Pharmacovigilance and Risk Management

Uwe Trinks, CIO Sentrx

PRISM Forum Special Interest Group

BMS, Lawrenceville, NJ, 21./22. October 2003

sentrx
safety matters

Acknowledgements

- Peter Honig, Global Head Risk Management, Merck&Co., former Head of Safety, FDA
- John Balian, Head Clinical Safety and Epidemiology, Pfizer
- Gerald Faich, former Head of Safety, FDA

“All medications are safe. They’re only toxic in humans.”

Gerald Faich, MD, MPH
Sentrx BOD member
former head safety, FDA

sentrx
safety matters

Public Citizen's Website

Risk Management

- Catch the snowball before it becomes an avalanche
- Analyze trends and spot signs before there are too many serious events
- Manage towards prevention
- Drive the process, don’t be driven by it

SADRs and their source

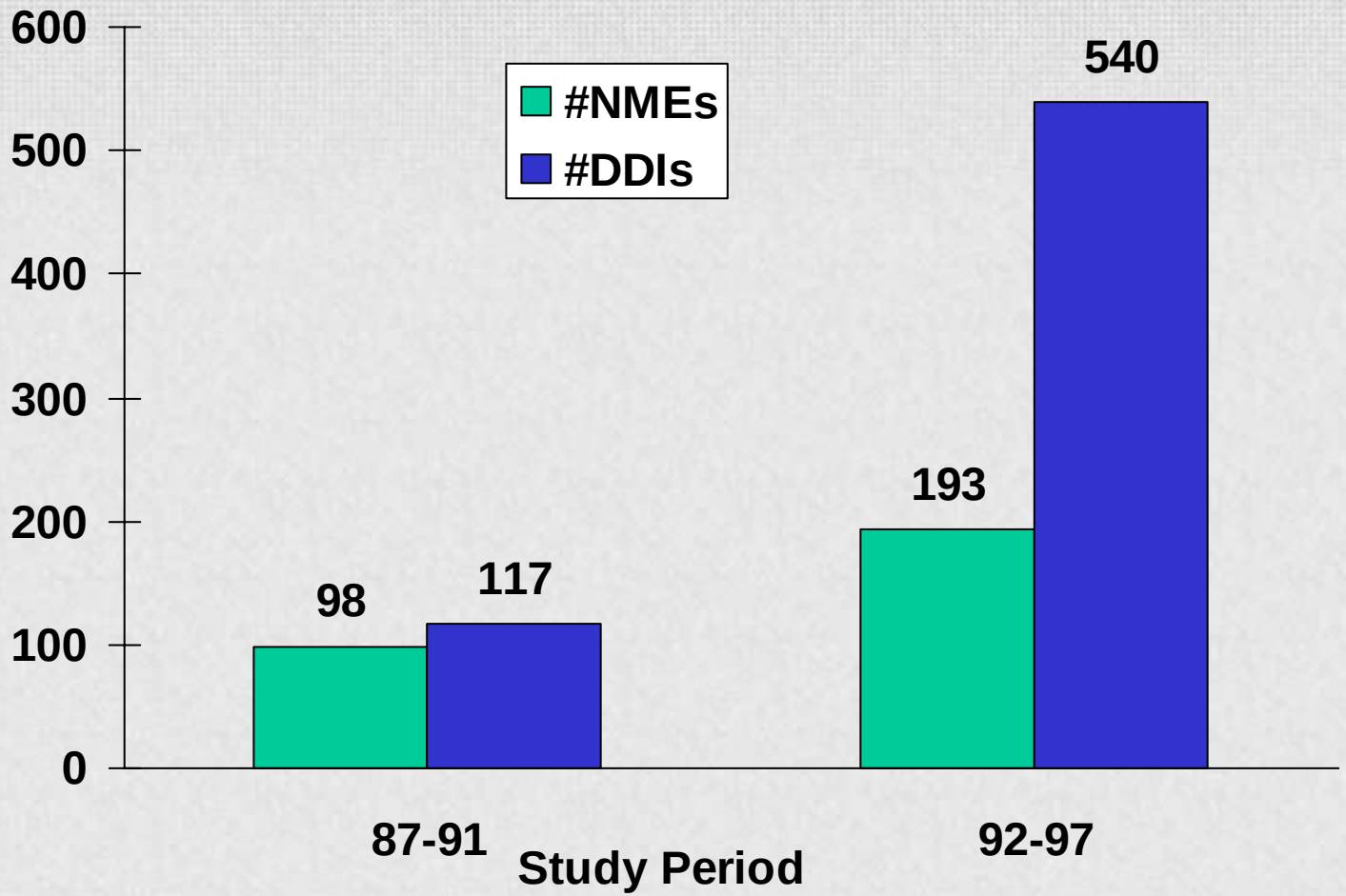
- Not Drug related
  - Disease related
  - Treatment-related (Hospitalization etc.)
  - Accidents
  - Suicide Attempts
- User or Physician “Errors”
  - Medication Error (Wrong Fulfillment)
  - Malprescription, Off-label Use
  - Intended Overdose (Non-compliance, Suicide Attempt)
  - Accidential Overdose (Non-compliance, Patient Education)

SADRs and their source

- Drug Titration Problems
  - Slow Metabolism
  - Multi-Drug Regimen (Each Enzyme Substrate is also an Inhibitor)
  - Nutritional Influences (Grapefruit Juice)
  - Gender/Racial Gap
- Drug/Drug Interactions (Fen-Phen)
  - Rare, but usually serious
  - Can happen to established drugs
- Genetic Susceptibility
  - Rare, but usually serious
  - Class related (e.g Rhabdomyolysis for Statins)
  - Drug related (specific metabolites etc.)

