What Constitutes a Robust Pharmacovigilance System?

Fiona Dunagan
Medical Affairs Manager
GlaxoSmithKline Consumer Healthcare
Pharmacovigilance Basics

- **Origin of the word**
  - Pharmakon *(Greek)*: Drug
  - Vigilare *(Latin)*: To keep awake or alert, to keep watch

- **Definition from the World Health Organisation**
  - The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems
What does Pharmacovigilance actually involve?

- Collecting adverse event information regarding our products
- Reporting adverse drug reactions to regulatory authorities
- Assessing the available safety data to identify any trends
- Evaluating trends to identify new safety signals, that is, side effects now considered to be related to treatment
- Ensuring the benefits of treatment continue to outweigh the risks associated with it
- Providing Healthcare Professionals and Consumers with the most up-to-date product information so that informed decisions can be made with respect to treatment. (e.g. warnings, precautions, contraindications, pregnancy category)
Why do we conduct Pharmacovigilance?

To protect patients and consumers

- A new drug is marketed for treatment of nausea in pregnancy. The promotional material describes it as "outstandingly safe". This product is marketed to pregnant women in 46 countries.

- The safety information reads: "It is said to be relatively free from side effects but occasionally causes dizziness and nausea."

- There are some reports of problems with patients' pregnancies. Doctors reporting incidents to the marketing company are told: "This is the first time we have heard of such a side effect". This situation continues for 5 years.

- Over 8,000 children in 46 countries were affected, commonly with: Missing arms, missing legs, missing ears, damaged sight or complete blindness and many others died at birth.

The drug was Thalidomide

This may have been limited if proper Pharmacovigilance systems had been in place at the time.
Why do we conduct Pharmacovigilance? (cont)

To comply with regulatory requirements

- The Sponsor must ensure that it has an appropriate system of pharmacovigilance in place in order to assure responsibility and liability for its products on the market and to ensure that appropriate action can be taken, when necessary.
What is an ‘Appropriate System for Pharmacovigilance’ made up of?

- Qualified Person for Pharmacovigilance (QPPV)
- Documented procedures
- Databases
- Contractual arrangements with other organisations
- Training
- Documentation
- Quality Management Systems
The Qualified Person Responsible for Pharmacovigilance (QPPV)

- Qualifications for the QPPV are ideally biological sciences/pharmacy or medical degree and some years experience in the field of pharmacovigilance
- If not medically qualified the QPPV should have access to a medically qualified person who is experienced in pharmacovigilance
Role of the QPPV

- Oversight of the pharmacovigilance system
  - Documented procedures
  - Databases
  - Contractual arrangements with other organisations
  - Training
  - Documentation
  - Quality Management Systems

- Preparation of Reports

- Respond to requests for information from the regulatory authority

- Ongoing safety monitoring

- Availability out-of-hours
There must be a process to ensure that all suspected adverse reactions with the sponsor’s products (active ingredients) are collected and collated.

Depending on the product range and number or reports this may be a paper based or electronic process.

Each report must have a unique identifier and all reports must be reconciled where they are transferred from different parts of the organisation (e.g., product information enquiries/QA/PV) or with licensing partners.

Checks should be made for duplicate reports.
What information to collect?

- Unfortunate medical occurrence (adverse experience or event)
- Use of a medicinal product during pregnancy
- Experience of lack of efficacy
- Overdose
- Drug interaction
- Abuse / misuse / unapproved (off-label) use of a medicinal product
- Medication error (or near miss)
Definitions

Adverse Event (AE)

An adverse event is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product.

Adverse Drug Reaction (ADR)

A reaction, in contrast to an event, is characterised by the fact that a causal relationship between the drug and the occurrence is suspected. For regulatory reporting purposes, if an event is spontaneously reported, even if the relationship is unknown or unstated, it meets the definition of an (suspected) adverse drug reaction.
Serious AE/ADR

A serious adverse event or reaction is any untoward medical occurrence that at any dose:

- results in death;
- is life-threatening (NOTE: The term "life-threatening" in the definition of "serious" refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/reaction which hypothetically might have caused death if it were more severe);
- requires inpatient hospitalisation or results in prolongation of existing hospitalisation;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect;
- is a medically important event or reaction.
Medical Dictionary for Regulatory Activities (MedDRA) is a clinically validated international medical terminology used by regulatory authorities and the regulated biopharmaceutical industry throughout the entire regulatory process, from pre-marketing to post-marketing activities, and for data entry, retrieval, evaluation, and presentation.

