Pharmacovigilance: The Way Ahead

Swimming Upstream in Muddy Waters

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Goals of Pharmacovigilance

- **Identify new safety hazards or changes in risk/benefit profile (normal clinical use)**
- **Assess risks & benefits to determine what action may be necessary**
- **Provide information to users to optimize safe & effective use**
- **Monitor impact of any action taken**
- **(Now called “Risk Management”)**

Waller, P.C. et al, Pharmacoepidemiology & Drug Safety 5(6):363-77, 1996

The Risk-Benefit Assessment Continuum

The River of Life (metaphor after William Blake)

Along the river of drug development, from the well spring (test tube) to the mouth (marketing), we encounter valuable landmarks (villages) that provide great potential wisdom.

“To see a world in a grain of sand…”

Nota bene –

“The hours of folly are measured by the clock: but the hours of wisdom, no clock can measure.”

Bergson

The River of Drug Development

The Drug “Cholestop” is floating along -

- In the first village (*in vitro*), tests in liver cells tell us the mechanism of action of Cholestop; it interferes with cholesterol metabolism, but not by inhibiting HMG-CoA reductase
- (this is good, it’s not another statin)
- Some crystal deposits are noticed in liver slice experiments

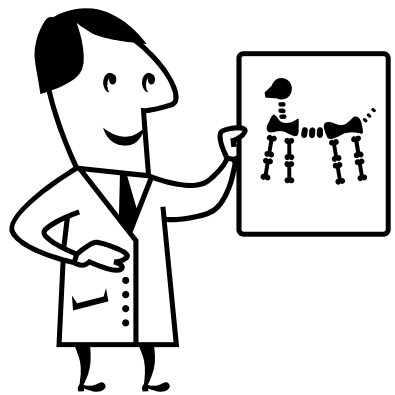
The River of Drug Development

The Drug “Cholestop” is floating along

In the second village, pharmacology, we learn that Cholestop prevents cholesterol from adhering to blood vessel walls; it also seems to re-distribute the cholesterol into other parts of the body, and/or into the bowel.

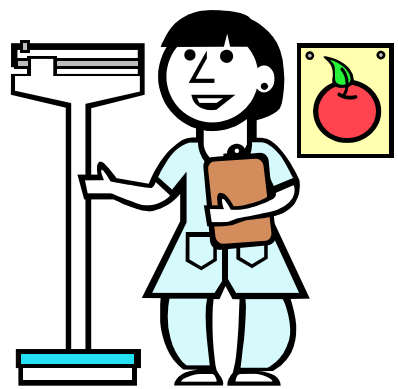
The River of Drug Development
The Drug “Cholestop” is floating along

- Toxicology, the third village, shows us that rats and mice (genetically hypercholesterolaemic) may live slightly longer since cholesterol is not deposited in blood vessels.
- Rabbits show signs of “visual disorders”, some have shiny eyes.



The River of Drug Development
The Drug “Cholestop” is floating along

- We begin our visit to “clinical trials”, even though the toxicology is not complete.
- Some patients in clinical trials experience steatorrhea (fatty bowel movements), but are otherwise “very healthy”.
- Longer term trials are planned next

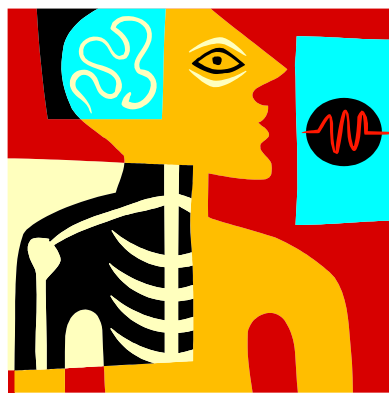


The River of Drug Development
The Drug “Cholestop” is floating along

- In the village of “shall we market this drug?”, the council of elders makes a decision:
  - Animal studies showed that cholesterol is not deposited in vessels, and rats live longer.
  - Patients are doing well in clinical trials
- It’s a go!