Response to Risk: DDI Studies

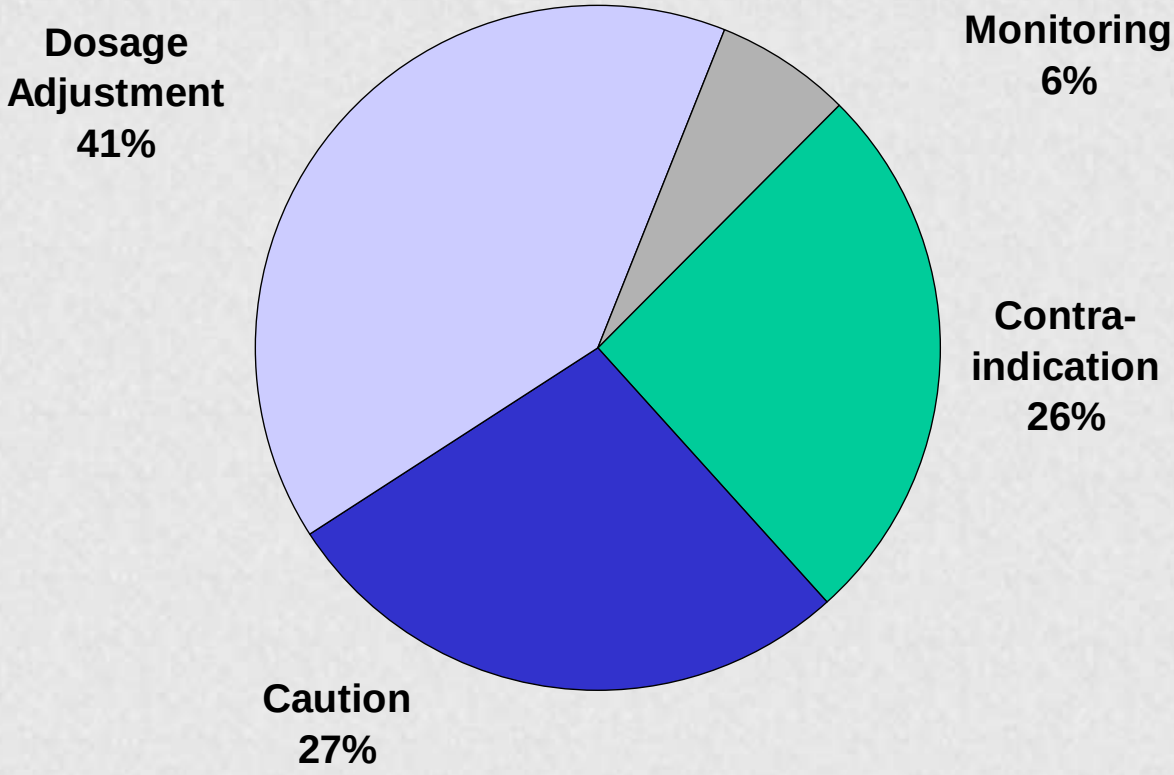
(Marroum, Balian, et al. CPT 2000)



Clinical Relevance of DDI

(Marroum, Balian, et al. CPT 2000)

28% of DDI studies found a drug-drug interaction
14 % of DDI studies resulted in a clinically relevant recommendation



The Genomics Promise

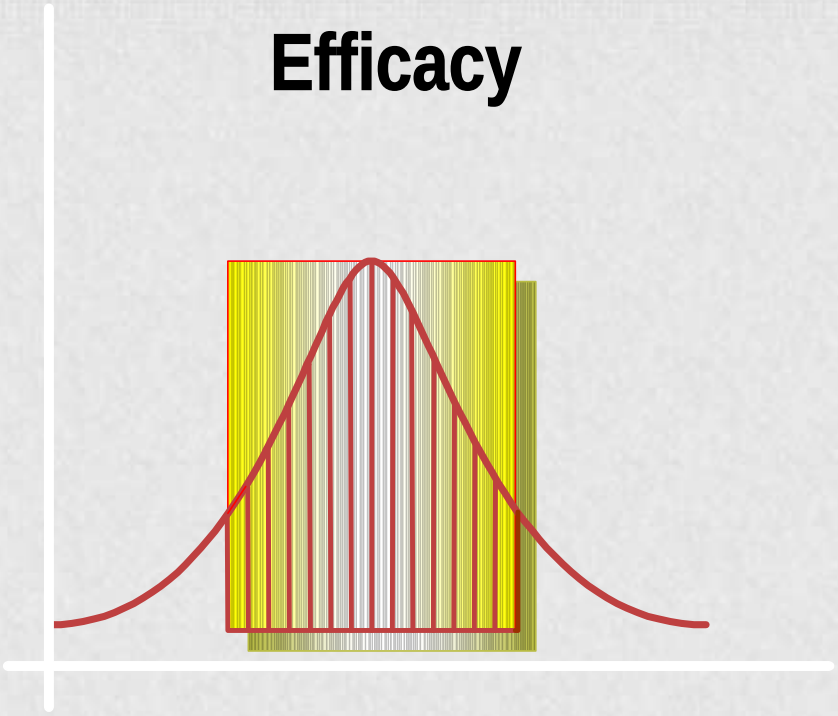
- SNP (Single Nucleotide Polymorphism)
  - Human Genome 3 Gigabases
  - Large Portions are Introns = Not expressed
  - SNP about every 1000 Base
  - Rapid hybridization (18-mers) allow fast analysis
  - Genotypes determine Phenotypes
- Many Adverse Reactions are dependent on Phenotypes
  - Susceptibility probably combination of SNPs
  - AE probably result of interference with major pathway
  - Similar SNP pattern very likely
- Once a pattern is found it is
  - Relatively easy to develop a lab test
  - Possible to determine the interference and develop better drugs

