Decision making and medication risk: from signal to policy and regulation

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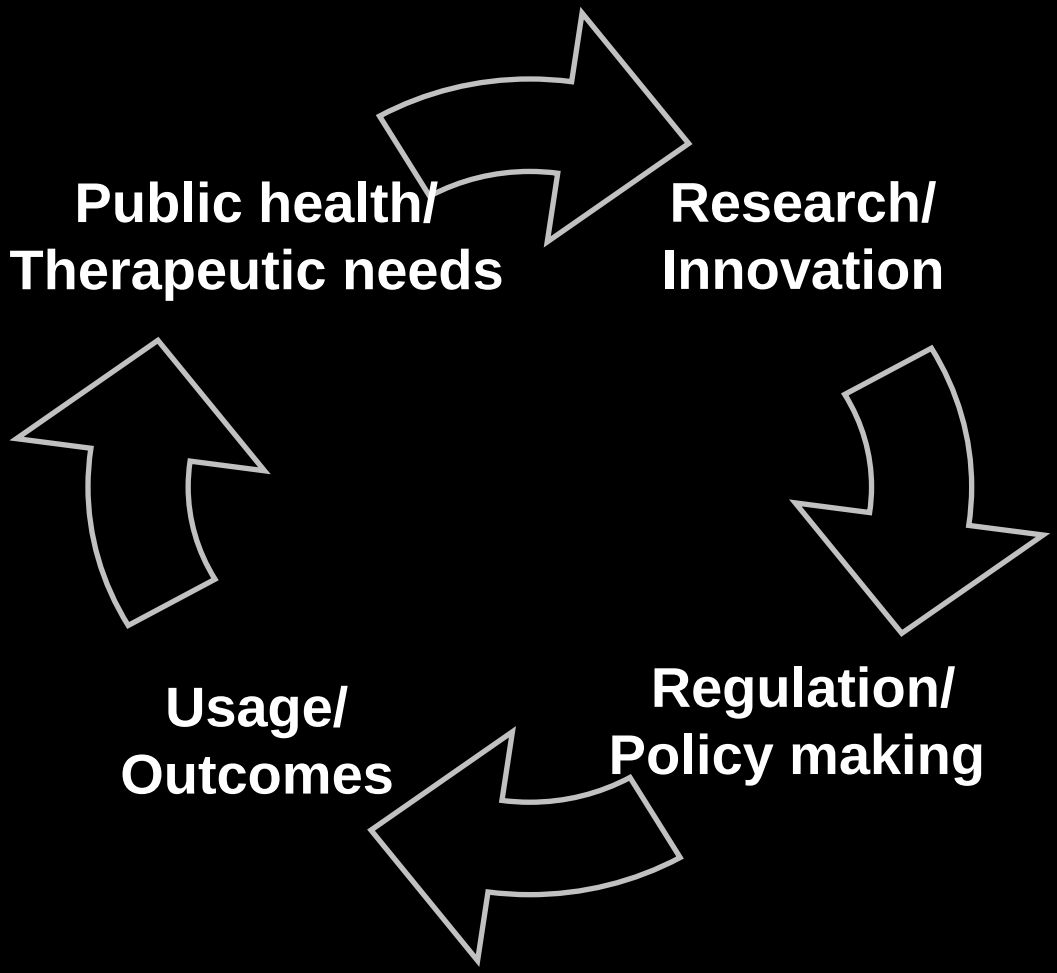
Public health effects of medicines

- Direct clinical effects (e.g. analgesics and pain relief, antivirals and AIDS survival, NSAIDs and GI bleeding).
- Disease prevention (e.g. vaccines and childhood disease, statins and prevention of CV risk).
- Effects on other medical interventions (e.g. PPIs and GI surgery, anaesthesia and surgery, cyclosporin and organ transplantation).
- Society effects (e.g. contraceptives and demographics, psychotropic drugs and transformation of the mental health system).