The River of Drug Development
The Drug “Cholestop” is floating along

- Our last village (at the mouth of the river) is Pharmacovigilance –
- Case reports indicate that patients taking Cholestop experience fatty diarrhea, diminished fat-soluble vitamin levels, and there are a few cases of cataracts (with crystalline deposits)
- Liver function tests are also troublesome in some patients



The River of Drug Development
The Drug “Cholestop” is floating along

- “Consulting as One Man above the mountain of Snowdon”…Blake, The Four Zoas.

- You weren’t paying attention to the wisdom of the various villages, in vitro, pharmacology, toxicology, clinical trials; they predicted what you see in Pharmacovigilance….

The New Era of Regulatory Harmonization and Risk Management (muddy waters)

- ICH – New Guidelines venturing into pharmacovigilance:
  - E2D - Post Approval Safety Data Management: Definitions and standards for expedited reporting
  - E2E - Pharmacovigilance Planning
- FDA proposed new Rule governing the reporting of safety information from clinical trials and marketed products

ICH E2D – Post Approval Safety Data Management:

Definitions and standards for expedited reporting

- New draft Guideline (Step 4) based on CIOMS V
- Practical suggestions for improving data management – good case management practice
- Definitions & terminology associated with post-approval drug safety experience (contrast to E2A which dealt with pre-approval data)
- Guidance for spontaneous cases, HCP & consumers; definitions for valid reports; other issues regarding literature reports; solicited reports; licensee-licensor interactions and regulatory authority sources
- Standards for expedited reporting –what & when to report; reporting timeframes and assessing reporter/patient identifiability

A few observations on ICH-E2D
Anything new or helpful?

- Refinement of E2A, explicitly for post-approval reporting
- Definitions supposed to add clarity
- Distinguishes Adverse Event and ADR
- For ADRs, acknowledges “regional regulations, guidance & practices”, i.e. FDA ain’t doin’ the ADR thing…

A few observations on ICH-E2D
Anything new or helpful?

- What to report – Expedited reports
  - Report all serious-unexpected ADRs
  - Serious-expected ADRs, where required

  [Weren't we trying to harmonize this stuff?]

  Report other observations… that could change the risk/benefit evaluation….suggesting a significant human risk

A few observations on ICH-E2D
Anything new or helpful?

- Good case management practices
  - Patient/reporter “identifiability” – local data privacy laws…might apply
  - One or more of these should automatically qualify a patient as “identifiable”:

Age (or category, e.g. elderly); gender, initials, DOB, name, patient ID No.

? Do you like a case report stating “an elderly patient experienced….? Is there any value in gathering vague data?

ICH-E2E Pharmacovigilance Planning PvP

- Newest initiative at ICH
- Early PV Planning to reduce risk and increase public health benefit
- Guidance for industry to develop PV plan for discussion with regulators during licensing assessment and before launch
- Scope to include new chemicals & biologics, new formulations, new indications & patient populations
- Output for industry to submit at time of licensing:
  - Document detailing PV specification & PV plan

ICH-E2E Pharmacovigilance Planning

- PV Specifications
  - Documents established risks – what has been studied
  - Unidentified risks - What has not been studied*
  - At risk populations
  - Situations not studied i.e. use in children

- PV Plan
  - Proposal for data collection post-approval
  - Describe milestones aligned with PSURs
  - Could state that routine PV is all that is required

Not á la Rumsfeld – we know what we know, and we know what we don't know, but we don't know what we might not know.....

What to Expect – when you're drug reaches the market

- New and Rare ADRs
- New risk groups and risk factors
- Drug interactions

From – Kusuri Canada Pharmacovigilance Training Course

And now, for something completely different -

- FDA proposed new Rule governing the reporting of safety information from clinical trials and marketed products
- 500 page document
- Entitled “Safety Reporting Requirements for Human Drug and Biological Products”
- Aims
  - harmonization with ICH standards
  - Improve quality of safety reports to FDA
  - Reduce the incidence of hospitalizations related to ADRs and medication errors

Highlights of FDA proposed new rule

- Expedited reporting
  - New definition **suspected** ADRs = **S**ADRs as causality “cannot be ruled out”
  - Medication errors
  - “always expedited” reports whether serious or non-serious
- Periodic reporting
  - Accept ICH PSUR timeframes, in addition to 7.5 and 12.5 yr; traditional PSR, Interim PSR
- Improved quality of data
  - Active query on all serious reports
  - Minimum and full data sets for all medication errors; all serious SADRs
  - MedDRA coded reaction terms (but watch SNOMED)
  - “licensed”physician responsible for the quality of reports