The Genomics Problem

- Finding a statistical relevant sample
  - Established Drugs withdrawn for 80-100 related deaths out of 1.8 Million Patients
  - Usually life-threatening diseases with multiple other causes
  - Filtering out all the non-Phenotype related causes
  - Post-Marketing Surveillance not reliable (3-5% initially)
- Getting Medical Data
  - Clinical Trials Numbers too low (several 1000 patients)
  - Patient Privacy Laws (HIPAA, EU Safe Harbor Act etc.)
  - Lawyers preventing lab tests
- Time Factor
  - Drug is on the Market
  - Large diverse population exposed

Looking for the Outlyer

Efficacy vs. Safety



Safety versus Efficacy

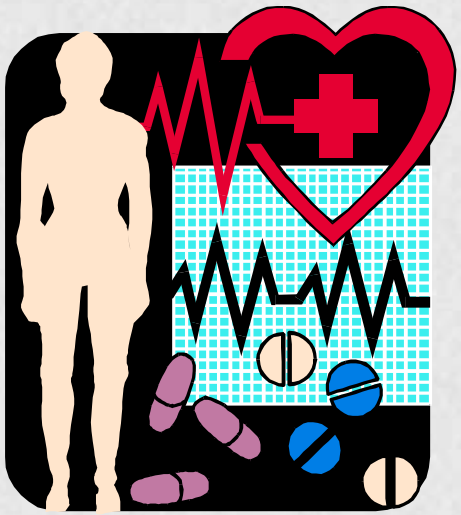
Safety

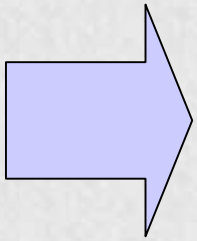
- Spontaneous
- Case driven
- Small # Statistics
- Unstructured data (Events)
- Medical Knowledge
- Unexpected
- Negative Result
- Individual dependent
- No final answer

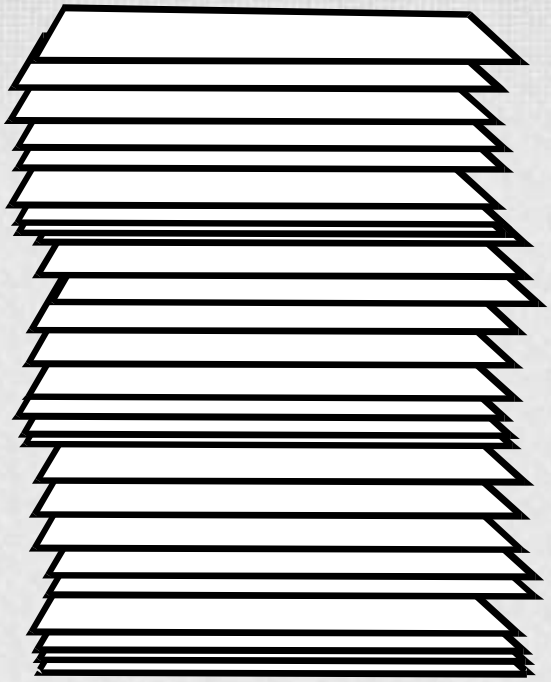
Efficacy

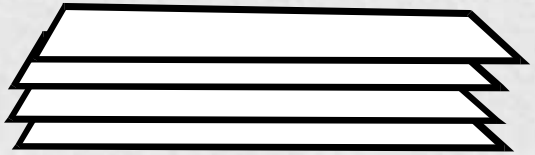
- Defined End Point
- Study driven
- Big # Statistics
- Structured data (Results)
- Data Management
- Expected
- Positive result
- Mass dependent
- Marketable result

Clinical Data Management (Per Patient)









Efficacy (CRF)

Safety (SAE)

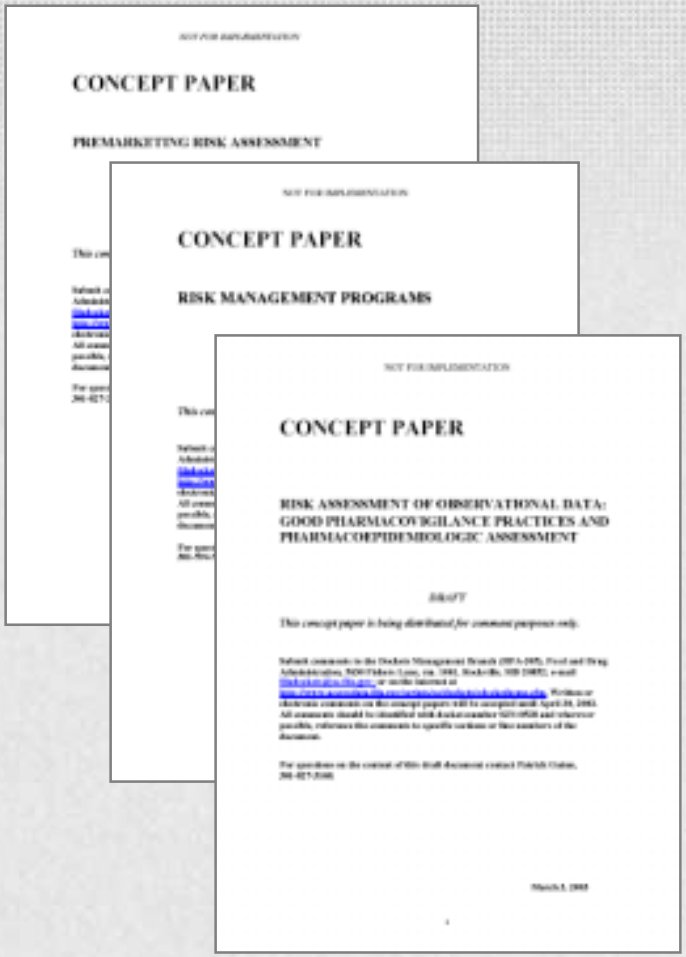
The Regulatory Environment

“FDA’s Motto”

In God we trust,

all others need to bring data!

