Inspiring consultation with patient and consumer organisations at the Medicines Evaluation Board in the Netherlands

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Declaration of interests

- Professor of Pharmacoepidemiology, Utrecht Institute of Pharmaceutical Sciences, 0.4 FTE.
- Chairman of the Dutch Medicines Evaluation Board (MEB), since mid 2007.
- Co-opted member of CHMP PhVWP, 2006-2009; since 2009 co-opted member of CHMP.
- Director WHO-Utrecht Collaborating Centre on Pharmaceutical Policy Analysis, since 2008.
- This talk reflects my personal views; I am being inspired and challenged on a daily basis by many colleagues from these ‘environments’.

Regulatory systems

- Patient benefit
- Public health
- Innovation

In addition, regulatory science should evaluate and study regulatory systems in terms of their ability to ensure patient safety, enhance public health, and stimulate innovation (*1*–*3*). During the past decades, the introduction of new innovative drugs has dropped, despite impressive investments and progress in biomedical research and development. Although the reasons for this innovation deficit are not fully understood, many observers see the increasing demands of the regulatory systems as one of the main drivers.

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Science 2011 Apr 8; 332(6026): 174-5.

MEB has developed closer interactions with patient and consumer organisations in order

- to become better informed about pertinent practice needs of patients in the drug usage system (operational goal),
- to learn about shared and different values and perspectives when regulating medicines (tactical goal),
- to promote transparency, accountability and trust about benefit-risk decisions made by the MEB (strategic goal).

Snapshot out of recent MEB/CHMP discussions

- Add-on therapy with existing cancer drug, randomisation within cohort of 615 pts with non-standard chemotherapy; sought indication for metastatic breast cancer; PFS of 2.9 months, no effect on OS or clinically relevant effect on HRQL; increased toxicity.
- MAB, extension indication to severe GI disease, placebo comparison, two dose schemes, only high dose shows effect; large number of non-responders; lack of comparative data; small number of reports B-cell lymphomas; uncertainty B/R of long-term use.
- Orphan drug sought indication for rare brain cancer; phase II study 40% reduction of tumor volume after 6 months; no further long-term data; data placebo controlled phase III awaited.
- MAB targeting CD52, sought therapy for MS, convincing efficacy data, concerns about thyroid safety, uncertainty B/R of long-term use, definition of indication, positioning in dynamic MS landscape.

Patients and consumers can bring four different features to the table

Expertise	Convey a combination of specific education, training or professional experience
Experience	Convey practical disease knowledge obtained from direct contact with the disease (affected person or close contact with affected person, e.g. family, carer)
Advocacy	Act on behalf of the affected patients in defence of their rights; provide patient-oriented public health / healthcare policy perspective
Empowerment	Participate in decision-making process within the committee; having access to information and process on behalf of patients