FDA Current & Proposed Expedited Safety reports

Current expedited report	**Proposed expedited report**	**Submission time frame**
Serious and unexpected adverse experience reports	Serious and unexpected SADR	15 calendar days
new	Medication errors – actual & potential	15calendar days
`` ``	Always expedited	15 calendar days
	Unexpected SADRs with unknown outcome	45 calendar days

SADRs that will be “Always expedited”

- Congenital anomalies
- Acute respiratory failure
- Ventricular fibrillation
- Torsades de pointe
- Malignant hypertension
- Seizure
- Agranulocytosis
- Aplastic anemia
- Toxic epidermal necrolysis
- Liver necrosis
- Acute liver failure
- Anaphylaxis
- Acute renal failure
- Sclerosing syndromes
- Pulmonary hypertension
- Pulmonary fibrosis
- Transmission of infections by marketed product
- Confirmed or suspected endotoxin shock

FDA Post marketing Periodic Safety reporting: CURRENT

- Quarterly/Annual Periodic report
- Descriptive information
  - Narrative summary and analysis of expedited reports submitted during reporting interval
  - History of actions taken
- Individual Case Safety Reports (in MedWatch)
  - Serious & expected AEs
  - All non-serious AEs

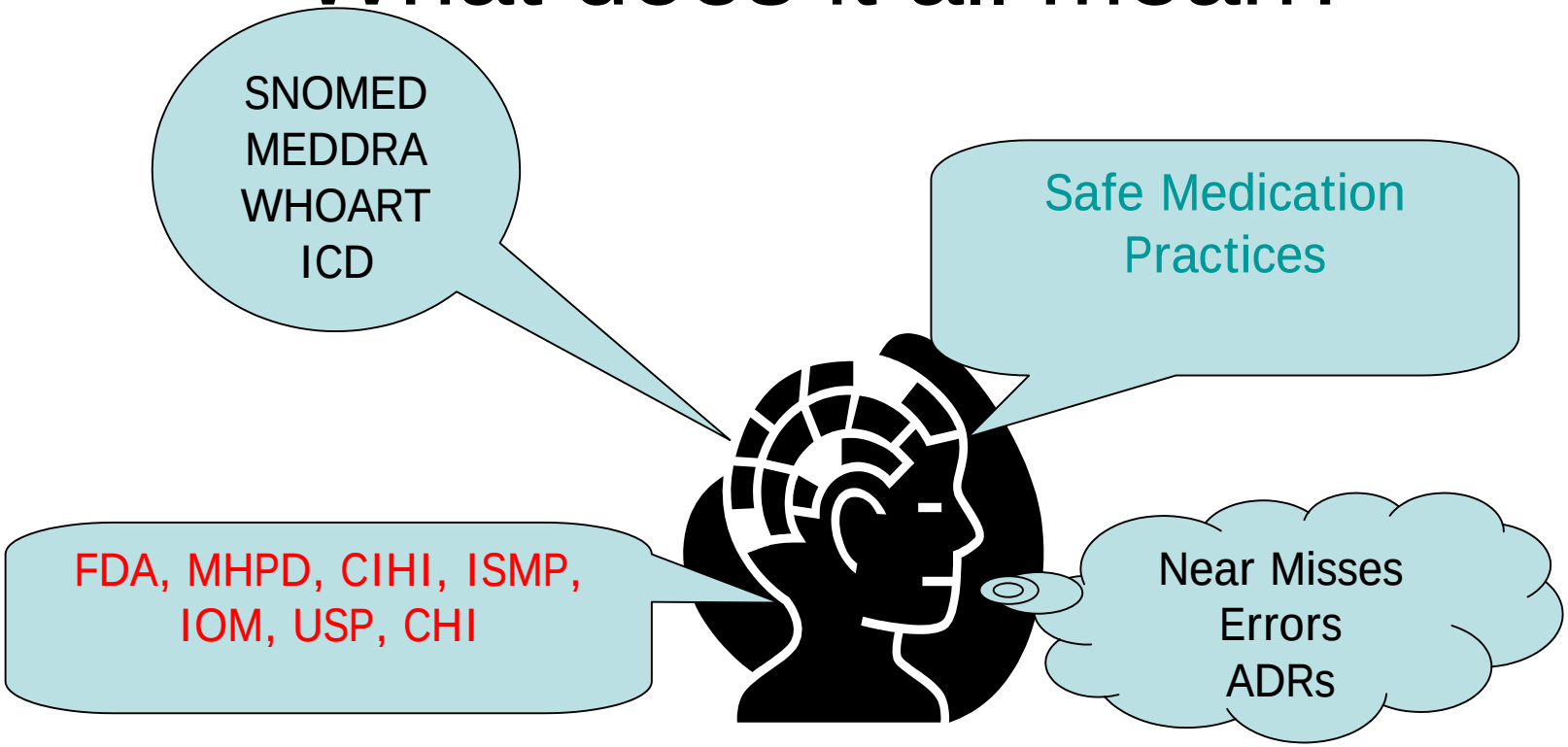
FDA Post marketing Periodic Safety reporting: PROPOSED