FDA Risk Concept Papers



FDA Concept Papers Issued March 2003

- Pre-Marketing Risk Assessment
  - Risk assessment concepts
  - Sources and use of safety data
- Risk Assessment of Observational Data
- Risk Management Programs
  - Design considerations
  - Criteria for and Selecting Interventions
  - Evaluation
- Pharmacovigilance and Pharmacoepidemiologic Assessments
  - Concepts
  - Signal identification
  - Interpretations

PDUFA III

- Shared Safety Reviews/Targeted Surveillance Strategies
- Risk management plan will be expected to be submitted with NDA
- Pre-NDA/BLA Meeting (ODS/CDER participation)
  - Define/quantify risks of potential concern
  - Assessment of RM tools
  - Suggestions for observational and phase 4 studies, if warranted
- NDA/BLA Review of Risk Management Plan (ODS/CDER)
- Peri-approval submission and review activities

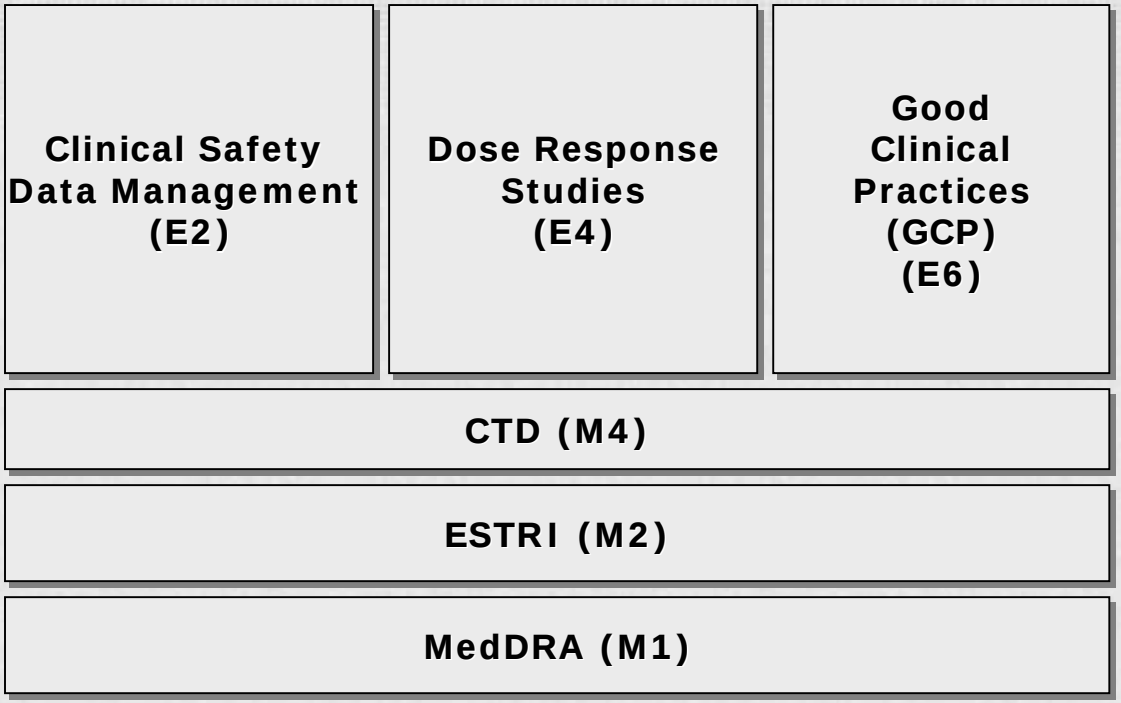
EMEA Pharmacovigilance Working Party

- Good risk assessment practices for regulators
- Good risk assessment practices for industry
- Good risk management/communication practices

ICH V3

- International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
- Prospective Planning of Pharmacovigilance (PPP)
- Harmonization of the principles is important
  - Structured approach to establishing and documenting risks
  - How to plan for PV activities
  - Design and conduct of postapproval safety studies (observational and prospective)
- Critical building blocks for risk management and risk communication activities

