Pharmacovigilance (PV) in the Philippine Setting

Noel Cruz MD
Developing a pharmacovigilance system in the Philippines, a country of diverse culture and strong traditional medicine background

Kenneth Hartigan-Go

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The Philippines PV System

• **February 1995**
  – Philippines obtained the status as member: Pharmacovigilance National Center
  – WHO Collaborating Center for International Drug Monitoring (now Uppsala Monitoring Center)
  – 1994-2002: 1600 reports/75 million population

• Aim- improve the quality of reporting (Thank you letters, follow-up letters, training (ADR or AE practical management, ADR prevention)
The Philippines PV System

• Started in **August 1994** to promote drug safety through ADR monitoring nationally (DOH, AusAID)

• Methods: training courses, notification system, hospital Therapeutics Committees, newsletters, ADR AV presentations

• Report form introduced

• Causality assessment process designed
CAUSALITY

1. Temporal relationship
2. Pharmacological/Biological Plausibility
3. Dechallenge
4. Rechallenge
5. Concomitant Drugs
6. Medical condition

Assessing Causality
Kenneth Hartigan-Go MD

Causality assessment provides the health professional some degree of certainty as to the adverse event being related to the drug product. It is not a perfect system.

An example of such a system is the Naranjo algorithm, which is easy to understand and basic to apply.

<table>
<thead>
<tr>
<th>Naranjo’s Algorithm: Determination of ADR Probability</th>
<th>YES</th>
<th>NO</th>
<th>DO NOT KNOW</th>
<th>SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Are there any previous conclusive reports on this reaction?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2. Did the adverse event appear after the suspected drug was administered?</td>
<td>+2</td>
<td>-1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3. Did the adverse reaction improve when the drug was discontinued or a &quot;specific&quot; antagonist was administered?</td>
<td>+2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4. Did the adverse reaction reappear when the drug was re-administered?</td>
<td>+2</td>
<td>-1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5. Are there alternative causes (other than the drug) that could, on their own, have caused the reaction?</td>
<td>-1</td>
<td>+2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6. Did the reaction reappear when a placebo was given?</td>
<td>-1</td>
<td>+1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>9. Did the resident have a similar reaction to the same or similar drugs in any previous exposure?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10. Was the adverse event confirmed by any objective evidence?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TOTAL SCORE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[ ] Highly Probable</td>
<td>[ ] Probable</td>
<td>[ ] Possible</td>
<td>[ ] Doubtful</td>
<td></td>
</tr>
</tbody>
</table>

TOTAL SCORE

> 9 | Highly Probable
5 - 8 | Probable
1 - 4 | Possible
≤ 0 | Doubtful
The Philippines PV System

• October 1997
  – The Bureau of Food and Drugs (BFAD) was designated as lead agency to undertake Pharmacovigilance activities
The Philippines PV System

- Focus: ADR case reports, health advisories, warnings to HCPs and the public
  - Adulterated Snake Bone Rheumatism pills
  - Drug-drug IV incompatibilities (ICU)
  - Misoprostol as abortifacient
  - Defective devices (change in procurement sources)
  - Therapeutic inefficacy
TYPES of ADR

• Augmented
• Bizarre
• Continuous
• Delayed
• Ending of use
• Failure of treatment
Focus of Philippine PV

- Promotion of the ADR monitoring programme
  Knowledge, information and education
- Promote safer medicines in the market
- Provide better communication of harm-benefit of drugs and their use.
- Aim for rational drug use and prevention of drug-related injuries.
ADR Reporting Systems for the Philippines

- Part of the public health system: “lessons learned in clinical cases for the public good”
- Suspected ADRs to be reported to BFAD for databasing and submission to the WHO (Uppsala Monitoring Center) for evaluation
ADR Confidential Report
ADR CONFIDENTIAL REPORT: TRANSFORMING TO A CULTURE OF SAFETY; ADR FOCUS

MEDICATION ERRORS (ranked 11th worldwide)

SERIOUSNESS, CRITERIA (LABELEDNESS, SUENATURE, SEVERITY, OUTCOME OF AE)
PQC
Therapeutic failure

Can the adverse reaction be due to:

1. Product quality defect:  No  Yes, Specify, encircle: color change; caking; powdering; counterfeit; odor change; defective container; contaminants; separation of components; undissolved suspension/powder
2. Therapeutic failure:  No  Yes, Specify, encircle: antimicrobial resistance, drug interaction, poor compliance, counterfeit, expired; improper storage; under-dosing, inappropriate medication; inappropriate route of administration; excipients/preservatives

*Suspected drug product(s)
Indicate brand name

<table>
<thead>
<tr>
<th>Daily Dose</th>
<th>Route</th>
<th>Date started</th>
<th>Date stopped</th>
<th>Reason(s) for using the product (Indication)</th>
<th>Manufacturer and Batch/Lot #</th>
</tr>
</thead>
<tbody>
<tr>
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</tbody>
</table>

List all other drug/s taken at the same time and/or 3 months before. If none, check box.

