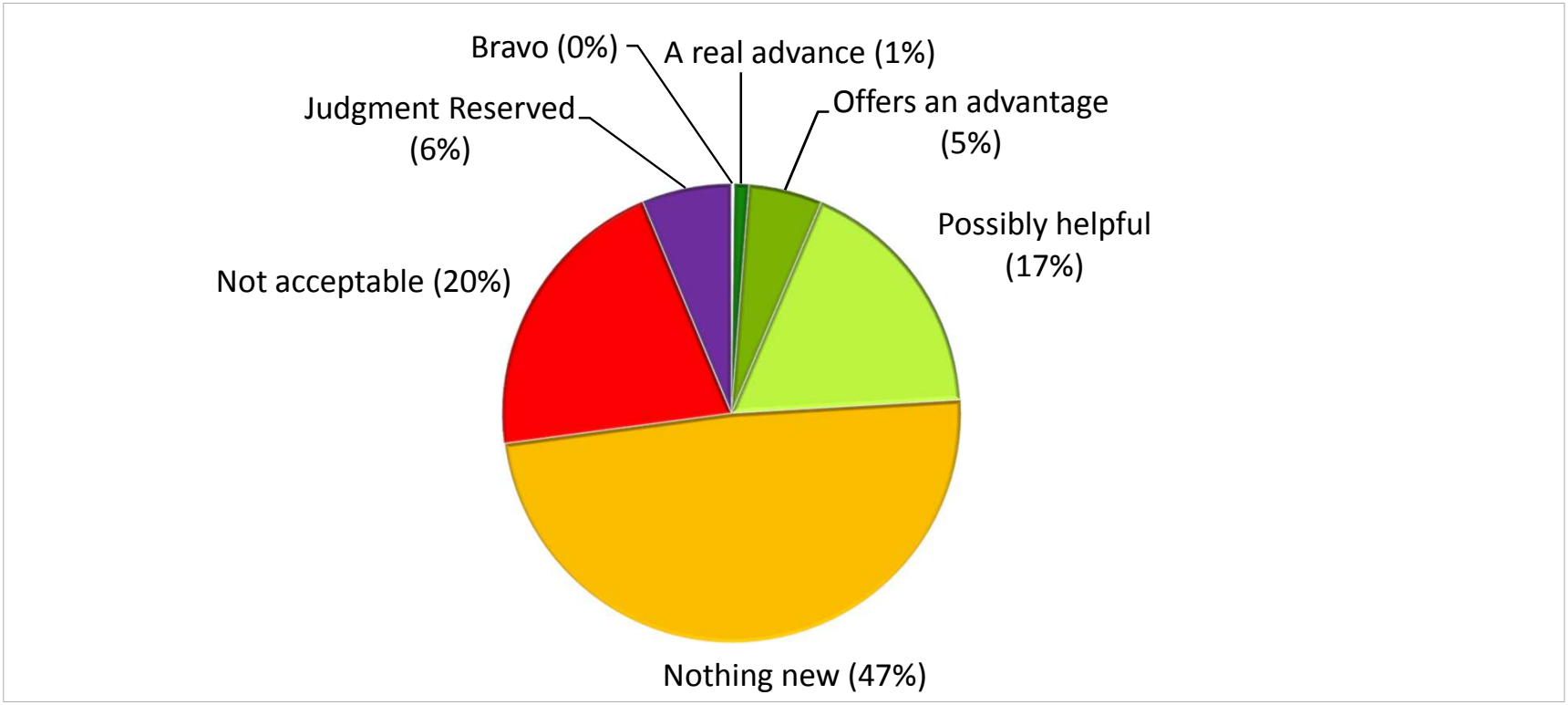
1. Debunking current myths
2. The role of regulators and worrying trends
3. Are the right questions being asked?

EMA: *“Current drug development and authorisation pathways are less than ideal and patients with serious diseases express desire for earlier access to beneficial new treatments”*

Assessing Therapeutic Advance by comparing

1. Efficacy
2. Harm (ADRs)
3. Convenience

Prescrire Ratings for new Indications 2005 to 2015 (percentage over 11 years)



“L'année du médicament : peu de progrès, et des menaces sur l'accès pour tous à des soins de qualité” *Rev Prescrire 2016*; **36** (388) : 133.