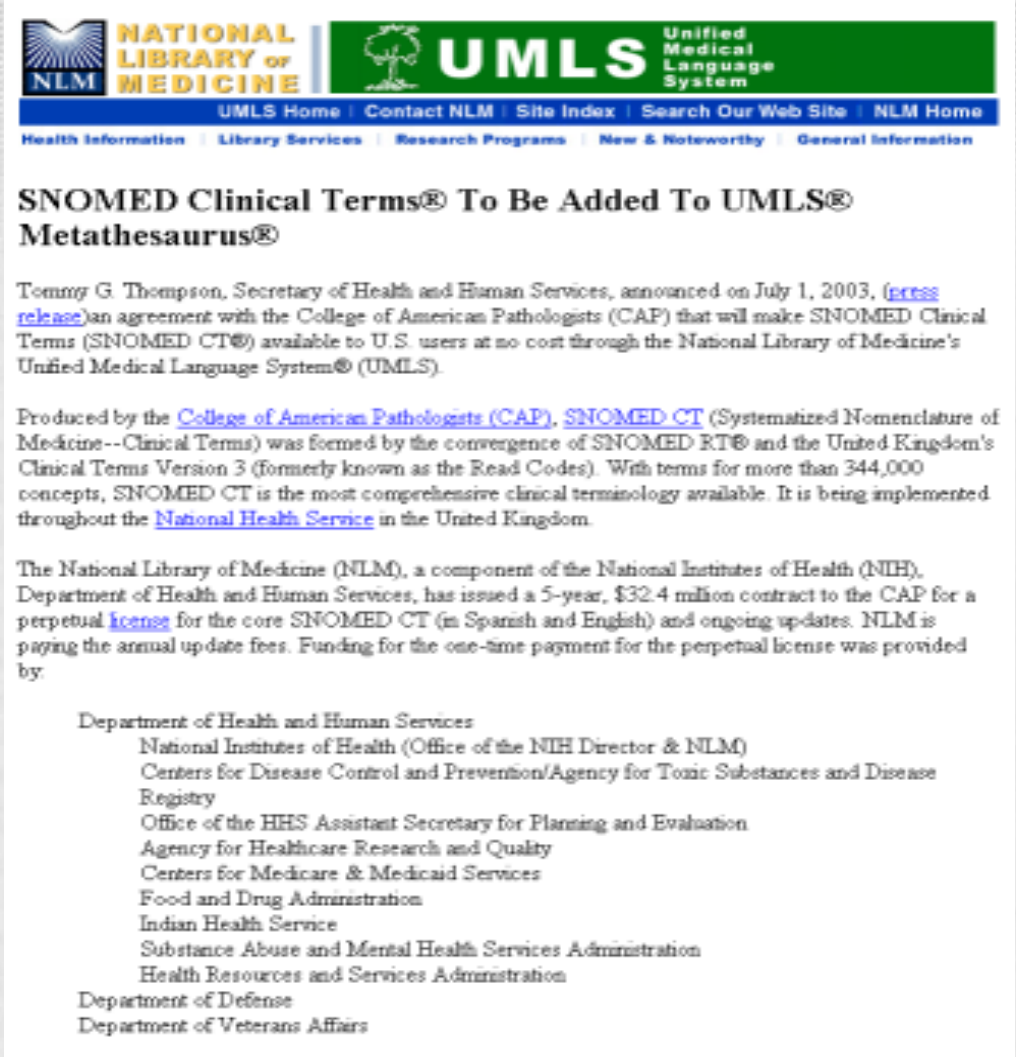
Example of ICH Initiatives



Other Important Initiatives

- WHO Council for International Organizations on Medical Sciences (CIOMS) V
- FDA's proposed Rule on Safety Reporting "The Tome"
- ICH E2E Pharmacovigilance Planning (proposed)
- Volume 9 of "The Rules governing Medicinal Products in the European Union"
- Health Insurance Portability and Accountability Act (HIPAA)
- EU Safe Harbor Legislation, such as the UK Data Protection Act
- FDA SNOMED (Systemized Nomenclature of Medicine) Initiative

SNOMED?



NATIONAL LIBRARY OF MEDICINE | UMLS Unified Medical Language System

UMLS Home | Contact NLM | Site Index | Search Our Web Site | NLM Home

Health Information | Library Services | Research Programs | New & Noteworthy | General Information

SNOMED Clinical Terms® To Be Added To UMLS® Metathesaurus®

Tommy G. Thompson, Secretary of Health and Human Services, announced on July 1, 2003, (press release)an agreement with the College of American Pathologists (CAP) that will make SNOMED Clinical Terms (SNOMED CT®) available to U.S. users at no cost through the National Library of Medicine's Unified Medical Language System® (UMLS).

Produced by the College of American Pathologists (CAP), SNOMED CT (Systematized Nomenclature of Medicine--Clinical Terms) was formed by the convergence of SNOMED RT® and the United Kingdom's Clinical Terms Version 3 (formerly known as the Read Codes). With terms for more than 344,000 concepts, SNOMED CT is the most comprehensive clinical terminology available. It is being implemented throughout the National Health Service in the United Kingdom.

The National Library of Medicine (NLM), a component of the National Institutes of Health (NIH), Department of Health and Human Services, has issued a 5-year, $32.4 million contract to the CAP for a perpetual license for the core SNOMED CT (in Spanish and English) and ongoing updates. NLM is paying the annual update fees. Funding for the one-time payment for the perpetual license was provided by:

- Department of Health and Human Services
  - National Institutes of Health (Office of the NIH Director & NLM)
  - Centers for Disease Control and Prevention/Agency for Toxic Substances and Disease Registry
  - Office of the HHS Assistant Secretary for Planning and Evaluation
  - Agency for Healthcare Research and Quality
  - Centers for Medicare & Medicaid Services
  - Food and Drug Administration
  - Indian Health Service
  - Substance Abuse and Mental Health Services Administration
  - Health Resources and Services Administration
- Department of Defense
- Department of Veterans Affairs

