

C B G

M E B



Bert Leufkens

Chairman
Medicines Evaluation Board

Never a dull moment at the MEB

- Problems at Organon/MSD fuel public debate about negative impact of drug regulation on innovation. July 2010. Is the MEB hampering bringing new drugs to patients?
- Health Care Insurance Board (CVZ) asks MEB for advice on switching biosimilar products in clinical practice. October 2010. How efficacious and safe are these products?
- Public debate about role French regulatory authorities in Mediator case. February 2011. Could this also happen at the MEB?
- Questions about the safety (narcolepsy) of pandemic vaccines. February 2011. Chair MEB provides the most recent evidence on prime time television. Are Dutch vaccinated children safe?
- Dutch pediatricians express concern that outcomes of EU Article 45/46 procedures do not match with views and experiences in clinical practice (April 2011). What is the role of the MEB in off-label prescribing?

Never a dull moment at the MEB

‘Op schoot bij de industrie’

■ Europees parlement wantrouwt toezichthouder geneesmiddelen

Joop Bouma

De Europese toezichthouder op geneesmiddelen, EMA in Londen, ligt onder vuur. Er is twijfel over de onafhankelijkheid van de dienst. Het Europees parlement besloot bijna unaniem (637 tegen 4 stemmen) de begroting van het European Medicines Agency niet goed te keuren. Het Parlement wil eerst een onderzoek van de Europese Rekenkamer.

Het EMA houdt toezicht op de veiligheid en de toelating van geneesmiddelen in Europa. De organisatie

wordt vrijwel geheel gefinancierd door de farmaceutische industrie. Volgens europarlementariërs loopt het EMA aan het handje van de industrie.

Deze week publiceerde de *British Medical Journal* een artikel van twee Deense onderzoekers die 1028 dagen moesten wachten op medische studies over omstreden geneesmiddelen. Het EMA weigerde ze vrij te geven om de commerciële belangen van farmabedrijven te beschermen. De onderzoekers stellen dat het EMA het belang van de fabrikanten boven

het belang van patiënten stelt.

Het Europees Parlement vindt dat het EMA onder meer faalde in het schandaal rond de slankmaker Mediator van het Franse farmabedrijf Servier, die enkele honderden mensen het leven kostte. Pas in 2009 werd deze pil van de markt gehaald, tien jaar na de eerste signalen over ernstige bijwerkingen.

Het parlement maakt zich vooral zorgen over het feit dat het EMA volledig wordt gefinancierd door de industrie. Dat geldt ook voor de Nederlandse toezichthouder, het College

ter Beoordeling van Geneesmiddelen. In 2009 ontving het CBG 36 miljoen van fabrikanten aan vergoedingen voor registratie en beoordelingen van nieuwe geneesmiddelen. De totale begroting was 37 miljoen.

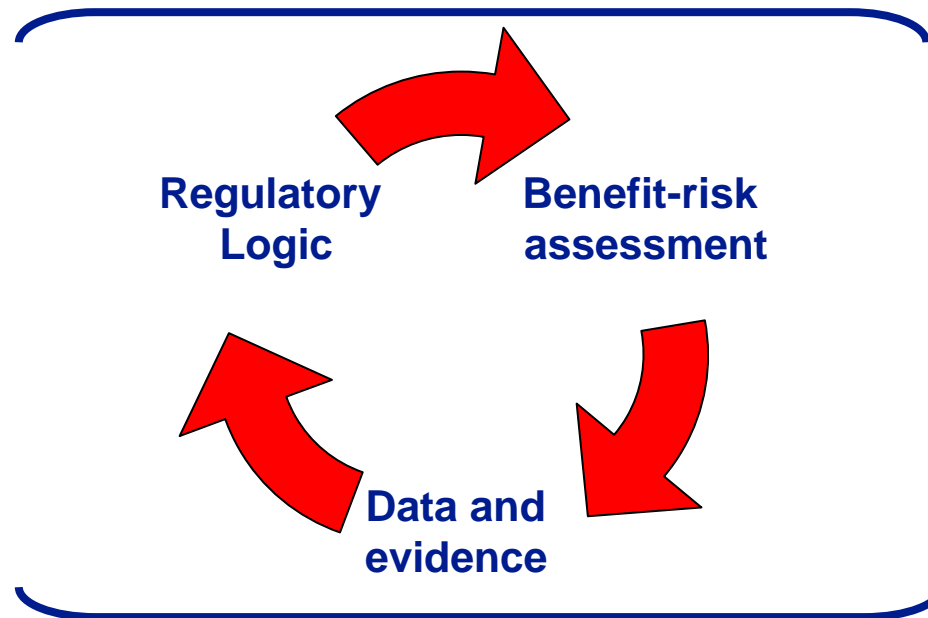
CBG-voorzitter Leufkens ziet geen zwakheden in het financieringsmodel van EMA en CBG. “Over de financieringswijze is altijd discussie denkbaar. Wij zijn ons daarvan bewust. In Nederland heeft de industrie geen bemoeienis met de daadwerkelijke besluitvorming, er zijn veel waarborgen voor onafhankelijkheid.”

What is at the top of our organizational radar screen?