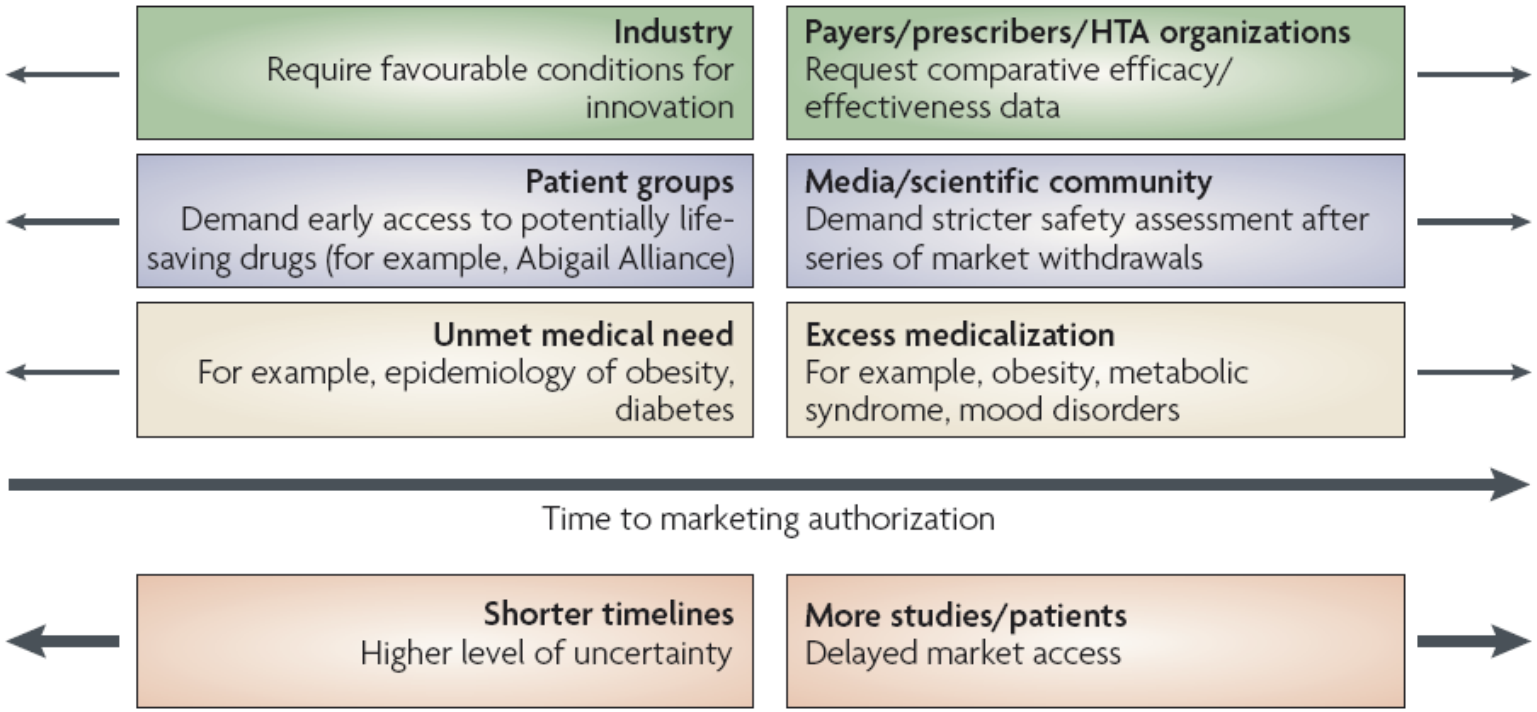
EMA. The role of patients as members of the EMA Human Scientific Committees, 2011.

Key hurdles in facilitating patients and consumers involvement in regulatory decisions

- Validity and representativeness
- Public health versus individual patient interest
- Conflict of interest

Thiel G van. UU-WHO Winter meeting on Priority Medicines, Utrecht, 2013.

The best moment to bring a product to the clinic?



Eichler HG, Pignatti F, Flamion B, Leufkens H, Breckenridge A. Balancing early market access to new drugs with the need for benefit-risk data. Nat Drug Discov 2008; 7: 818-26.

PPI, paradoxes and Plato: who's sailing the ship?

Table 1 Rationales for patient and public involvement (PPI)

	PPI as 'means to an end'	PPI as 'end in itself'
Model	Consultation by invitation	Partnership/alliance
Approach	► Top down ► Pragmatic ► Outcome orientated	► Bottom up ► Rights based ► Process orientated
Purpose for research	► Increases the relevance of the research ► Increases the quality of the research (adds insight to the design, methods and findings; assists in dissemination and implementation)	► Representation of community values and preferences ► Transparency and accountability ► Equalising elitist and exclusionary power imbalances between the public and the academic community
Nature of involvement	► Information giving about decisions made ► Invitation to respond	► Encourage new ideas and joint decision making
Relationship	Transactional	Cooperative

Ives J, Damery S, Redwod S. J Med Ethics (2012). doi:10.1136/medethics-2011-100150.