Risk Management

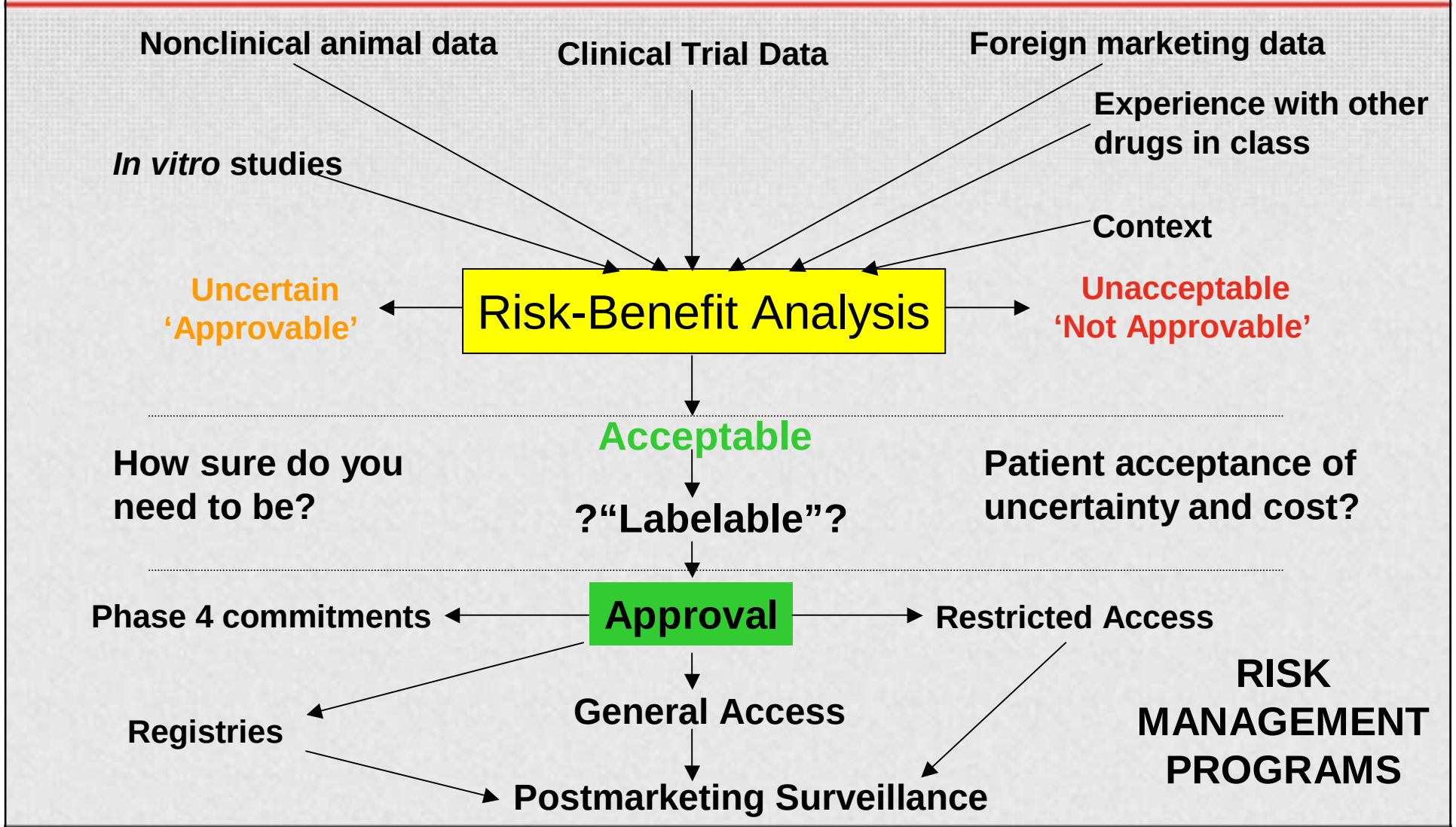
The Basics of Risk Management

- Effective drugs have been withdrawn because of preventable adverse reactions that have tipped the benefit:risk balance
- Industry is incorporating formal risk management concepts into product development
- Robust risk assessment is the foundation of rational drug development and risk management
- ‘Labelability’ and previous experience with the system being able to manage risk:benefit are factors in considering a drug for approval
- The game is won and lost in before the drug is licensed

an Innovative Solution?

Risk-Benefit Management: “Tolerable Uncertainty”

(P.Honig, DIA 2003)