☐ No Other drug/s taken

<table>
<thead>
<tr>
<th>Brand name of the drug</th>
<th>Daily Dose</th>
<th>Route</th>
<th>Date started</th>
<th>Date stopped</th>
<th>Reason(s) for using the drug</th>
<th>Manufacturer and Batch &amp; Lot No.</th>
</tr>
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</tbody>
</table>

* MANAGEMENT OF ADVERSE REACTION

Was treatment given?  ☐ No  ☐ Yes (If yes, please specify): __________________________
Outcome:
☐ Recovered (Date of recovery): _______________  ☐ Unrecovered
☐ Fatal (Date of death): _______________  ☐ Unknown  Other diseases: __ liver  __ renal  __ HPN
☐ Sequela/e: (any permanent complications or injuries as a result of the ADR) _______________  Re-challenge?  ☐ Yes  Result: _______________

☐ Yes (Please specify)  ☐ No  ☐ Unknown  ☐ No

* REPORTER'S PARTICULARS
TRANSFORMING TO A CULTURE OF SAFETY (ADR FOCUS):

- DRUG INTERACTIONS
- VACCINE-RELATED INJURY
- CLINICAL TRIALS
- SUBSTANDARD AND COUNTERFEIT PHARMACEUTICAL PRODUCE (ranked 7th worldwide)
Other PV-relevant information

• Product exposure (including maternal, paternal or fetal exposure) associated with a pregnancy with or without an adverse reaction
• Trans-mammary exposure of an infant (transmission via breast milk) to a product with or without an adverse reaction
• Overdose (with or without an adverse reaction)
• Abuse or misuse (e.g. use for non-clinical reasons) with or without an adverse reaction
Other relevant PV information

- Off-label use with or without an adverse reaction
- Inadvertent or accidental exposure with or without an adverse reaction
- Occupational exposure with or without an adverse reaction
- Suspected transmission of an infectious agent, which will be classified as a serious adverse reaction
- An unexpected therapeutic or clinical benefit from use of the product
PV Stakeholders & Responsibility in the Proper Communication of PV Info

• Government
  – Provide information (drug bulletins, national formulary, drug poison/information centre)
  – Legislation

• Health professionals
  – To produce independent information for publication
  – Have a critical mind
PV Stakeholders & Responsibility in the Proper Communication of PV Info

- **Patient/Consumer**
  - Consumer organization to inform patients about rational use of drugs
  - Target information to specific patient groups

- **Pharmaceutical Company**
  - Adhere to legislation on advertising and promotion
  - No disguised promotion
  - Clinical trials informative not promotional
  - Provide up to date information to professionals and public
PV Stakeholders & Responsibility in the Proper Communication of PV Info

• Medical Schools

To include in curriculum:

- interpretation of clinical trials
- benefit-risk assessment
- rational use of drugs (efficacy, safety, cost, suitability)
- communication with patients
- training of clinical pharmacologists and pharmacists
PV Stakeholders & Responsibility in the Proper Communication of PV Info

• **Media**
  – Have regard to consequence of stories
  – Check validity of story before publication
  – Adhere to code of practice
  – To refrain from acting as spokesperson in a promotional campaign
PV continues to evolve to keep with the demands of society

• Guidance on the future of PV
  – Erice Declaration (Transparency) 1997
  – Erice Manifesto 2007 (Global reform of the safety of medicines in patient care)
Drug safety information must serve the health of the Public

Education in the appropriate use of drugs, including interpretation of safety information, is essential for the public at large, as well as for health care providers.

All the evidence needed to assess and understand risks and benefits must be openly available.

Every country needs a system with independent expertise to ensure that safety information on all available drugs is adequately collected, impartially evaluated and made accessible to all.

Innovation in drug safety monitoring needs to ensure that emerging problems are promptly recognised and efficiently dealt with, and that information and solutions are effectively communicated.