Once reports are coded they can be more easily analysed and reviewed for trends.
Expedite Reporting to TGA

- Individual serious expected and unexpected adverse experience reports occurring in Australia must be reported within 15 days.
- Any serious safety issue must be reported within 72 hours.
- What constitutes a significant safety issue may require judgement on the part of the sponsor but would generally include any matter about the safety of the product which results in:
  - Withdrawal or suspension of availability of the product in another country.
  - The addition of a contraindication warning or precaution statement to the PI or label.
  - The modification for safety reasons of an existing contraindication warning or precaution statement in the PI or label. As well as the modification or removal of an indication for safety reasons.
Clock Start Date (Day 0)

- Date report received by
  - Employee or contractor of the sponsor
  - QPPV
  - Licensing partner

- Awareness in any published worldwide scientific/medical literature by any personnel of the sponsor
Sources of Suspected Adverse Reactions

- Companies should be pro-active about the process of collecting suspected adverse reactions
- Potential sources are:
  - Product or medical information enquiries from consumers or HCP
  - “Contact us” emails or website enquires
  - Product quality complaints
  - Sales representatives
  - Published literature
  - Regulatory authority
  - Licensing partners
Literature Searching

- Maintain awareness of any worldwide published literature by conducting a review of a reference database such as Medline or Embase once weekly.
- Searches should be performed to find reports based on active ingredients and not brand names only.
- Articles with expedite reports may be excluded from reporting if another Brand is specified but if there is no brand specified then it should be reported.
- Day 0 for reporting would be based on the date that the literature search was conducted.
Safety Database – Factors to consider

- Off the shelf or bespoke safety database or hybrid (e.g., paper based + spreadsheet)
  - Is it possible to check for duplicate reports?
  - How can cumulative data be analysed?
  - How are data extracted from the system to produce regulatory reports?
  - Is there access to the data in a timely manner if there is a regulatory enquiry?

- Privacy
- Data protection
- Validation of the database
- Disaster recovery and back-up procedures if the electronic system is not working
Signal Detection

- Ongoing monitoring of the risk-benefit profile of medicines
- Ensuring appropriate action is taken if there is new evidence that impacts on the known risk-benefit balance
- Keeping consumers and HCPs informed of changes in the risk-benefit balance
Methods of Signal Detection

- Individual case review
- Systematic Review of multiple case reports
  - change in frequency of AEs over time
  - Proportional reporting ratio (PRR) – this is an automated statistical method which compares the proportion of reports for a specific suspected adverse reaction for a medicinal product with the proportion for the same suspected adverse reaction for all other drug (requires large numbers of reports).
  - Bayesian methods which uses the same principle as PRR but is more stable with smaller numbers of reports
- Periodic Safety Update Reports
- Other sources of information eg clinical trials, surveys
Investigation of Potential Signals

- QPPV / medically qualified person to review and make decision if data support a new signal
- Re-evaluation of the risk-benefit profile of the medicine
Communication of Potential Signals

- **Regulatory Authority**
  - QPPV is responsible for notifying the relevant regulatory authority immediately of any change in the risk-benefit balance for a medicine.
  - A data package should be provided to the regulatory authority which should provide a comprehensive discussion of the issue in the context of the benefits of the product.

- **HCP communications**
  - Dear HCP letters eg recall of a product for safety reasons or important changes to the product information in relation to safety.
Company Core Safety Information (CCSI) document
- Indications
- Contraindications
- Precautions/Warnings
- Use in pregnancy
- Drug Interactions
- Adverse Reactions

Information for HCPs and Consumers which is consistent with the CCSI
Training

- WHAT is an AE
- WHAT other safety information needs to be collected, such as pregnancies, reports of lack of effect etc
- WHAT information needs to be collected
- WHO to report the information to
- HOW to report the information
- WHEN the information needs to be reported eg within 24 hours or as soon as possible

REMINDEERS & REFRESHER TRAINING
- Posters
- Newletters/bulletins
- Company webpages
- Credit card
Safety Evaluation and Risk Management Overview

- Published Literature
- Spontaneous AEs
- SAEs from Clinical Trials
- Safety Database
- Signal Detection
- Safety Evaluation
- Update Core Safety Information
- PSUR
- Labelling Updates
- Serious Adverse Experience Reports to Regulatory Authority
- Dear HCP Letter
- Alert Regulatory Agency of significant safety issue
References