SHORT COMMUNICATION

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Good Pharmacovigilance Practices
Technology Enabled

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Abstract

The assessment of spontaneous reports is most effective it is conducted within a defined and rigorous process. The framework for good pharmacovigilance process (GPVP) is proposed as a subset of good postmarketing surveillance process (GPMSP), a functional structure for both a public health and corporate risk management strategy. GPVP has good practices that implement each step within a defined process. These practices are designed to efficiently and effectively detect and alert the drug safety professional to new and potentially important information on drug-associated adverse reactions. These practices are enabled by applied technology designed specifically for the review and assessment of spontaneous reports.

Specific practices include rules-based triage, active query prompts for severe organ insults, contextual single case evaluation, statistical proportionality and correlational checks, case-series analyses, and templates for signal work-up and interpretation. These practices and the overall GPVP are supported by state-of-the-art web-based systems with powerful analytical engines, workflow and audit trials to allow validated systems support for valid drug safety signalling efforts. It is also important to understand that a process has a defined set of steps and any one cannot stand independently. Specifically, advanced use of technical alerting methods in isolation can mislead and allow one to misunderstand priorities and relative value.

In the end, pharmacovigilance is a clinical art and a component process to the science of pharmacoepidemiology and risk management.

The existing spontaneous report handling and regulatory reporting process and the information technology (IT) systems which support this process, is really a sub-process. True risk-management requires a rigorous postmarketing surveillance (PMS) process to assess the safety of a companies' products in the worldwide marketplace. This PMS process is the parent process.

A rigorous 'good postmarketing surveillance process' (GPMSP)[1] includes an integrated philosophy of drug safety, sources of quality data, good scientific practices and skills, specified output products, clear decision points and action plans, and is supported by good data and document management processes and clear and enforced set of standard operating procedures (SOPs).

The goal of this GPMSP is to understand the safety profile of all a companies' products in the clinical practice environment. The philosophy of integrated drug safety is to continue to build on the knowledge database begun in the premarket sections of the new drug application (NDA) or market application. In line with this philosophy, a companies' PMS programme should be capable of assembling a continued integrated safety summary (i.e. a continual-ISS) in the form of an International Conference on Harmonisation (ICH)-E2C compliant periodic safety update report (PSUR) that contains an actively assessed safety profile. Multiple sources of good quality data from the environments of clinical practice will be required to develop and assemble such a PSUR. These data should include, but not be limited to, spontaneously reported adverse reactions.

The standard method sequence for spontaneous report-centric postmarketing surveillance is: alerting → signal generation → confirming → hypothesis testing → quantification.

In the best case, a careful analysis of spontaneous reports can only alert, signal, and confirm an association. In certain circumstances, one high quality and carefully documented report with a successful dechallenge and a positive drug rechallenge may have sufficient internal validity to declare a causal association. Other than this scenario, spontaneous case reports cannot demonstrate a definitive causal relationship.

The methods of pharmacoepidemiology are needed for hypothesis testing and risk quantitation in observational data. Methodologies of clinical pharmacology and clinical trials should also be used when appropriate and ethical. Corporate PMS staff members need to have 'live' access to these data sources and possess the skill to know when and how to utilise them. Some examples of observational data sources currently available include: Boston Collaborating Drug Study Unit (BCDSP), United Health Care (UHC), General Practice Research Database, prescription-event monitoring (PEM), Medicines Monitoring Unit database, Medicaid database, etc.

Corporate PMS staff members also need to be capable of producing high quality assessments of their products' safety profile in specified formats for internal discussion, administrative records and regulatory submission. These should include: single-case assessments, case series work-ups, safety assessment work-ups, observational study results, and PSURs.

Clear decision points, procedures and action plans are required to document both emerging signals and their subsequent assessment. PMS staff need to know when and how to elevate potential issues to the specified level of management. All detected alerts must be monitored, assessed and decided upon as to need for and type of action. Components of this effort include a safety review team and an issue management plan.

Support by good data and document management processes that are as integrated as much as possible with premarketing enterprise software and of similar rigor is essential for the validity of the corporate PMS process.

Figure 1 illustrates the new drug development continuum, the continual roles of industry and regulators and the tools used to acquire knowledge about a drug's safety profile after marketing.

Therefore, a rigorous and valid corporate PMS process has the following component sub-processes:

- pharmacovigilance process
- pharmacoepidemiological process
- drug safety assessment process
- decision and action process, including a safety review team and an issue management plan
- data handling and management process
- document handling and management process
- special focus on newly launched products.

