

## Introduction to Pharmacoepidemiology

### Pharmacovigilance

2012 Mid-Year ISPE Meeting  
Miami, April 21-23, 2012

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### Conflict of Interest Declaration

- The opinions expressed in this presentation are those of the presenter and do not necessarily reflect those of the *Université de Montréal* or the *Government of Canada*.
- No other conflict of interest to declare.

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### Pharmacovigilance Definition

Science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem [WHO]

- Preventing harm from adverse reactions in humans arising from the use of authorised medicinal products within or outside the terms of marketing authorisation or from occupational exposure; and
- Promoting the safe and effective use of medicinal products, in particular through providing timely information about the safety of medicinal products to patients, healthcare professionals and the public.

EMA 2012 *Guideline on good pharmacovigilance practices (GVP)*

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## Important Concepts in Pharmacovigilance

### Adverse Event (AE)

Any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment.

### Adverse (Drug) Reaction (ADR)

A response which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.

### Causal relationship

A relationship between one phenomenon or event (A) and another (B) in which A precedes and causes B. In pharmacovigilance; *a medicine causing an adverse reaction.*

*the UMC (2012)*

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## Classification of ADRs

- Type A: **Augmentation** or exaggerated and dose related response (e.g. Digoxin toxicity, NSAIDs induced Lithium toxicity)
- Type B: **Bizarre** and unpredictable (e.g. Anaphylaxis & Penicillin, Aplastic Anemia & Clozapine)
- Type C: **Chronic** or long-term related (e.g. Drug tolerance; Withdrawal effects)
- Type D: **Delayed** (e.g. Cancer; Birth Defects)

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## Historical Perspective

### International Drug Monitoring

- 1961 The supposedly "safe" sleeping thalidomide pill disaster
- 1962 Request from the World Health Assembly to the WHO General Director to study ways to make drugs safer.
- 1967 The development of an "International System" was initiated (20<sup>th</sup> World Health Assembly)
- 1968 First country members: Australia, *Canada*, Germany, Netherlands, New Zealand, Sweden, UK and U.S.A.
- 1972 WHO Technical Report "International Drug Monitoring: The Role of National Centres"
  - Pilot results (30,000 case reports / 12 countries).
  - Reporting standards
  - Adverse reaction terminology
  - List of all drugs reported
  - Signal reports are regularly distributed to participant members

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**Some of the Reasons That Results of Randomized, Controlled Trials May Not Be Available for Assessment of Adverse Events Associated with Prescription Drugs.**

- Trials powered for efficacy may be too small to detect adverse events.
- Monitoring of adverse events may not be sensitive or specific for the actual events caused.
- Duration of trials may be too short for detection of events requiring longer exposure.
- Stopping rules in clinical trials may further shorten the duration of exposure after randomization.
- Enrollment criteria may exclude susceptible subgroups.
- For industry-sponsored trials, head-to-head comparison of adverse events due to drugs from different manufacturers may not be available.
- Follow-up studies to detect adverse events that involve the denial of an efficacious medication to patients may be deemed unethical. Patients may not wish to enroll in such a study.
- Funding to conduct trials solely to quantify adverse events may be difficult to obtain.

Hunter D. NEJM 2006

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**Clinical Trials: “Gold standard methodology” to study safety of drugs ?**

“Regardless of improvements that we may see in the area of measuring adverse effects, we think that regulatory agencies, authors of compendia, practicing physicians, and the general public must better appreciate the limitations of what can be learned about medication-related harms from randomized trials and other studies. *Case reports and observational studies will remain essential for identifying late appearing and uncommon serious adverse events*”

Ioannidis JP, Mulrow CD and Goodman SN. Editorial *Annals Internal Medicine*, 21 February 2006

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**Pharmacovigilance - Context**

...the study of the safety of marketed drugs under the practical conditions of clinical use in large communities

RD Mann & E Andrews. *Pharmacovigilance* (2007)



Data ☉

- ADR Reporting (ICSR; PSUR (PBRER))
- Phase IV studies (most often observational studies)

Analysis ☉

- Signal Detection (Identification)
- Signal Assessment

Risk Minimisation

- RMPs / REMS
- Benefit/Risk Assessment

Tools

- Multiple disciplines including medicine, pharmacology, PE, IT, statistics, etc.
- Communications
- Legal (Laws and Regulations)
- Crisis & Risk Management

Others

- Medication Errors
- Drug Abuse, Poisoning
- Drug Effectiveness

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## Data Elements for Transmission of ICSRs ICH Guideline E2B(R2)

**Administrative Information:** Country, report ID, type and date of report, source(s) of information, sender, etc.

**Case Information:** Patient, age, weight, height sex, relevant medical history & concurrent conditions

**Reaction(s)/Event(s):** Description, start & end reaction date, exposure-reaction interval and duration, lab tests & procedures, outcome (autopsy if fatal?).

**Drug(s) information** (both suspect and concomitant medications): Name, batch/lot #, indication, dosage & route of administration, start date, duration, action taken, rechallenge (and effect)?

