

THE REGULATOR'S APPROACH TO THE SAFELY AND EFFICACY OF NEW MEDICINES HINDERS THE DEVELOPMENT AND SUPPLY OF NEW AGENTS (YES)

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This session will review the current international legislation and objectives of the regulation of medicinal products so that new medicinal therapies have an acceptable and appropriate safety and efficacy profile. Regulatory regimes have to ensure that the correct balance is struck between commercial investment needs of the development of innovative therapies and the overarching needs of the public for safe and effective medicines.

Before thalidomide there were no effective legislative regulatory regimes for medicines. Thalidomide was the catalyst for the generation of the European Medicines Directive and the European Product Liability Directive. The disaster recognised the need for pre-clinical toxicology and evaluation of teratogenic potential of new compounds. Overall the disaster led directly to statutory regulation for the effective control of drugs. These included standards for the clinical demonstration of safety and efficacy, comprehensive regulation of the requirements for safety, efficacy and quality when determining an application, procedures for the suspension revocation and variation of licences, the administration and performance of clinical trials, promotion and advertising and enforcement of the regulations. In parallel a body of law on consumer protection/product liability and product safety law was promulgated. Data, statistical analyses and evaluations of efficacy and safety are submitted to the regulatory authorities for their assessment of risk and benefit.

Despite the ever increasing breadth and depth and intensity of this regulatory legislation and scrutiny worldwide, manufacturers and regulators have failed to make an appropriate evaluation of risk: benefit. We will discuss several examples where these regulations have failed, for example Vioxx, seoxat, and TGN1412.

These examples of difficult and ultimately erroneous decisions regarding causation and risk: benefit of drug-induced adverse events, illustrate a common theme. The statistical and epidemiologic methodology for attributing causation and measuring the strength of associations and causal relationships are highly useful and practical in achieving robust and practical conclusions. However, the methodology is only as good as the integrity, comprehensiveness and quality of the data analysed. A common theme running through the Vioxx and Seroxat examples is that in each case allegation have been made that the manufacturer may have failed to report material data to the regulator. If that is right, whether this was the result of a deliberate attempt to mislead or inadvertent errors matters not. The fact that the regulator had to work with erroneous and incomplete databases led to false assumptions as to causation of injury, adverse events and risk: benefit.

The case of Vioxx in particular represents the lost opportunity of a major advance in therapeutics. Similarly the damage to the therapeutic credibility of the anti-psychotic/ major antidepressant Sertindole by inappropriate regulatory conclusions on the potential clinical importance of observations of a low relative risk of prolonged QT interval exemplify the problems of a large and rigid bureaucracy incapable of the need to respond to individual problems of risk: benefit on a sui generis basis. In particular it should never be forgotten that the iconic drug disaster of the 20th Century was resolved not by layer upon layer of regulatory bureaucratic and resource intensive methodology and infrastructure but by simple yet sound and robust clinical observation.