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Evaluation of Oncology Drugs at the European Medicines Agency and US Food and Drug Administration: When Differences Have an Impact on Clinical Practice

Francesco Trotta, Hubert G.M. Leufkens, Jan H.M. Schellens, Richard Laing, and Giovanni Tafuri

Franceso Trotta, Giovanni Tafuri, Italian Medicines Agency, Rome, Italy; Hubert G.M. Leufkens, Jan H.M. Schellens, Giovanni Tafuri, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht; Hubert G.M. Leufkens, Jan H.M. Schellens, Medicines Evaluation Board, The Hague; Jan H.M. Schellens, The Netherlands Cancer Institute, Amsterdam, the Netherlands; and Richard Laing, WHO, Geneva, Switzerland.

A B S T R A C T

Purpose
The aims of this study were to compare the approaches of the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) in the evaluation and approval of new anticancer indications and to identify possible clinical implications associated with these differences.

Methods
Information on the European Union therapeutic indications for the cohort of anticancer drugs was extracted from the European Public Assessment Reports and from the FDA review reports.

2011; 29: 2266-72.

EXPERT VIEW

FDA's Avastin decision: into the minds of regulators

The FDA last week laid out its big decision on Avastin's breast cancer indication in a 69-page ruling. The document had two somewhat distinct sections: known-knowns whereby one could see about five months ago how this movie was probably ending.

And then came a new part, intriguing for different reasons. The last 16 pages outlined some decisions and thinking by the commissioner on the known-unknowns.

This part otherwise could be called the "wildcard" section. It tackles seven main arguments whereby Genentech sees the potential for the FDA commissioner to play the "wildcard" and exercise discretionary powers to continue Avastin's US breast cancer indication in some form. In here, we can see a brief glimpse into the mind of a regulator on some very recurrent themes in the global pharmaceutical industry.

big regulatory questions

What are these known variables with unknown potential to sway the use of wildcard powers?

All of them were declined obviously. But they are all relatively big regulatory questions. I have

Other Drug Comparisons: One of Genentech's arguments was that Eli Lilly's Gemzar (gemcitabine) has approval for first-line metastatic breast cancer with data comparable to Avastin's, with a somewhat similar safety profile. The FDA is quite terse here, saying each decision like this is based on a product's own merits. Another thing is remarkable here. Doesn't the industry prefer the FDA (and payers too for that matter) to focus on safety and efficacy of the product at hand – not in relation to others? The FDA quickly moves on with no signal of irony.

Advisory Committee Panel Members: The argument here was that the advisory panel "lacked clinical experience with breast cancer and Avastin" and was predisposed against the progression-free-survival (PFS) measurement for approval. Dr Hamburg summarily rejects this, saying it was her decision alone and Genentech's failure to show PFS gain, not bias against that measurement.

Scrip 2011 Nov 25:18.

FROM THE ANALYST'S COUCH

Factors influencing non-approval of new drugs in Europe

Michelle Putzeist, Aukje K. Mantel-Teeuwisse, Bo Aronsson, Malcolm Rowland, Christine C. Gispen-de Wied, Spiros Vamvakas, Arno W. Hoes, Hubert G. M. Leufkens and Hans-Georg Eichler

Table 1 | **Summary scorecard of EMA assessment of 68 MAAs***

Development plan	Clinical outcome	Clinical relevance	Non-approved ($n = 23$)	Approved ($n = 45$)
+	+	+	0	8
+	+	–	0	6
+	–	+	0	2
+	–	–	2	0
–	+	+	2	18
–	+	–	2	6
–	–	+	5	3
–	–	–	12	2

Nat Rev Drug Discov 2012; 11: 903-4.

Biomarkers variation in eff
Knowledge Mgmt
Access to computational data b
Risk - Benefit - Role of Patien
Mechanism of Disease - Funding
Regulators looking at therapeuti
Unmet needs - Who should deter
Role of patients group + Fundin
How to involve
Learning from failures / Scientific Adv
Transparency in Advice & Regulatory
Scientific information -
Society / Company dialogue -
Pharmaco economic burdens
Conditional approval with Phase
Access Issues (Mondrian)
Utilization Innovation + therapeutic out
Phase 4

system: The Escher-project