A proposed definition of GPMSP is: process rigor and scientific validity with documentation and source validation within an *a priori* risk-management strategy. Within this framework, both pharmacovigilance (PV) and pharmacoepidemiology (PE) need to be conducted with explicit and accepted 'good practices'. Good practices are the standards for implementation of the various com-

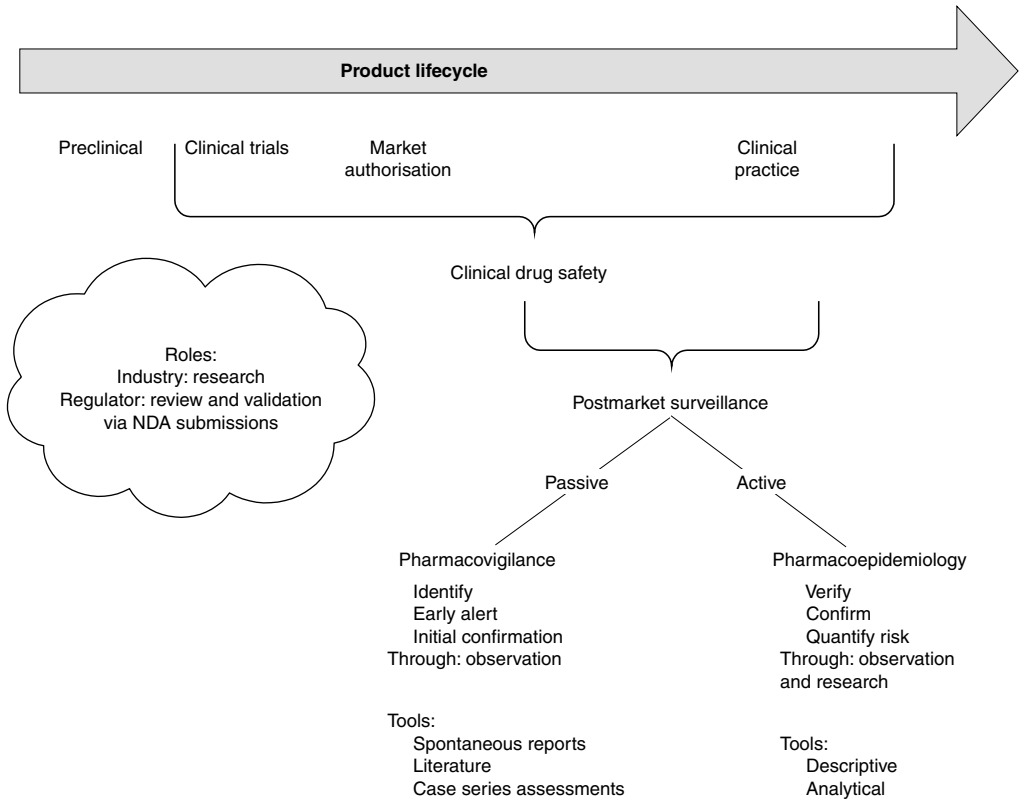

Fig. 1. New drug development/new drug application (NDA) continuum.

ponents of an overall process. As important, both need good quality data!

GPMSP provides the functional structure for a corporate risk-management strategy. GPMSP is both a solid public health risk management tool and a corporate risk management tool.

1. Initial Focus on the Assessment of Spontaneous Reports: Good Pharmacovigilance Processes

Spontaneous reports have been the historical cornerstone of the pharmacovigilance component of PMS. The scientifically supported maximal use of these reports is a central goal of the pharmacovigilance.

Good pharmacovigilance processes (GPVP) focus on the enhancement of the reports that are most likely to be important. In parallel to any regulatory reporting (submission) triage these reports need to have both their potential maximised and the value measured. That measurement must be both as an individual and in a case-series. All activity must be well documented.

The goal of GPVP is to clearly and accurately identify rare, serious, unusual or unexpected adverse drug reactions as soon as possible after market launch. This plays to the few strengths inherent in this type of anecdotal observational data.

The basic tenets of pharmaceutical industry's GPVP are:

- Effectiveness: rigorous alerting, signal detection and handling.
- Efficiency: focus on 'important' reactions.
- Consistency: one global corporate opinion on the nature and level of causality of the reaction.
- Validity: evaluation and assessment tools yield correct results.