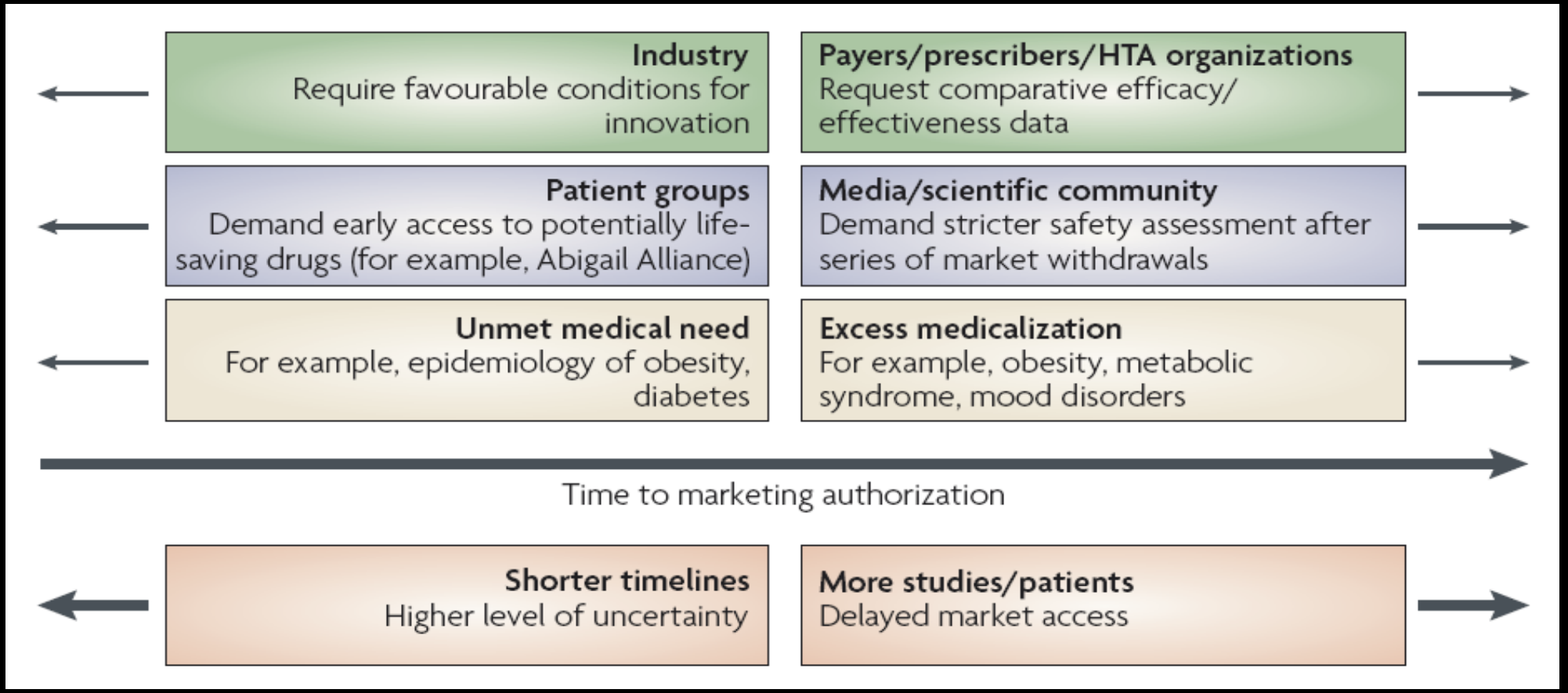
Medicines that changed our thinking

Case drugs	Learning points
Mebefradil	B/R is dependent of quality of drug usage; industry awareness of ‘We can’t control prescribing’
HIV drugs	Transformed AIDS to a chronic disease; drugs don’t work if not used; access to medicines is critical
Thalidomide	Drug induced harm; reinvention given effective risk minimization; listening to patients is important
Rofecoxib	Erratic marketing hurts all parties; dose and duration of use drives B/R; poor external validity of RCTs
Natalizumab	Biologicals are powerful drugs; uncertainties about rare, severe ADRs; listening to patients is important
Antibiotics	Are essential medicines; are often misused leading to resistance; empty pipeline symbolic for market failure

Continuum of pharmaceutical policy



Is there a good moment to bring to and keep a drug on the market?