In reality…

- Most new drugs are “me-too” drugs
- Modalities are available to provide faster patient access to new medicines when there is unmet health need.
- Timelines for drug licensing have halved over the last 20 years posing threats to patient safety.
- For orphan drugs, cancer treatments and recently Hep C, the major limiting factor to patient access is price.
- The pharmaceutical industry generated higher profit margins than any other industrial sector in 2013. It is likely to have remained the most profitable sector in 2014.
- Profits are mainly redistributed to shareholders, rather than reinvested in R&D.

1. Greater dependence from the pharmaceutical industry over time

- EMA's contribution from industry (1)
  - €39 million in 2000 ⇔71% of overall budget
  - €251 million in 2015 ⇔83% of overall budget
- Fees from:
  - Marketing authorisations
  - Scientific advice
  - Pharmacovigilance

(1) Garatinni S. The European Medicines Agency is still too close to industry. BMJ 2016; 353:i2412 doi:10,1136/bmj.i2412

2. Conflicts of interest policies fall short

- Experts with ties to pharmaceutical companies are invited to share views on products
  - 25% of the 4,528 experts included in the EMA's database were considered to be at 'high risk' of conflicts of interest (Lexchin, 2010)
- Scientific Advice: EMA + companies = capture?
- Majority of patient organisations working with EMA are funded by pharmaceutical companies.

3. Lowering the bar during marketing authorisation decision-making?

- Accepting lower evidence requirements: no tangible evidence of a favourable benefit/harm balance
  - Adopting surrogate markers
  - Allowing methodological shortcuts
  - Accepting shorter and smaller trials
- Early market approval is sometimes associated with higher rate of post-marketing safety warnings.

The idolatry of the surrogate

- Showing an impact on a surrogate endpoint is no guarantee of positive impact on patient's health status. (1)
- The use of surrogates often lacks formal verification of the surrogate-survival association (2)
- 67% of cancer drug approvals by the FDA from 2008 to 2012 were made on surrogate end points. From these, 86% had unknown effects on overall survival or failed to show gains in survival. (3)
- Surrogates are often biased, may overestimate drug benefits (4)

(1) - Prescrire Editorial Staff "Inflation of endpoints" *Prescrire International* 2014; **23** (155): 286.

(2) - Kim C, Prasad V. Strength of validation for surrogate end points used in the US FDA Approval of oncology drugs. *Mayo Clin Proc.* June 2016; 91 (6):713-725

(3) – Kim C, Prasad V. "Cancer Drugs approved on the basis of a surrogate end point and subsequent overall survival: an analysis of 5 Years of US FDA approvals." JAMA Internal Medicine. 2015;175(12):1992-1994.

(4) - Fleming TR "Surrogate endpoints and FDA's accelerated approval process" *Health Affairs* 2005 ; **24** (January (1)) : 67 :68

4. No proof of therapeutic advance

- Many approvals based on placebo-controlled trials without having shown equivalence, non-inferiority, or superiority to existing alternatives.
- 1999-2005: 122 EMA-approved medicines, only 13 (10%) were shown to be superior to already available medicines, showing a statistically significant difference in primary clinical endpoints. (1)
- Industry claims that active comparator trials are expensive and time-consuming.
- Demanding comparative evidence during approval could encourage manufacturers to focus on therapeutic areas with limited treatment options.

(1) - Van Luijn, Johan C. F., Frank W. J. Gribnau, and Hubert G. M. Leufkens. “Superior Efficacy of New Medicines?” *European Journal of Clinical Pharmacology* 66.5 (2010): 445–448. *PMC*. Web. 27 Sept. 2016.

4. No proof of therapeutic advance (2)

- A recent example: Idebenone (Raxone®) (1)
- Indication: Leber's optical neuropathy (hereditary genetic disorder)
- One blinded RCT versus placebo, in 82 patients was submitted, drug was no more effective than placebo.
- 2013 - Marketing authorisation first refused by the EMA.
- The company added non-comparative data and resubmitted.
- 2015 – Market authorisation granted for a drug despite no proven efficacy and potentially serious side effects

(1) – "Idébénone et neuropathie optique de Leber". *Rev Prescrire 2016*; **36** (395) : 651-652.