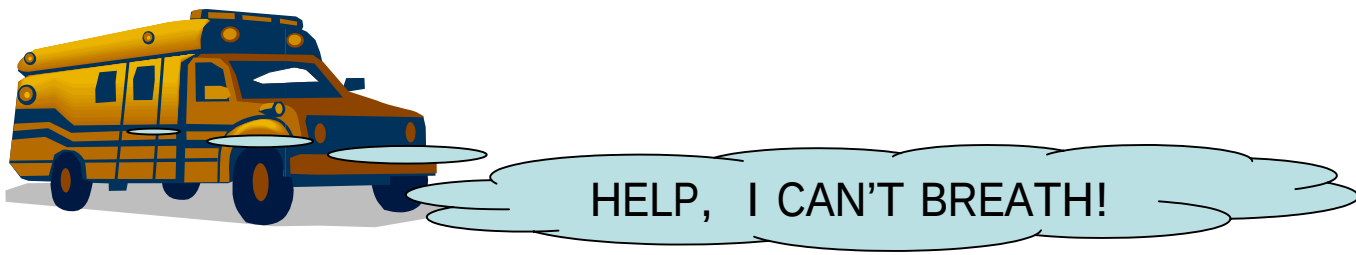
- Two separate reports
- Descriptive information
  - Traditional periodic safety report (TPSR)
  - Periodic safety update report (PSUR) – ICH q 6mos for 2 yr, annual for 3 years, then q 5 years
  - Interim periodic safety report (IPSR) at 7.5 & 12.5 years
- Individual Case Safety reports
  - No longer submit non-serious expected except for vaccines
  - Submit foreign serious, expected SADRs
  - Semi-annual submission

Meanwhile….

- There are other initiatives brewing in the US and Canada:
  - Patient safety: Achieving a new standard for care (IOM report)
  - CMIRPS (Canadian Medication Incident Reporting and Prevention System)

What does it all mean?





Does all this help in Risk Management?

- Principles of Risk Management –
- Identify
- Quantify
- Assess options
- Act
- Monitor actions

Risk Management -

- The physician decides to prescribe Cholestop
- Assesses patient characteristics
- Assesses drug characteristics
- Determines where potential conflicts may exists between 1 & 2

Risk Management

- Assess drug characteristics –
  - Known ADRs
  - Pharmacology; pharmacokinetics
  - ADME; interactions
- Assess population characteristics –
  - Subgroups at risk
  - Susceptibility factors
- Determine where conflicts exist