At a conceptual level, GPVP is simple: The appropriate persons throughout the steps of this process need to look, need to see, need to assess, need to place in context, and need to inform (discharge the corporate 'duty to warn').

In practice, of course, it is much more complex. At the functional level, history, evolution, time, and loss of focus have created an environment in which PV has taken a secondary role to time-compliant adverse drug reaction report submission. To rectify this misalignment, a PV process is offered.

GPVP for spontaneous reports is proposed as a step-wise approach: (i) step 1 – data triage; (ii) step 2 – information acquisition; (iii) step 3 – single case assessment; (iv) step 4 – technical checks; (v) step 5 – case-series (content and context assessment); (vi) step 6 – interpretation; and (vii) step 7 – communication.

This functional step-wise approach runs parallel to multiple process defined decision points: Is this report important? Could this reaction, if true, be a 'drug killer'? What is the single case causality assessment? How do I judge that alert from context matrix? How do I judge that alert from technical checks? After a case series content/context assessment do I judge this alert to be a signal? What is the urgency of this signal? What extent of effort and research will this signal work-up need? How do I confirm or validate this signal? What external data sources can I bring into play? Is it important to quantitate this signal? If so, with what data sources or study designs? Is it appropriate to notify internal stakeholders? Is it appropriate to notify external stakeholders? How can the most informative and accurate benefit-risk reassessment be performed? How is the public health impact of the reaction assessed? What is the companies' plan for action?

All of these questions need to be actively asked as a new spontaneous report moves through the steps of GPVP. This GPVP and its parallel decision points are in addition to the sub-process used for handling these reports for regulatory submission.

2. Step 1 – Data Triage

The first step in GPVP is a rules-based data triage. An active effort must be applied to sort those reports that are more likely to be important from those that are less likely to be important. This dichotomy correlates with, but is not defined only by, regulatory requirements. In current times, the volume of spontaneous reports is extremely high, with much of this volume being reports on drug-outcome relationships that are already recognised and labelled. These known reports then become less important to the main utility and goal of a spontaneous reporting paradigm. Quality is far superior to quantity when spontaneous anecdotal reports comprise your data set.

In GPVP, 'important' is currently defined by reports meeting any of these criteria: (i) the ICH-E2A regulatory definition of 'serious'; (ii) if a reaction is judged to be medically significant; (iii) if it involves any of the outcomes 'usually related to drugs (e.g. toxic epidermal necrolysis, torsade de pointes, Stevens-Johnson syndrome, agranulocytosis, aplastic anaemia, Guillain-Barré syndrome, pseudomembranous colitis, tardive dyskinesia, neuroleptic malignant syndrome, anaphylaxis, anaphylactoid reactions, angioedema) or; (iv) any company specific outcome deemed appropriate. These inclusion criteria can be modified in any way to best fit the needs of a specific company.

This triage is critical to success because in many companies, especially those with a significant US market, a very high proportion of their reports are non-serious and/or from consumers. These reports need not be reviewed as individuals, but can be data-mined in the aggregate. This is a pivotal concept in GPVP: only those reports that are triaged to the 'important' category require a clinical review at the individual case level. All the 'less than important' cases are reviewed only if the met an alert-

ing threshold defined in step 4 (see section 5), of if suspicion warrants.

3. Step 2 – Information Acquisition

Enhanced information acquisition is the rationale for step 2 of GPVP. There needs to be an active query performed for 'important' reports at the point of initial contact. That is, maximal data collection with the goal of increasing the likelihood of making a causality determination. This is the only method that can relieve the true type of 'under-reporting' that is related to spontaneous reporting, i.e. poor quality data!

For a subset of those important reports involving organ systems that are historically linked to drug toxicity, the proper use of the late Professor Benichou's data collection instruments provide efficient, effective and structured query.[2] Given the nature of these reports it is critical to ensure that the reporter is accurate in citing an outcome. Case validation is important. It is also recommended for those extremely important outcomes that a 'swat team' for 'drug killers' be authorised. This means that corporate SOPs are in place and administrative pathways are created to have a quick response team go to the reporter's site to secure the relevant laboratory or biopsy materials. Payment to the reporter for his/her time is usually required.

In essence, GPVP created two parallel functional processes: regulatory reporting and pharmacovigilance. Each has its own triage rules, audits trails, personnel, and products. The later is *not* bound to the reporting timeframes of the former.