**Sender or Reporter Comments**

The image shows a sample of the ICH E2B(R2) form, which is a standardized format for reporting individual case safety reports (ICSRs). The form is divided into several sections, including administrative information, case information, reaction/event information, drug information, and sender/reporter comments. The form is titled 'Canada' and includes a 'PROTECTED' stamp.

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## ADR Reporting Time Frames Expedited Reporting (ICH-E2A)

- Fatal or Life-Threatening Unexpected ADRs: ...ASAP but no later than 7d after first knowledge by the sponsor
- Serious and/or Unexpected ADRs: ...ASAP but no later than 15d after
- ...all other (PSUR)

### Minimum criteria for reporting (for regulatory purposes)

- Identifiable patient;
- Suspect medicinal product;
- Identifiable reporting source;
- Event or outcome that can be identified as serious and unexpected, and for which, in clinical investigation cases, there is a reasonable suspected causal relationship.

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## Imputability (Causality Assessment)

1. Global Introspection (e.g., WHO)
2. Algorithms (e.g., RUCAM)
3. Bayesian probabilities

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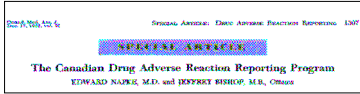
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## The Pigeonhole File System (1966)



" Upon receipt, the reports are acknowledged and filed in a "pigeonhole" file. Coloured markers are attached to reports of severe and unusual reactions; those reactions that resolved when the drug was discontinued and reappeared when the patient was rechallenged with the drug; reports of fetal abnormalities suspected of being due to a drug administered during pregnancy; and reports of deaths associated with the administration of a drug. This system of coloured markers facilitates surveillance of the files and provides an early alert to developing trends."



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## SIGNAL – CIOMS VIII (2010)

"Information that arises from one or multiple *sources* (including observations and experiments), which suggests a *new* potentially causal association, *or a new aspect* of a known association, between an intervention and an *event or set of related events*, either *adverse or beneficial*, that is judged to be of sufficient likelihood to *justify verificatory* and, when necessary, remedial actions."

Adapted from Hauben & Aronson. *Drug Safety 2009*

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## Characteristics of Signals

- Are working hypothesis
- May point to unknown adverse reaction associations for:
  - Old or new drugs
  - Drug-drug or other type of interactions
  - General or restricted group populations
- Are not by themselves proof of causal relationship
- Require always further evaluation
- May or may not lead to specific market interventions

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## Approaches for Signal Detection from ADR Databases

### TRADITIONAL

- Manual** review of all incoming reports by PV staff
- Structured** review of PV studies (PEM)
- Crude frequency counts and/or reporting rates**

### AUTOMATED

- Automatic / Periodic** screening of ADR-DB (PEM & SRS)
  - *Data Mining Algorithms (DMA)*: e.g.; PRR [UK], BCPNN [WHO], EBGM [FDA]
  - *Pattern recognition & Graphical display* of "outliers" (PEM & SRS)

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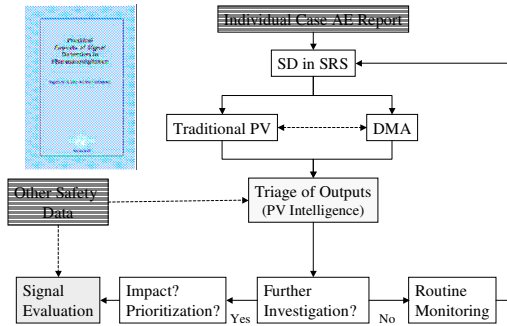
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## CIOMS VIII Signal Management Process




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## Future ADR Data Sources ?

**Spontaneous Reporting Systems**

**Administrative / Claims / Other Databases**

"...Automated signal detection (...and DMAs) can be applied to observational studies, drug utilisation studies and clinical trials."  
 Shakir, *SAW Drug Safety*, 2007, 30, 7, 603-606

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## Signal Assessment

“ Time and again there has been confusion, for regulators, companies or the media, following from the uncertain nature of signals generated by spontaneous reporting and the inherent limitations of the system to produce secure and quantitative information.

**Spontaneous reporting** has been designed as a system for **hypothesis generation** in the first place. As a rule, further study, using the most appropriate (and usually different) method, is needed to put the hypothesis to the test. ”

*Meyboon et al. 2002*

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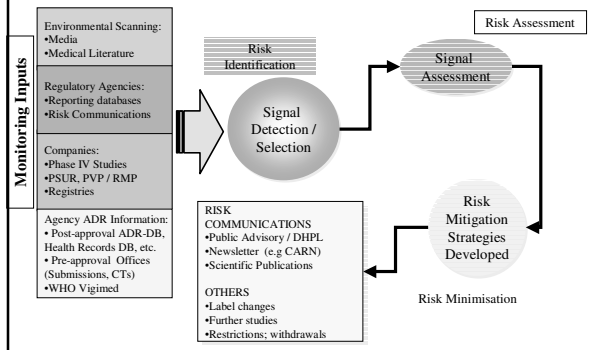
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## Post-Market Surveillance & Risk Management (Regulatory Perspective)



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**Muchas Gracias !**



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