Erice Declaration (Transparency) 1997
The active involvement of patients and the public in the core debate about the risks and benefits of medicines, and in decisions about their own treatment and health

The development of new ways of collecting, analysing and communicating information about the safety and effectiveness of medicines; open discussion about it and the decisions which arise from it

The pursuit of learning from other disciplines about how PV methods can be improved, alongside wide-ranging professional, official and public collaboration

The creation of purposeful, coordinated, worldwide support amongst politicians, officials, scientists, clinicians, patients and the general public, based on the demonstrable benefits of PV to public health and patient safety

Erice Manifesto 2007
Most common PV methods to guarantee safety, recent developments

- CLINICAL TRIAL DATA
- SPONTANEOUS REPORTING
  - LITERATURE SURVEILLANCE
  - CASE-BY-CASE ANALYSES (Probable, SUE)
  - DATA MINING TECHNIQUES (hidden patterns of associations or unexpected occurrences, safety signals in large databases)
- Others (Intensive monitoring, Database studies)
### Table 1 Drug safety concerns that have arisen in Europe since 1995 and evidence for these

<table>
<thead>
<tr>
<th>Drug</th>
<th>Safety concern</th>
<th>Key evidence</th>
<th>Regulatory action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trovofloxacin</td>
<td>Hepatotoxicity</td>
<td>Spontaneous ADRs</td>
<td>Withdrawn</td>
</tr>
<tr>
<td>Tolcapone</td>
<td>Hepatotoxicity</td>
<td>Spontaneous ADRs</td>
<td>Suspended</td>
</tr>
<tr>
<td>Cisapride</td>
<td>QT prolongation; cardiac arrhythmias</td>
<td>Spontaneous ADRs</td>
<td>Patient registration licences subsequently cancelled</td>
</tr>
<tr>
<td>Bupropion</td>
<td>Seizures; drug interaction</td>
<td>Spontaneous ADRs</td>
<td>Posology change, Warnings</td>
</tr>
<tr>
<td>Cervastatin</td>
<td>Rhabdomyolysis</td>
<td>Spontaneous ADRs</td>
<td>Withdrawn</td>
</tr>
<tr>
<td>Hormone replace therapy</td>
<td>CVS risk; cancer long term</td>
<td>Epidemiological studies</td>
<td>Warnings and restriction of indication</td>
</tr>
<tr>
<td>SSRIs</td>
<td>Suicidal behaviour in children</td>
<td>Clinical trials</td>
<td>Warnings accompanied by clinical guidance</td>
</tr>
<tr>
<td>COX IIs</td>
<td>CVS risk</td>
<td>Clinical trials</td>
<td>Warnings and clinical guidance</td>
</tr>
<tr>
<td>Topical macrolide immunosuppressants</td>
<td>Risk of cancer</td>
<td>Spontaneous reports</td>
<td>Restriction of use, Risk management plan</td>
</tr>
</tbody>
</table>

SSRI, selective serotonin reuptake inhibitors, CVS, cardiovascular safety; ADR, adverse drug reaction


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CLINICAL TRIAL RESULTS THAT DIRECTED RENEWED ATTENTION TO PV

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiovascular Events Associated with Rofecoxib in a Colorectal Adenoma Chemoprevention Trial

MAIN CONCERN: FDA is not able to protect the public from drug risks as efficiently as it might.
Benefits of rosiglitazone outweigh its risks within the framework of its approved indications. Need constant revision/revision of PI and continued monitoring of ADR.
Developments: Conditional marketing authorisation Granted in the absence of comprehensive clinical data referring to the safety and efficacy of the medicinal product. Criteria:
1. A positive risk–benefit balance of the product
2. Likeliness that the applicant will be in a position to provide the comprehensive clinical data
3. Unmet medical needs being fulfilled
4. The benefit of the immediate availability of the medicinal product to public health outweighing the risk inherent in the absence of additional data
Monitored Release Prior to Approval of General Use

Investigational New Drug (IND), New Drug (ND) and Newly Introduced Drug (NID) will be required to complete pharmacological studies and pass through a 3-year monitored release before becoming eligible for application and approval for general use. They are referred to as Post Marketing Surveillance (PMS) studies.