- Further strengthening of our internal processes in order to keep up with timelines, underpinning the scientific basis and maintaining consistency in regulatory decision making.
- MEB has been elected as public organization of the year 2011 (Ambtenaar 2.0) for its innovative performance in organizational change; move to Utrecht campus.
- Setting policy standards on transparency, conflict of interests and good governance, both in terms of people, dossiers, assessment reports, meetings (minutes) and decision making.
- Implementing new EU pharmacovigilance legislation: patient and public health first; decisions about medicinal products are about harms and benefits.
- International leadership in bridging regulatory processes to science, clinic and public health; strengthening of regulatory science.

Regulating the life-cycle of a medicinal product

Regulatory governance



Regulatory science

Efficacy-effectiveness gap in B/R assessment



Eichler HG. Escher Workshop, April 28 2010, Leiden

Is quantitative benefit–risk modelling of drugs desirable or possible? ☆

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Preliminary research results with drug regulators in several European Agencies show that quantitative models developed with groups of assessors and specialists can integrate scientific data with expert value judgements, thereby extending the capabilities of regulators, and stimulating new insights about key trade-offs. As a result, the rationale for the benefit–risk balance becomes more transparent, communicable and consistent.

Welcome to DrugIS.org

At drugis.org (Drug Information Systems), we are developing prototype software, to discover how ICT may assist or change the way in which pharmaceutical research and regulation is done. We work in an agile way, which means that we aim to deliver valuable, working software early on in the development process. It also means that we do not expect to know now what our software will be able to do in a year's time, but rather that we continuously work with the users of our software to discover their current, and changing, understanding of what is important and valuable. **Contact us** if you have any questions.

The Escher Project

Our work is funded by the Dutch **Top Institute Pharma**, specifically through the Escher Project workpackage 3.2. The goal of the Escher project is to "energize pharmaceutical R&D by identifying, evaluating and removing regulatory barriers to bring efficacious and safe medicines to patients in an efficient and timely fashion."

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News

ADDIS v1.6 released
ADDIS v1.6 has been released, introducing

Four recent suspensions because of negative B/R

| Rimonabant and CNS risk | Efalizumab and PML risk | Sibutramine and CV risk | Rosiglitazone and CV risk |
|--------------------------------------|--------------------------------------|--------------------------------------|--------------------------------------|
| Known effect, B/R initially positive | Known effect, B/R initially positive | Known effect, B/R initially positive | Known effect, B/R initially positive |
| Usage too short to see benefit | Usage in high risk patients | Usage in high risk patients | No benefit to outweigh risk |
| NL/MEB (Co)Rapporteur | NL/MEB (Co)Rapporteur | NL/MEB Concerned | NL/MEB (Co)Rapporteur |

Safety-Related Regulatory Actions for Biologicals Approved in the United States and the European Union

JAMA 2008; 300: 1887-1896.

Thijs J. Giezen, PharmD

Aukje K. Mantel-Teeuwisse, PhD

Sabine M. J. M. Straus, MD, PhD

Huub Schellekens, PhD

Hubert G. M. Leufkens, PhD

Antoine C. G. Egberts, PhD

Context Biologicals are a relatively new class of medicines that carry specific risks (eg, immunogenicity). However, limited information is available on the nature and timing of safety problems with their use that were identified after approval.

Objective To determine the nature, frequency, and timing of safety-related regu-

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

2011 Jun 1;29(16):2266-72.

BIOLOGICALS, DEFINED AS PRODUCTS of which the active substance is produced by or extracted from a biologic source, represent an important and growing part of the therapeutic arsenal.¹ In the United States, the first bi-

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

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.

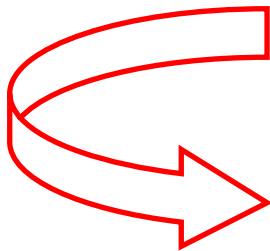
Methods

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.

Francesco 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.

Risk based evaluation of B/R and dossier/SPC updating during a product lifecycle

- Population exposure
- Multiple MAHs for the same product
- No recent/planned other regulatory updates
- Specific risk groups (e.g. children, elderly, pregnant women)
- Complex drug delivery forms
- Product used as OTC



2011 menu chart

Ibuprofen
Metoprolol
Dextrometorfan
Doxycycline
Aspirin (for CV and neurological indications)
Human Chorionic Gonadotrofin (Pregnyl)

Regulatory systems

- Patient safety
- 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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H. G. LEUFKENS^{1,3}

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

'Regulators': sheriffs of supporters van 'public health'?



US Bureau of Chemistry scientists around 1900 (pre-FDA) charged with tracking down and analysis of food and medicines.

Summarizing

- Lifecycle management of the B/R of a medicinal product is a key activity of drug regulators (e.g. MEB, EMA, FDA); the lifecycle virtually never stops.
- Collaboration between MEB, Lareb, IGZ, CCMO, RIVM, academia and the clinic fuels the R&D of the regulatory system, but is also beneficial for clinical practice.
- Regulators are always too strict, too slow, too fast, too forgiven, too cozy, etc. Alignment with the clinic ensures the relevance of regulatory system for the patient.
- It is undesirable, and virtually impossible, to untangle weighing benefits and harms of medicinal products.
- Innovation is more than bringing new molecules to the market; it also about improving medicines' use.

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