5. Shifting the burden of evidence from pre-marketing to post-marketing

- Adverse events often poorly ascertained in clinical trials → emphasis on post marketing studies
- For orphan drugs: Post-marketing research did not satisfactorily cover the deficit of knowledge since their licensing in 2004 (1)
- Pharmaceutical companies do not honour post-marketing commitments on time (2)
- Public authorities will face patients' opposition if they finally decide to stop reimbursing a drug or to withdraw its marketing authorisation.

(1) Joppi et al. Letting post-marketing bridge the evidence gap: the case of orphan drugs. *BMJ* 2016;353:i2978

(2) Hoekman J. et al. Characteristics and follow-up of post-marketing studies of conditionally authorised medicines in the EU. *Br J Clin Pharmacol*. 2016 Jul;82(1):213-26. doi: 10.1111/bcp.12940.

5. Shifting the burden of evidence from pre-marketing to post-marketing (2)

- The EMA has never withdrawn a conditionally-approved drug despite lack of compliance by pharmaceutical companies. (1)
- Inadequate or limited measures to ensure appropriate use once a drug is in the market
- Great potential for drug-induced harm

= greater burden to society!

(1) Banzi R, et al “Approvals of drugs with uncertain benefit–risk profiles in Europe” Eur J Intern Med (2015), http://dx.doi.org/10.1016/j.ejim.2015.08.008

Ignoring warning signs?

- Naltrexone + bupropion (amfebutamone) combination (Mysimba®) (1)
- Indication: Overweight & Obesity
- Antagonist of opioid receptors + Appetite suppressant
- Rejected by FDA in 2011; trial needed to assess drug's cardiovascular effects.
- December 2014: EMA CHMP recommends approval. France and Ireland vote against.
- Interim analysis data released to media reporting reduction in heart attacks.
- Once complete data set was analysed, the protective effect was no longer observed.
- March 2015: EU marketing authorisation granted. EMA establishes risk management plan.
- FDA has placed a boxed warning as it affects mood and increases likelihood of suicide.

Naltrexone + bupropion

NOT ACCEPTABLE

Five placebo-controlled trials showed that, on average, obese or overweight patients taking *naltrexone + bupropion* lose only a few kilograms. There is no evidence that this combination prevents complications of obesity. In contrast, its neuropsychiatric adverse effects are numerous and potentially severe. There is also a risk of hypertension, cardiac arrhythmia and gastrointestinal adverse effects. In 2015, there is still no acceptable drug treatment for obesity.

Rev Prescrire 2015; 35 (380): 406-412.

Random clinical trials (RCTs): still the best design for better evidence

- RCTs have been used to increase rigor in medical science
- Still the best design to make a therapeutic recommendation, as they minimize bias
  - RCTs are able to show whether an intervention works/harms
- Many efforts to tarnish the gold standard, pushing a lesser evidence agenda
- Observational studies can generate important data, but they have limitations
- The solution to a bad RCT is a better RCT, not no RCT.

Are the right questions being asked?

Is this medicine likely to be used off-label?

What is the reference treatment (gold-standard)?
A non-drug option?
Another medicine (already existing)?

Table 1. Features to consider in appraising whether clinical research is useful.

Feature	Questions to Ask
Problem base	Is there a health problem that is big/important enough to fix?
Context placement	Has prior evidence been systematically assessed to inform (the need for) new studies?
Information gain	Is the proposed study large and long enough to be sufficiently informative?
Pragmatism	Does the research reflect real life? If it deviates, does this matter?
Patient centeredness	Does the research reflect top patient priorities?
Value for money	Is the research worth the money?
Feasibility	Can this research be done?
Transparency	Are methods, data, and analyses verifiable and unbiased?

