

Therapeutic risk management is required to ensure that the benefits of a particular drug outweigh its risks in general practice. Current handling of risk management is inconsistent around the world, and the reasons behind different decisions are unclear.

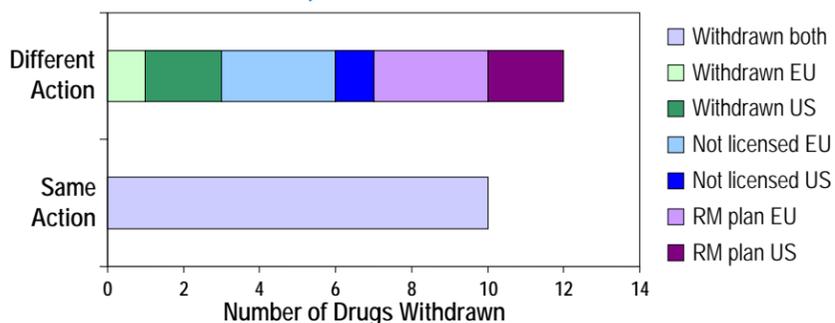
“If greater international consistency is to be achieved, these reasons need to be explored, in the first instance through retrospective study of recent major decisions.”

Waller & Evans, 2003

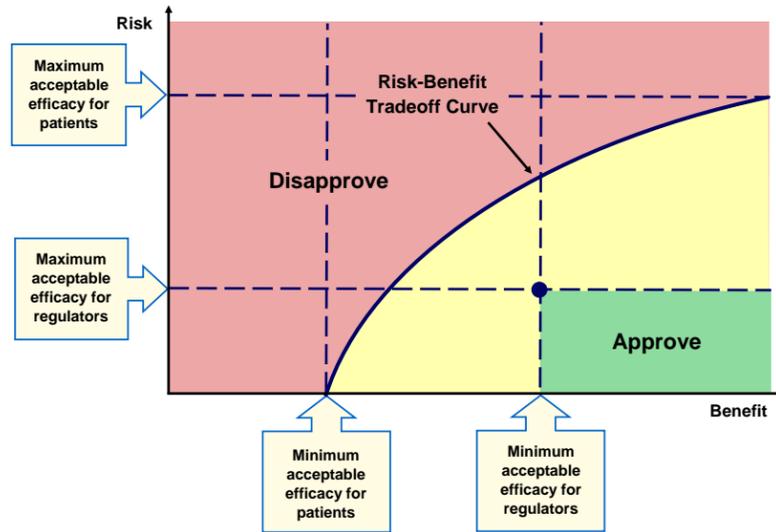
METHODS: We conducted a literature review of previous cases to consider the reasons and possible solutions for the current lack of international agreement. In addition, we compared the regulatory systems, healthcare systems, and culture in worldwide geographic regions.

RESULTS: In the context of healthcare and regulatory settings, we examined well-known cases in which regulatory actions were unsuccessful or contentious. Of 22 drugs withdrawn in the US or EU from 1997 to 2005, the regulatory action differed in more than half (see figure below). In five cases, a risk management plan was used to limit known adverse events and thus allow the drug to remain on the market. Regulatory action on a drug in one part of the world may have serious repercussions in other countries, particularly where epidemiological evidence upon which to base decisions are inherently incomplete, as in the cases of cisapride and oral contraceptives (see table).

Regulatory Actions in 22 Drugs Withdrawn, US and EU



Theoretical Depiction of Drug Approval and Risk Management



Key issues were

- Lack of epidemiological evidence
- Poor communication
- Differing thresholds for action

Furthermore, healthcare setting and sophistication of regulatory systems differ radically between regions. Risk management strategies that may be successful in one region may not transfer well to a different setting. The following table gives examples of international risk management planning.

Examples of International Risk Management for Selected Drugs

Product	Key Issues
Cisapride	Inconsistent, non-robust responses to unsuccessful risk minimization efforts due to lack of epidemiological evidence of a favorable risk-benefit balance.
Dofetilide	Mandatory implementation of a restrictive risk management plan proved inhibitive and costly to prescribers and companies in the US, while EU regulators have an unrestricted license (now withdrawn by MAH due to US situation).
Isotretinoin	Proactive data collection around the world allows consistent understanding of risks and benefits of drug and RM, and revision of programs to suit setting.
3rd-generation oral contraceptives	Poor communication, differing thresholds for action, and inconsistent evaluation of risk-benefit tradeoff, plus caused public health scares in some regions.
Thalidomide	Mandatory registries allow consistent collection of data from EU and US and successful RM with no fetal exposures in over 80,000 treated patients.
Bosentan	Well-designed RM tailored to US and EU setting resulted in early full licensing: in US, mandatory prescriber training and patient tracking; in EU, controlled distribution and voluntary prescriber tracking, totalling over 16,000 pt/years use.

RM = risk management; MAH = Marketing Authorisation Holder

CONCLUSIONS: Examination of case studies showed that discrepancies may be due to differences in health care systems, regulatory procedures, culture, and lack of evidence. While recent international guidance on risk management, such as ICH and CIOMS guidance, may improve international communication, collaboration, and consistency, the appropriateness and effectiveness of risk management interventions in different regions should be examined and international strategies fine-tuned for each regional healthcare setting. A key area of improvement is the implementation of proactively planned and systematic conduct of safety research.

Hirst C, Cook S, Dai W, Perez-Guttham S, Andrews E. A call for international harmonization in therapeutic risk management. *Pharmacoepidemiology and Risk Management* 2006; 15(12): 839-49.