4. Step 3 – Single Case Assessment

This third step in GPVP has two parts: initial single case assessment and signal-based evaluation. The initial assessment is an 'on the way in' to the database review, and is a step conducted before regulatory submission. This function includes addition of a quality score using one of the accepted causality algorithms (e.g. imputability,[3,4] Naranjo,[5] etc.), all of which crudely sort a report into one of three quality 'piles'.

Also added is the company opinion of this case that is a probabilistic determination of the level of certainty of the causal association. This same global company opinion should appear on *all* documents [i.e. individual safety report CIOMS (Council for International Organizations of Medical Sciences) comment, case-series, PSUR] in which this case is referenced. These steps need to be included within the 15-day regulatory timeframe, if it applies.

After the case is sent to the database and submitted from there to the regulators, the main PV assessment and evaluation occurs. Utilising the electronic inbox of the specialised computer system that supports this GPVP, the professional risk assessor compares that new 'important' case to 'similar'[exact and related Medical Dictionary for Regulatory Activities (MedDRA) preferred terms and grouped terms, high level terms (HLT) and high level group terms (HLGT)] cases already in the in-house database. This is made possible by using a context matrix (see table I for an example). The context matrix has the potential to be the most powerful tool a computer system can produce for the clinical art of PV. The context matrix is constructed as a product of the quality triage at the front end of the process and by level of MedDRA. It allows the learned reviewer a view of quality, quantity and dispersion of previous reports related to the new one just received. Any cell of that matrix can be 'drilled down' to view its component cases.

Table I. Context matrix

Level of Medical Dictionary for Regulatory Activities (MedDRA) term	Poor (no./score)	Possible (no./score)	Probable (no./score)	Total (no./score)
Preferred term	2/0	3/5	1/5	6/10
High level term	7/0	14/22	1/5	22/27
High level group term	12/0	30/45	3/17	45/62

A further drill down can be made to reveal the individual case data.

By definition, all 'important' reports are deemed alerts in this GPVP. An alert is simply considered an initial warning to look at the data. These are criteria or rule-based and therefore, are defined and pre-programmed into the supporting computer system. An alert differs from a signal, which is an alert that is judged to have apparent substance that requires further investigation. Therefore, a signal is context and judgement based.

5. Step 4 – Technical Checks

A vital component of GPVP are the technical checks. They are necessary for the efficient and effective utilisation of GPVP since we often need to assure ourselves that there are no sharp needles hidden in the ever-growing haystacks of reports. However, as important to GPVP as they are, these statistical and graphic techniques can only be complementary methods to context matrix and case-series analyses (see step 5, section 6).

A variety of technical checks or data-mining techniques [i.e. WHO's Uppsala Monitoring Centre's neural networks, vector analyses, proportional analyses such as UK Medicines Control Agency's proportional reporting ratio (PRR) or US Food and Drug Administration's pilots using a Baysian ratio] need to exist is any system that supports GPVP because the majority of the incoming are not evaluated as individual case reports.

The primary purpose of these technical checks within GPVP are to send alerts, based on pre-defined and adjustable thresholds, up into the reviewers electronic inbox for assessment and judgement as to whether or not it is a true signal. It is vital that the corporate users be assured that any data or sets of data that may have a causal link to one of their drugs be detected as an alert for further evaluation by the clinical risk assessor.

6. Step 5 – Case-Series (Content and Context Assessment)

The case-series is the true unit of analyses in pharmacovigilance and the content assessment of that case-series is the clinical mainstay. There is substantially more to be learned from a properly assembled series of like cases then could ever be extracted from the isolated review of an individual case. Here in step five of GPVP, the electronic inbox of the specified clinical reviewer is loaded with alerts defined from important new cases and the thresholds set in the various technical checks. The reviewer uses the tools provided [context matrix with drill down to individual cases, ability include/ exclude cases from the series, ability recode, reassess (causality score and MedDRA term) single case, *ad hoc* query tool, all technical checks in an active query mode, within case-series management environment]. The clinical reviewer assembles the sets of cases for content analyses. Case-series investigations can amplify the signal above that which could be seen with usual individual reports. This is the first time that the risk assessor views these cases with both a clinical and an epidemiological eye. Risk is contextual to use. Risk is usually contingent on dose. Quality becomes quantity at a certain point, and 'under-reporting' of spontaneous reports is not a limitation as long as 'sufficient reporting levels' of quality reports exist. It is after an initial case-series assessment that a judgmental determination as to signal status is made. If made, two discrete activities are initiated: (i) the proper level of corporate management is informed and; (ii) a full signal work-up effort and report is required.