The model protocol for monitored release would include an uncontrolled clinical study reporting the therapeutic effects and adverse reaction for 1000 patients per year or 3000 patients over 3 years, provided however that if the drug product is for a very limited therapeutic indication the 1000/year patient requirement will be waived and only 10% of the total patients given the drug will be required to be monitored and reported...
Nonbinding Recommendations

Guidance for Industry

Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

March 2005
Clinical Medical

Current Challenges in Pharmacovigilance: Pragmatic Approaches

Report of CIOMS Working Group V

Geneva 2001
Harmonization: Good ICSRs and Good PSUR

GOOD CASE MANAGEMENT PRACTICES
Introduction: Clinical Evaluation of Cases
Assessing Patient and Reporter Identifiability
Criteria for Seriousness
Criteria for Expectedness
Case Follow-up Approaches
Role of Narratives

GOOD SUMMARY REPORTING PRACTICES: PSURs RECONSIDERED
Proposals for PSUR Content Modification
Proposals Relating to Frequency and Timing of Reporting
Miscellaneous Proposals for Managing PSURs
Good pharmacovigilance practices (GVP) replaced EU vol 9A

- Set of measures drawn up to facilitate the performance of PV in the European Union
- The legislation is accompanied by the implementing regulation.
- This is a **legally binding act** published by the European Commission in June 2012
Guideline on good PV practices (GVP)

• Module I – Pharmacovigilance systems and their quality systems
• Module II – Pharmacovigilance system master file
• Module III – Pharmacovigilance inspections
• Module IV – Pharmacovigilance audits
• Module V – Risk management systems
Guideline on good PV practices (GVP)

• Module VI – Management and reporting of adverse reactions to medicinal products
• **Module VII – Periodic safety update report**
• Module VIII – Post-authorisation safety studies
• Module IX – Signal management
• Module X – Additional monitoring
• Module XV – Safety communication
• Scope, objectives, format and content
• Required format and content of PSURs in the EU are based on those for the Periodic Benefit Risk Evaluation Report (PBRER) described in the ICH-E2C(R2) guideline
• PBRER replaces the PSUR format previously described in the ICH-E2C(R1). In the EU, the report shall be described and named as PSUR
Developments: Risk management plans

- To identify, characterise, prevent or minimise risk relating to medicinal products, including the assessment of the effectiveness of those interventions.
- May need to be submitted at any time in a product’s life cycle: pre-authorisation and post-authorisation phases.
RISK

- Harm (Physical)
- Loss of Trust (less tangible form)
- Damage arising from deception
- Failure to comply
- Patients do not feel safe
RISK MANAGEMENT

• Not Primarily Regulatory
• Primarily Scientific
• BUSINESS CONCERN
Risk Management Concept
ISO 14971 Model

- Risk Analysis
  - Risk Assessment
- Risk Evaluation
- Risk Control & Mitigation
- Monitoring

“Business! Not Regulation!”
Risk Management Program

• Strategic safety effort to reduce risk
  – \( \geq 1 \) risk reduction goal
  – \( \geq 1 \) intervention (tool) in addition to PI
• Tool examples: education, forms, processes, and other methods to influence CONTROL OF A PRODUCT:
  – Prescribing
  – Dispensing
  – Use
“LEVELS” of RMP

- **Level 1**: Package Insert only
- **Level 2**: Adds education and outreach tools
- **Level 3**: Level 2 plus systems guiding prescribing, dispensing, and/or use
- **Level 4**: Access to products requires adherence to specific program elements
RMP REQUIRED

- All new active substances
- Significant changes in established products (e.g. new form/route of administration)
- Established products introduced to new populations
- Significant new indications
- Unexpected hazard is identified
PSUR and RMP

• Consider whether any **identified or potential risks discussed within the PSUR** is important and requires an update of the RMP. In these circumstances, an updated RMP including the **new important safety concern** should be submitted with the PSUR and assessed in parallel, following the timetable for the assessment of PSUR as described above.

• If important safety concerns are identified during the assessment of a PSUR and no updated RMP or no RMP has been submitted, recommendations should be made to submit an **update or a new RMP** within a defined timeline.
EU RMP consists of two parts

• 1\textsuperscript{st} Safety specification and a pharmacovigilance plan

• 2\textsuperscript{nd} Evaluation of the need for risk minimisation activities and if necessary, a risk minimization plan
risk minimization plan is only required

• Where the standard information provision, by means of a medicine’s summary of product characteristics, is considered inadequate
• Insufficient patient information leaflets or inadequate labelling of the medicine
PARADIGM SHIFTS

• BLAME CULTURE TO CULTURE OF SAFETY
• PV has been most concerned with finding new ADRs, now pharmacovigilance should be less focused on finding harm and more focused on extending knowledge of safety

There are four myths in medicine that we must remember:

- All medicines work.
- Medicines in the market are 100% safe.
- There is a pill for every ill.
- People will use drug rationally as intended.

DR. KENNETH HARTIGAN-GO
Thank you!