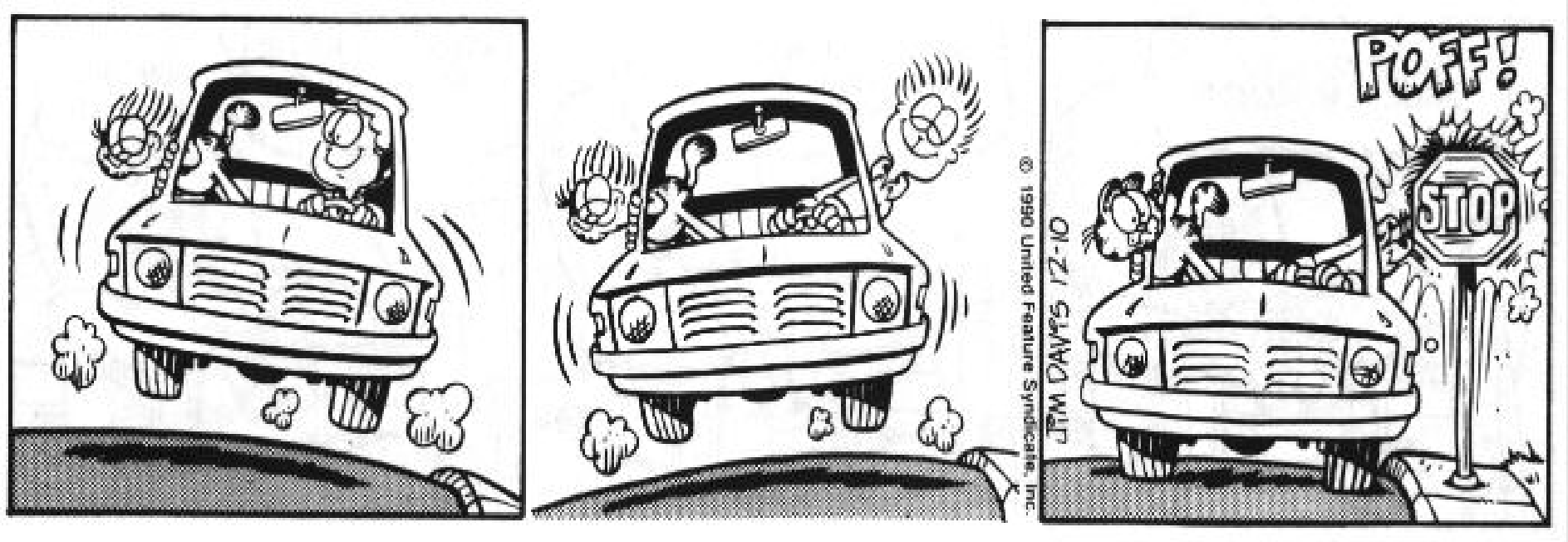


sentrx safety matters

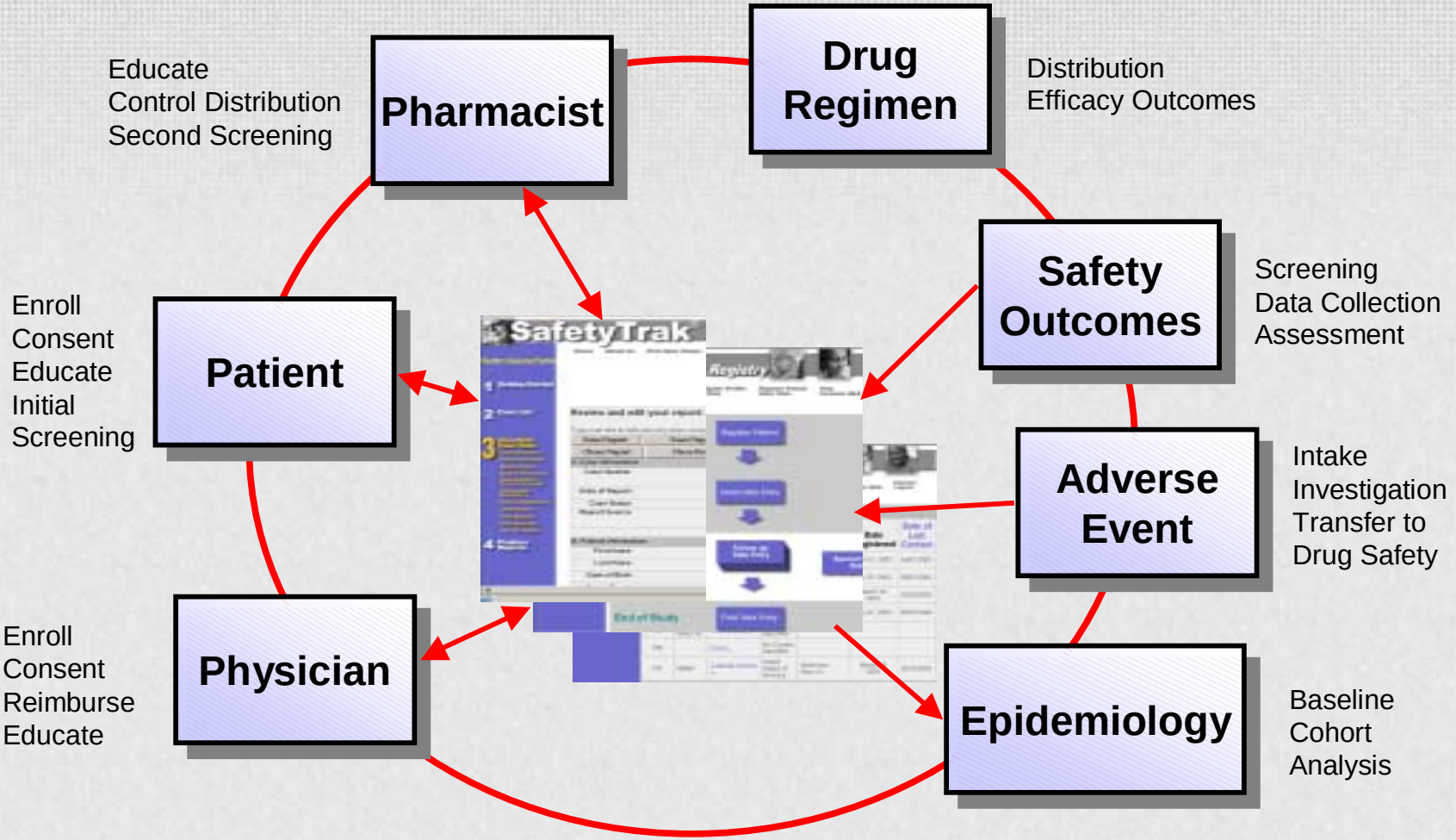
Risk Management Programs

- Labeling, +/- ‘directive monitoring’
  - Remains primary risk management tool
- Patient Package Inserts & Medication Guides
  - Effect on patient behavior unknown, Penetration and impact unquantified
- Patient registries
  - Useful for tracking outcome and processes of risk management interventions
  - Don’t manage risk *per se*
- HCP education/certification
  - Suggestive evidence they limit drug use
  - Typically a part of restricted distribution
- Restricted distribution programs
  - Apparently effective in reducing AE
  - Difficult to implement for already-approved products
- Linked prescribing/dispensing to lab tests
  - Closest to foolproof, but large investment/burden
  - Used for uniquely efficacious drug products *in lieu* of withdrawal or non-approval

What suits one program might not suit the next...