Eichler H-G, Pignatti F, Flamion B, Leufkens H, Breckenridge A. Balancing early market access to new drugs with the need for benefit-risk data: a mounting dilemma. Nature Drug Disc 2008; 7(10): 818-26.

Record on compliance with postapproval commitments gives concerns

A study released on May 20 by the FDA reveals that of 1,963 postmarketing studies committed to by industry since 1991, only 20% have been completed, and 45% have yet to begin. Although most of these stud-

Bouchy A. Industry reneges on postmarketing trial commitments. Nat Biotechnol 2003; 21: 718.

Drug regulation and policy mainly driven by ‘disasters’

- The Elixir Sulfanilamide disaster of 1937.
- First appearance of Thalidomide in Germany on 1st October 1957.
- Withdrawal of rofecoxib (Vioxx®) in 2004.
- Heparine, 2008.

Drug regulatory systems must foster innovation and public health

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.

Prioritizing in pharmaceutical innovation: ‘gap analysis’

	Viral infections	Schizo-phrenia	Diabetes
New basic knowledge			
Better molecules			
Better delivery systems			
Better/safer usage systems			

Availability and Choice of Antimalarials at Medicine Outlets in Ghana: The Question of Access to Effective Medicines for Malaria Control

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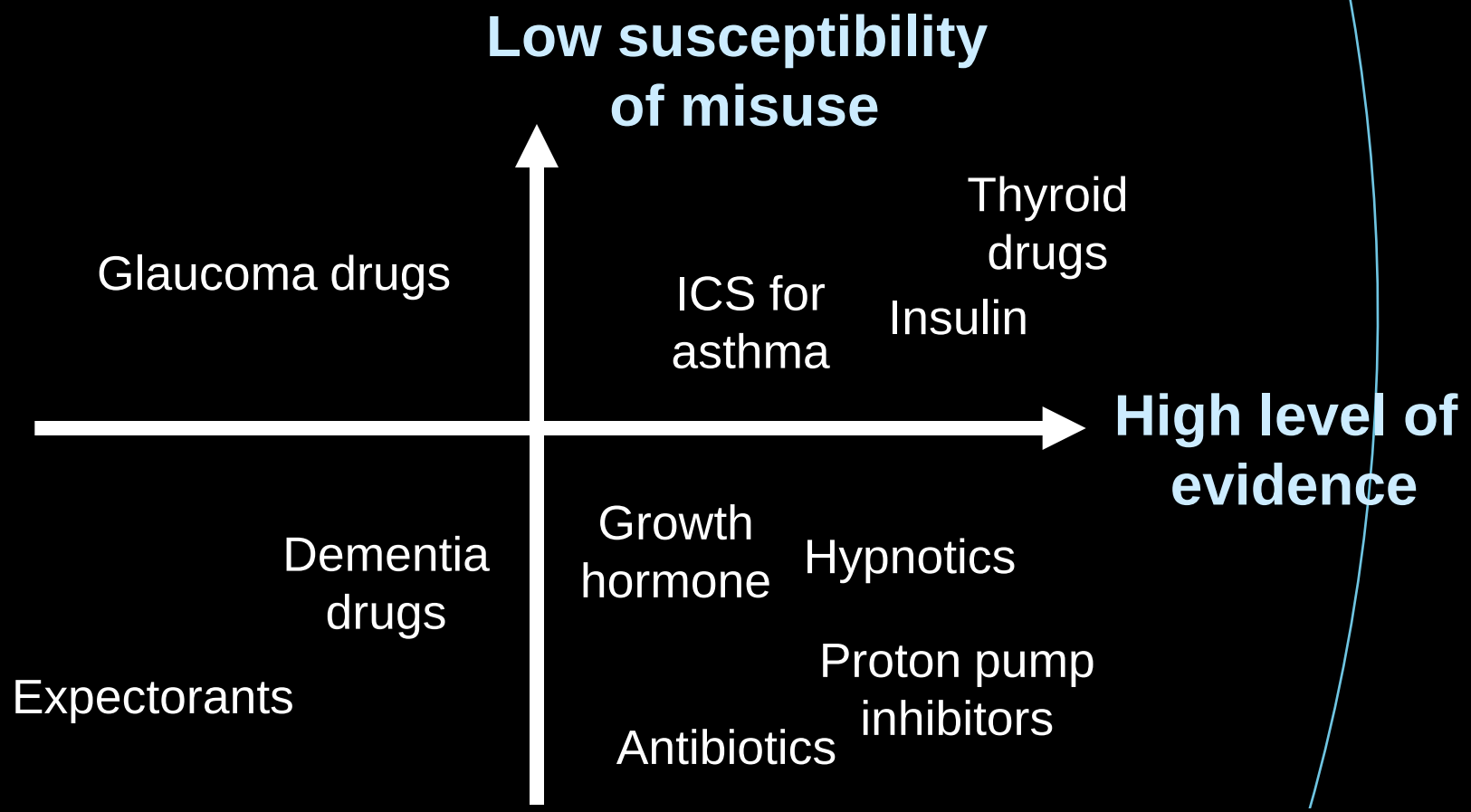
Although national and international efforts to combat malaria have intensified over the years, problems with availability, distribution, and choice of antimalarials at medicine outlets in Africa continue to exist. This article presents the results of an indicator-based assessment of availability and choice of antimalarials at 130 licer reco by re Anti