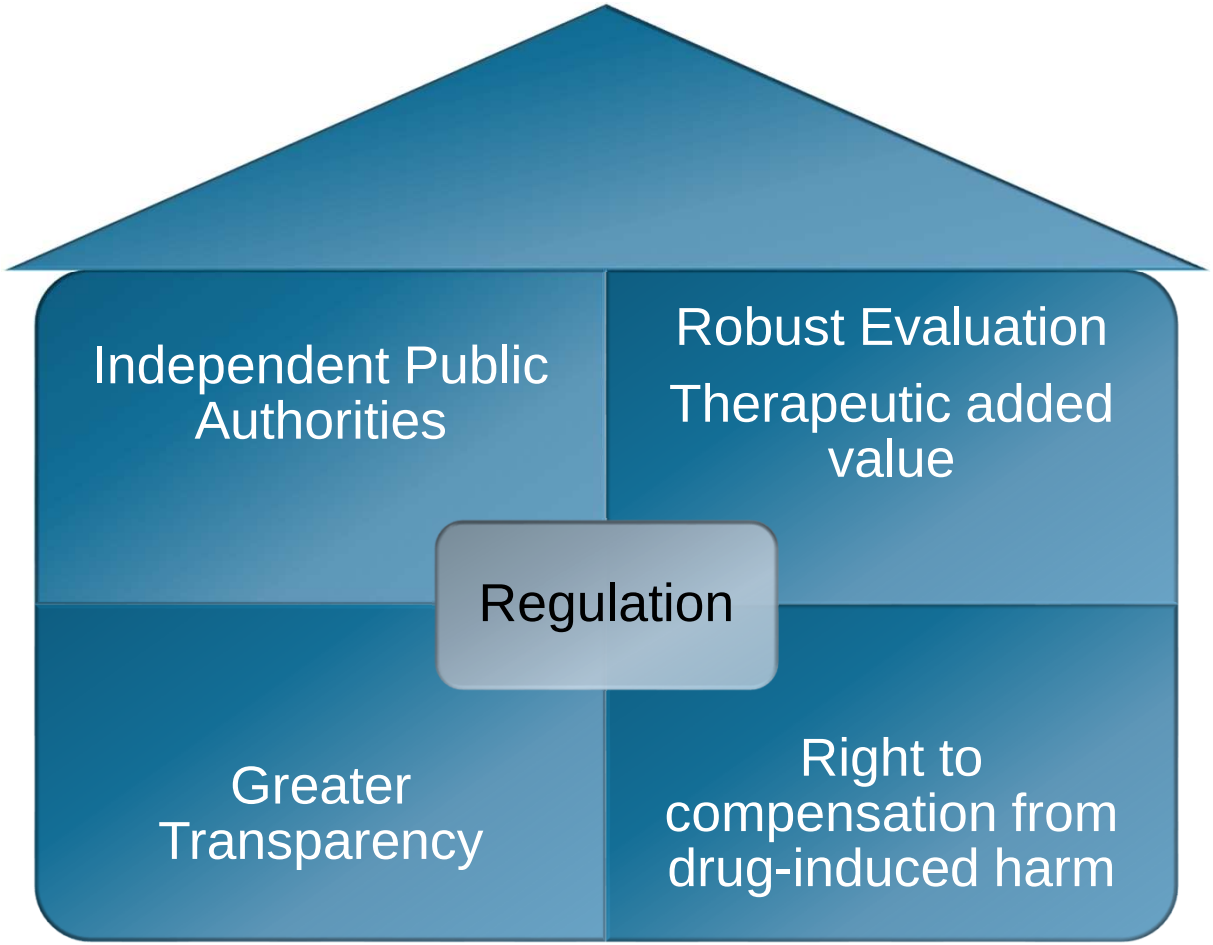
doi:10.1371/journal.pmed.1002049.t001

What is the natural outcome of the condition?

Do we have evidence to suggest any potential safety problems?

Ioannidis JPA. “Why most clinical research is not useful”. PLoS Med 13(6): e1002049

What is needed?



See No Evil, Hear No Evil, Speak No Evil
by Keith Haring

Thank you

More information?
Please email talves@prescrire.org
or visit
http://english.prescrire.org

Extra slides

Prescrire's Ratings

Added Therapeutic Value

BRAVO:
The product is a major therapeutic advance in an area where previously no treatment was available.

A REAL ADVANCE:
The product is an important therapeutic innovation but has certain limitations.

OFFERS AN ADVANTAGE:
The product has some value but does not fundamentally change the present therapeutic practice.

POSSIBLY HELPFUL:
The product has minimal additional value, and should not change prescribing habits except in rare circumstances.

No (or questionable) Added Therapeutic Value

NOTHING NEW:
The product may be a new substance but is superfluous because it does not add to the clinical possibilities offered by previous products available. In most cases it concerns a me-too product.

JUDGEMENT RESERVED:
The editors postpone their rating until better data and a more thorough evaluation of the drug are available.

NOT ACCEPTABLE:
Product without evident benefit but with potential or real disadvantages.