A typical Risk Management Solution



The IT Challenge

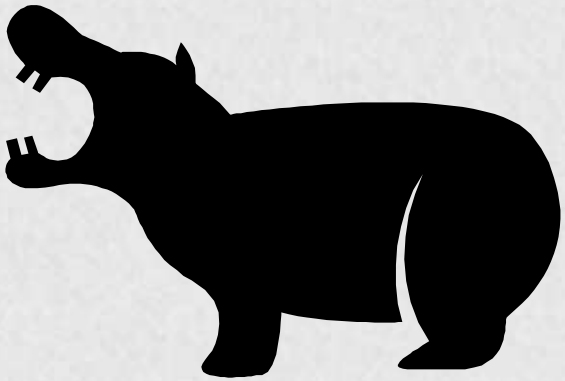
- Large existing Pharmacovigilance Systems
  - Validated, slow moving change management
  - Used by Clinical (reconciliation with CDMS) and Post-Marketing
  - Systems Upgrades and Dictionaries Maintenance
  - Global Reporting Requirements
  - Largely used by HCPs
  - Not suitable for Risk Management
- Rapidly Changing Regulatory Environment
  - Bipolar (FDA – EMEA)
  - Risk Averse (for good reasons)
- Rapidly Changing Healthcare Landscape
  - Mail-order Drugs
  - Nutraceuticals
- Rapidly rising importance of Drug Safety/Risk Management

The IT Challenge II

- Risk Management Concepts in Flux
  - Drug specific
  - Usually negotiated with Regulators pre-NDA
  - Little IT involvement
  - Little Pre-Planning
- Difficult Global Implementations
  - CCSI vs local Label
  - Extensions of Use
  - Regional HCP environment
- Organizational Challenge
  - Who owns Risk Management?
  - Who wants to own Risk Management?
- Funding

Security/Privacy Challenge

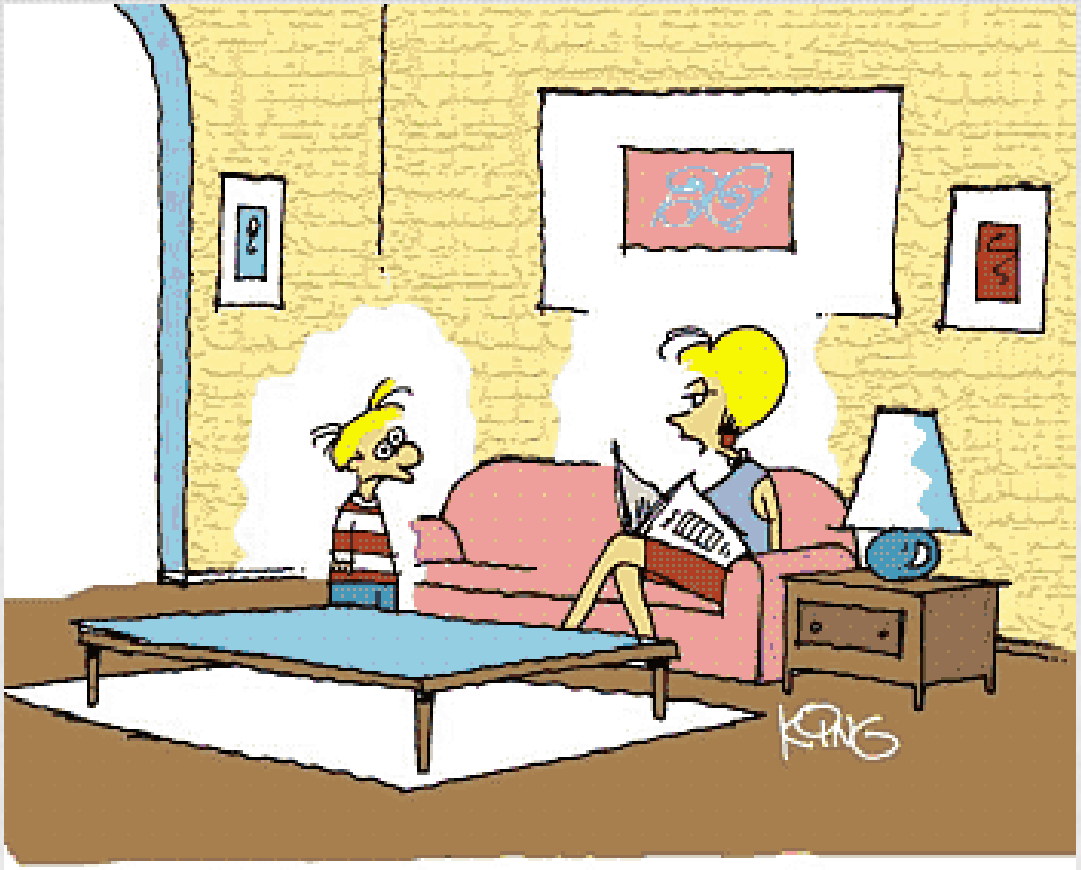
- 21 CFR Part 11
  - New FDA Guidance Document
  - *http://www.fda.gov/cder/guidance/index.htm*
- HIPAA
  - Security Rule (April 20, 2005)
  - Privacy Rule (April 14, 2003)
- European “Safe Harbor Regulation”
  - E.g. UK Data Protection Act of 1998, 8th Principle



The answer

Your Turn!

The next Generation….



"No, you weren't downloaded.
Your were born."

uwe.trinks@sentrx.com

sentrx
safety matters