Table 2 Availability of medicines recommended in the national policy for malaria therapy in Ghana

Antimalarial	Community pharmacies ($N = 35$) (n (%))	Hospitals and clinics ($N = 31$) (n (%))	Licensed chemical shops ($N = 64$) (n (%))
Sulfadoxine/pyrimethamine tabs	35 (100)	24 (77)	62 (97)
Quinine inj. and tabs	27 (77)	21 (68)	28 (44)
Artesunate/amodiaquine and / or artemether/lumefanthrine tabs or susp.	28 (80)	24 (77)	18 (28)
Artesunate/amodiaquine tabs	17 (49)	21 (68)	17 (27)
Artemether/lumefanthrine tabs or susp	24 (69)	5 (16)	4 (06)
Artemether inj. or rectal artesunate	20 (57)	13 (42)	3 (5)

Inj., injections; rectal, suppositories; susp., suspensions; tabs, tablets.

Ranking ‘evidence’ and ‘susceptibility of misuse’



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Bégaud B, Bergman U, Eichler H-G, Leufkens HG, Meier PJ. Br J Clin Pharmacol 2002; 54: 528-34.

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

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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 regulatory actions for biologicals following approval in the United States and/or the European Union.

Design and Setting Follow-up of a group of biologicals approved in the United States and/or European Union between January 1995 and June 2007. Vaccines, allergenic products, and products for further manufacture and transfusion purposes were excluded.

Main Outcome Measures Nature, frequency, and timing of safety-related regulatory actions defined as (1) dear healthcare professional letters (United States) and direct healthcare professional communications (European Union), (2) black box warnings (United States), and (3) safety-related marketing withdrawals (United States and European Union) issued between January 1995 and June 2008.

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

JAMA 2008; 300: 1887-1896.