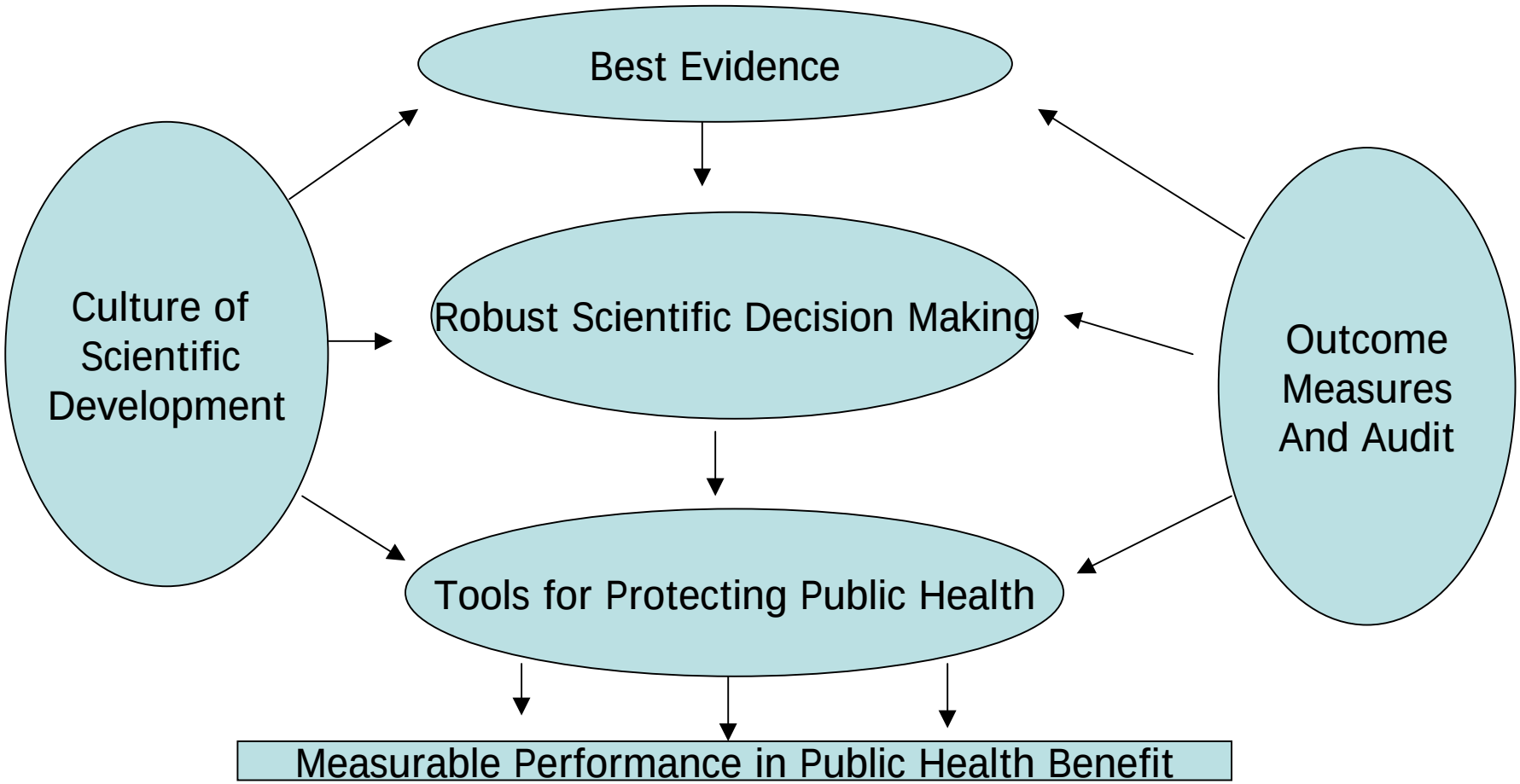
Risk Management

- A better approach would be to try to anticipate the question, generate data proactively and be able to address the question if it arises. When a question emerges from SRS, it is not enough to say only ‘these are poor and incomplete data’. Rather researchers should access other databases or conduct a prospective surveillance study to answer the question.

Risk Assessment of Drugs, Biologics and Therapeutic Devices; Present and Future Issues (Workshop on Risk Assessment, CERTs)

Pharmacoepidemiology & Drug Safety, 2003:12; 652-62.

The Future of Pharmacovigilance



Waller, PC and Evans, SJW, A Model for the Future Conduct of Pharmacovigilance

Pharmacoepidemiology and Drug Safety, 2003; 12:17-29

Risk Management

- If you’re drowning in terms and reporting requirements you might not be able to see the boat coming at you
- Confusion leads to delusion
- ICH-E2E will likely be helpful because it requires forward thinking!
- The concept of proportionate risk can be used in pharmacovigilance planning