Whitehall Training

Pharmacovigilance
Drug Safety

What is Pharmacovigilance?

Pharmacovigilance (GPvP) is name given to the science and activities relating to the collection, detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem.

GPvP is needed to…

- Protect patients from unnecessary harm
- Reduce or manage the risks of, and increase the benefits of products
- Communicate the rational use of medicine and adherence to usage instructions.

Where did Pharmacovigilance come from?

Modern drug safety and adverse event reporting had its origins after the Thalidomide disaster. This drug was prescribed in many countries around the world to alleviate morning sickness in pregnant women.

Thalidomide is a teratogen and caused extreme birth abnormalities. However, these were not reported as adverse events since there was no proper reporting system. Because of this, it took a few years before people realized what was happening.

In 1962, the US brought in legislation that required tests for safety during pregnancy before a drug could be approved for sale. Other countries / regions enacted similar legislation. The US rules also mandated that pharmaceutical manufacturers having a New Drug Application (NDA) must report adverse events to the FDA.

In 1968, the World Health Organisation (WHO) began pooling adverse drug reactions from multiple countries.

Since then, most countries have bought in mandatory pharmacovigilance rules with mechanisms for standardised reporting of adverse events for both pharmaceuticals and medical devices.

Adverse Events during drug development

There are several obvious advantages to detecting adverse events (AEs) before a drug is launched on the market.

- The drug is being used in a controlled environment
- Only patients that meet strict criteria have been given the drug
- The exact number of patients having the drug is known, which makes it easy to calculate accurate incidence figures
- All the data is captured in a standard way by trained medical professionals
- The patients are tracked so follow up data is available

However, despite its advantages, pre-market adverse event testing does have its problems. Even the largest of clinical trials only has a tiny sample size compared with a commercially available product. Also trials, cannot hope to perfectly mirror the population at large — e.g. groups like the elderly or children etc may be under represented, and it is not practical to assess the effects of the drug being used alongside all possible concomitant medications. Finally, clinical trials only run for a limited time so long term (latent) effects may not be shown.

Adverse Events after market launch

Checking for AEs once a drug has been launched gets around many of the limitations of pre-market detection. There is a high volume of users across the whole spectrum of groups and effects over time will become apparent. Despite this, there are clear disadvantages.

Reports of post-market AEs can come from many different sources and may be inaccurate or incomplete. There can be duplication, for example a patient could separately report their suspected side-effect to their pharmacist and doctor, plus they may do so on the manufacturer's website. It is also hard to establish truly accurate incidence figures as the only way of measuring usage is using sales data.

Ultimately, both pre- and post-market AE detection are essential as together they form the best possible picture of a drug's risk spectrum. Used properly, they enable a drug to be launched with the risks properly assessed as well as allowing a mechanism for modifying the usage advice should new or revised evidence of potential adverse events become available.

AEs, ADRs & SUSARs

Terminology is crucial in pharmacovigilance. Some terms, like Adverse Event (AE) do not necessarily imply a causal link to a drug, whereas terms like Adverse Drug Reaction, imply that there is a definite link. Others may have a slightly different definition depending on whether they are being used to describe something that is occurring pre or post-market launch.

Here are two useful definitions—

Adverse Drug reaction

- **Pre-market**, all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions.
- **Post-market**, a response to a medicinal product that is noxious and unintended - Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

SUSAR is a term often used in pre-market pharmacovigilance. As the name suggests, it applies to any serious adverse event that is suspected to be causally linked to the test drug and is unexpected based on prior knowledge. SUSARs are subject to expedited reporting.

It is often difficult to make a definitive causal link between a drug and a particular adverse event, but some things can make the link a lot more likely.

For an event to be considered **definitely related**, it cannot be explained by other things, such as the disease the drug is treating and there must be a plausible relationship to the timing of the drug being administered. The most conclusive evidence is provided by a **positive re-challenge**, which is where an effect occurs when a drug is given, disappears or improves when the drug is removed, and then reappears of worsens when the drug is re-started.

At the other end of the spectrum, something that is considered **unlikely to be related** may be plausibly explained by other things, such an underlying disease or other drugs. It may also be unlikely because the timing does not seem to bear a relation to the use of the drug in question.

Expectedness is an other important aspect of the SUSAR. An expected AE is any adverse event whose nature and severity have been previously observed and documented for the study product.

An "unexpected" AE is any adverse event not previously observed, whether or not it has been anticipated because of the pharmacological properties of the study.

Reporting

Of course, detecting an AE and linking it to a particular drug is only part of the story. A vital part of the pharmacovigilance process is the means by which the information is reported so that it can be acted on appropriately and effectively. Reporting related to AEs usually falls either into the category of **expedited** or **aggregate** reporting.

Expedited reports

In general, expedited reporting of serious and unexpected ADRs is required as soon as possible, but in no case later than 15 calendar days of initial receipt of the information by the holder of the marketing authorisation. Time frames for other types of serious reports vary among countries, depending on source, expectedness and outcome.

Regulatory agencies should be notified as soon as possible but no later than 7 calendar days after first knowledge by the sponsor that a case qualifies, followed by the complete report within 8 additional calendar days.

All reports need to include at least an identifiable patient, an identifiable reporting source, the details of the drug believe to have caused the AE and details of the serious event or outcome.

Aggregate reports

As the name suggests, these are periodic reports that contain a compilation of AE data. Annual aggregate reports are required for medical trials in both Europe and the US. Once a drug has been launched on the market in the US, the company holding the marketing authorisation must submit a **Periodic Adverse Drug Experience Report** (PADER) quarterly, for the first three years from the date of approval, and annually thereafter.

The European equivalent of the PADER is the **Periodic Safety Update Report** (PSUR) and variations of this are used outside Europe too. The PSUR acts as a critical evaluation of the risk-benefit balance of the product.

Whitehall Training

This is the end of Whitehall Training's short **Pharmacovigilance** course.

Expanded online versions of this training, complete with exam and certificate, are available from the Whitehall Training website – **https://www.whitehalltraining.com/all-pharmacovigilance-courses**