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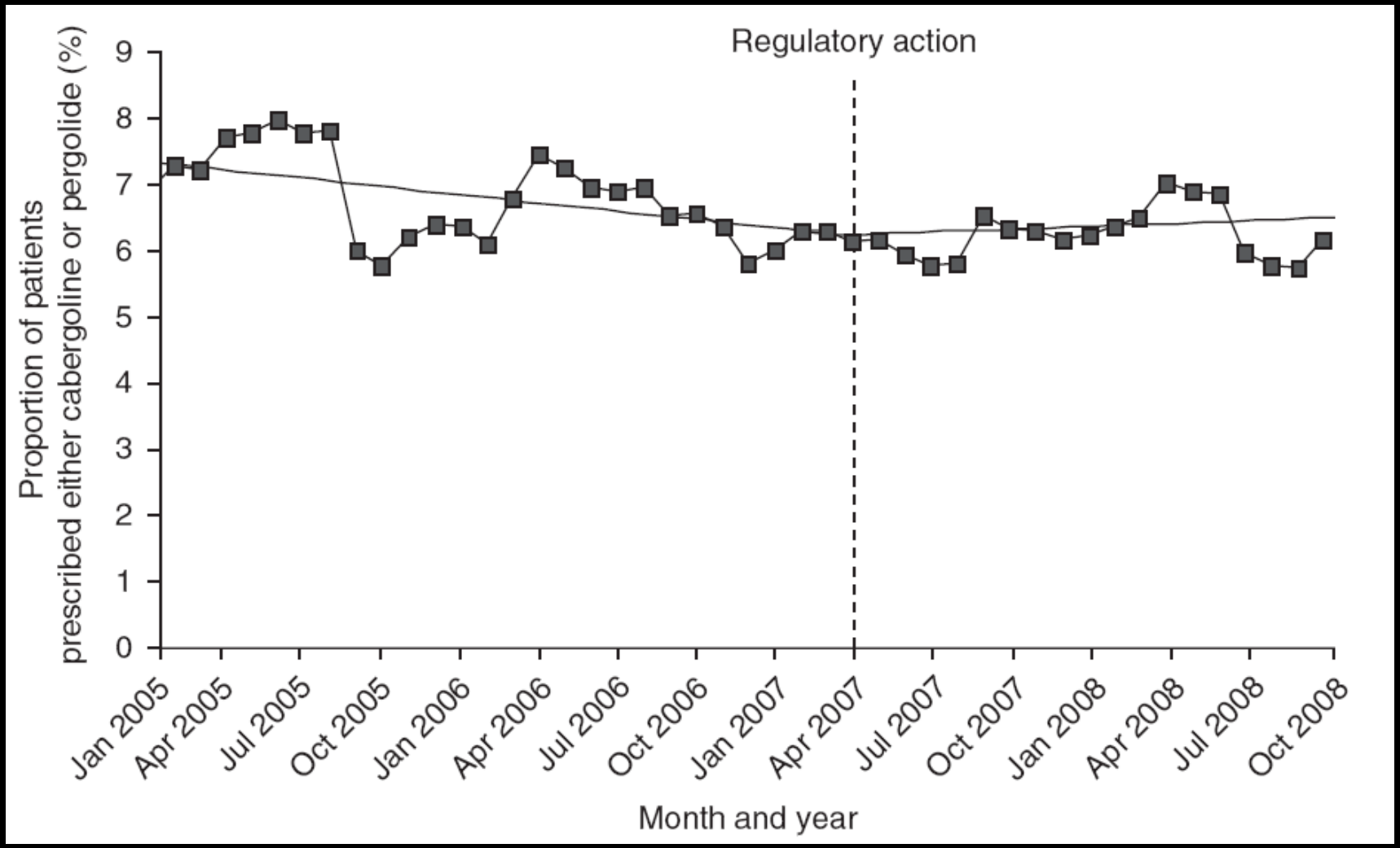


Ooba N et al. The impact in Japan of regulatory action on prescribing of Dopamine Receptor Agonists: analysis of a claims database between 2005 and 2008. Drug Saf 2011; 34: 329-338.

70+ year olds			
GI deaths (observed–expected)		AMI deaths (observed–expected)	
USA	−219	USA	−414
UK	−129	UK	−226
France	−45	France	−161
Netherlands	−36	Norway	−130
Sweden	−19	Germany	−126
Croatia	−8	Netherlands	−51
Slovenia	−8	Spain	−50
Finland	−5	Czech	−40
Malta	−2	Sweden	−23
Luxembourg	−1	Finland	−20
Iceland	0	Slovenia	−18
Norway	+1	Austria	−5
Czech	+9	Iceland	−3
Austria	+27	Luxembourg	+12
Spain	+31	Malta	+12
Japan	+47	Croatia	+37
Germany	+91	Japan	+189

Metcalfe C et al. International regulatory activity restricting COX-2 inhibitor use and deaths due to gastrointestinal haemorrhage and myocardial infarction. Pharmacoepidemiol Drug Saf 2010; 19: 778–785.

Depletion of susceptibles over time as found in the Swedish ARTIS registry

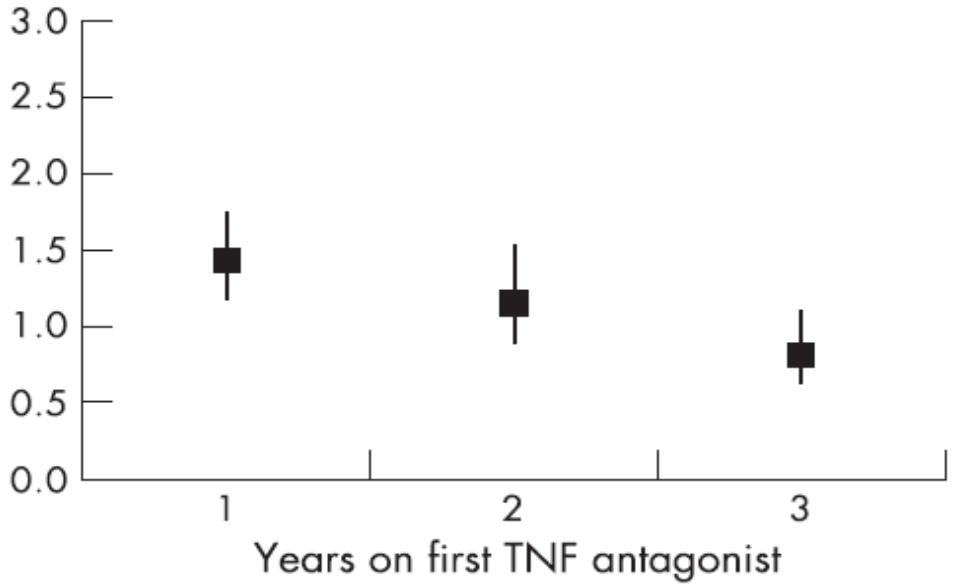


Figure 1 RRs for hospitalisation with infection during time on first tumour necrosis factor (TNF) antagonist treatment 1999–2003 in the Swedish Inpatient rheumatoid arthritis (RA) cohort, by time since start of TNF antagonist treatment, among 44 946 RA patients of whom 2692 patients started treatment with a first TNF antagonist. RRs estimated through Cox regression.

Askling J et al. Time-dependent increase in risk of hospitalisation with infection among Swedish RA patients treated with TNF antagonists. Ann Rheum Dis 2007; 66: 1339-44.

Cancer pharmacoepidemiology is still in its infancy

- Historical examples (e.g. DES and cancers in next generation, HRT and breast cancer, statins and various cancers, aspirin and colon cancer) show all the methological struggles and pitfalls.
- Key issues are: no reliable trial data, clear understanding of the hazard function, duration of follow-up, exposure dynamics, multiple cancers with different etiologies, underlying disease/co-morbidities and 'competing' morbidities.
- Although progress is being made, see the insulin glargine series of studies.
- New data sources are becoming available e.g. Nordic registries, ENCePP, and new linkage systems (Herk-Sukel MP van. New opportunities for drug outcomes research in cancer patients: The linkage of the Eindhoven Cancer Registry and the PHARMO Record Linkage System. Eur J Cancer 2009 Oct 5.)

Assessment and weighing of different drug characteristics

	HTA	Registration
Quality	-	+
Efficacy	+	++
Effectiveness	++	+/-
Comparative effectiveness	++	+/-
Safety	-	++
Costs	++	-

Rawlins M. CMR Workshop. Review and Reimbursement, London, Sept 27 2009

There has been always the philosophical question:

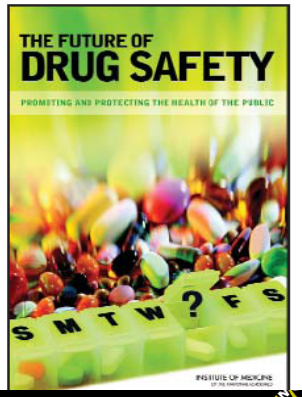
Can people who approve technologies (e.g. medicines, airplanes, cars), also be the same to carry responsibilities for safety monitoring and protecting the public from harm?

INSTITUTE OF MEDICIN

REPORT BRIEF • SEPTEMBER 2006

THE FUTURE OF DRUG SAFETY: ACTION STEPS FOR CONGRESS

The Institute of Medicine's Committee on the Assessment of the U.S. Drug Safety System intends that the 25 recommendations in its report will bring the strengths of the preapproval process (data, regulatory authority, organizational function and capabilities, and resources) to the postapproval phase in order to fulfill a lifecycle approach to the study, regulation, and communication about the risks and benefits of drugs.



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Lancet urges greater EMA transparency

May 21, 2010 — 9:55am ET | By Liz Jones

The European Medicines Agency has come under fire in *The Lancet* for what critics call questionable decisions related to drugs from Roche and AstraZeneca (NYSE: AZN). As *Reuters* notes, the criticism is similar to past attacks on the FDA, and the journal questions not only the EMA's handling of adverse event reports, but also its licensing decisions.

In an article, the journal cites the EMA's handling of a case involving Roche's acne drug Accutane, which has been linked to inflammatory bowel disease and other serious adverse events. In April 2008, Liam Grant of Dublin, Ireland, whose son had committed suicide in 1997, asked the EMA for reports on suspected serious adverse reactions to the drug. The regulator denied his requests, arguing that EU transparency rules did not apply to serious adverse reaction reports. Their release, the EMA maintained, "would not benefit EU citizens because it could result in circulation of data that might prove to be misleading or unreliable."

Is it justified to let medicines fly without a black box?

Citation: Leufkens HG. Is it justified to let medicines fly without a black box? Southern Med Review (2010) 3; 2:1-1

On July 21 2010 the Australian scientist David Warren who invented the flight data recorder, since then coined the 'black box', died at the age of 85. Warren designed the first flight data recorder in 1956, triggered by the complicated investigation of the mysterious crash in 1953 of the first jet airliner, the Comet. He felt strongly committed to airline safety given that his own father was killed in a plane crash in 1934. The concept of the 'black box' has had a major impact on safety analysis in the aviation world with the opportunity to learn from previous mistakes. Not only technically speaking, but also in terms of appropriate recording of their fate' through medical practice leaving health care professionals, policy makers and regulators in the dark when it comes to adequate data on medicines' usage and what it brings to patients and society at large. In effect there is no pharmaceutical black box! In many African countries cohort event systems are developed to evaluate the safety of new anti-malarial drugs[4]. This is good news, but a recent survey of pharmacovigilance activities in 55 low- and middle-income countries showed that only in a limited number of countries' sentinel sites or active surveillance systems were in place to