7. Step 6 – Interpretation

Once the case-series are assessed and a determination has been made that they represent a signal, a full context evaluation leading to an interpretation is the next step.

The logic behind GPVP has shifted emphasis from single data handling to case-series assessment. In line with that shift and a result of front-end triage efficiencies, human resources within a company's drug safety unit could have been freed to focus on these case-series within a system environment with a full array of tools for analyses and management of information.

Factors to consider in this signal work-up include:

- probabilistic logic and balance
- epidemiological context
- exposure data for context *not* rates
- age, gender, indication demographics
- natural history of underlying disease *and* the noted outcome
- alternate risk factors
- biological plausibility
- signal confirmation (good pharmacoepidemiological practices)
- internal/external.

This assessment is conducted in a systems based signal work-up environment using an expectation based work template that is modelled after that for a scientific manuscript. The assessment work product or signal work-up, gets sent to regulators, and is copied as a listing of all similar analyses in the next PSUR.

Therefore the four pharmacovigilance products from GPVP for industry are:

- regulation compliant single case reporting
- high-quality individual safety reports for 'important' reactions
- case-series analyses (in context)
- comprehensive PSUR.

8. Step 7 – Communication

Step 7 is the final linear step in GPVP and concerns risk communication. Components here include both inside and external communication. Internally, archived documentation and notification to management are important. External communi-

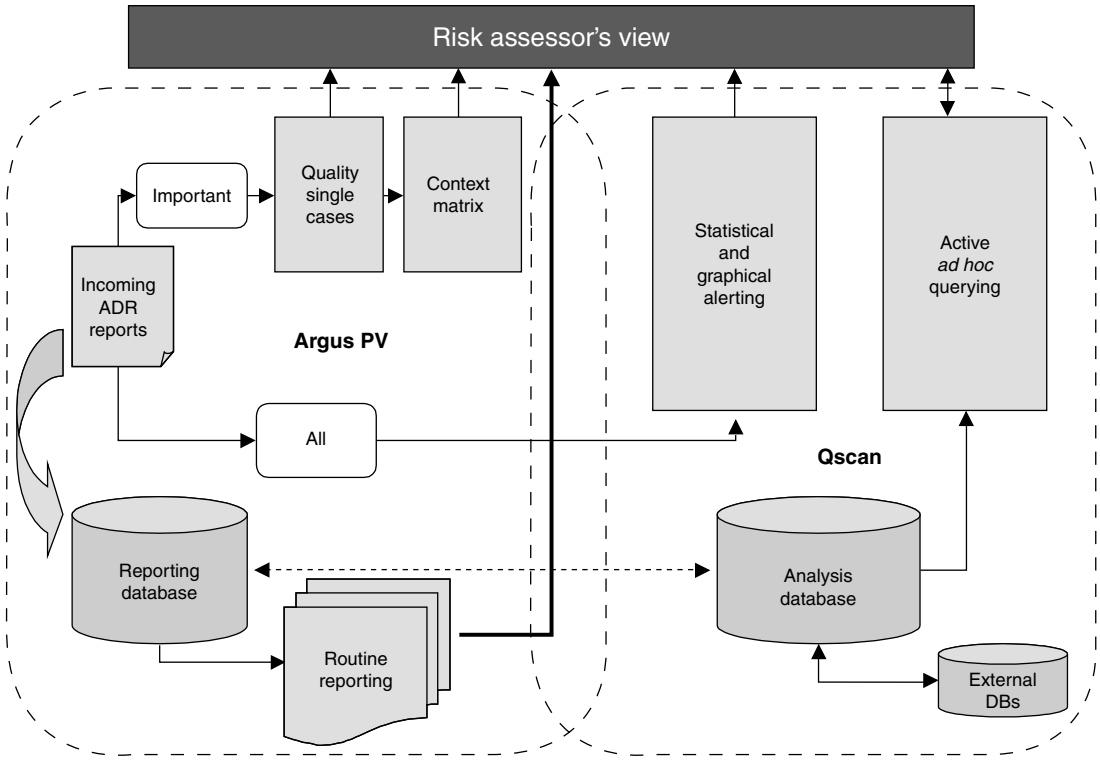

Fig. 2. Technology enabled good pharmacovigilance processes. **ADR** = adverse drug reaction; **DBs** = databases; **PV** = pharmacovigilance.

cation includes notification at the information level (not just at the data level) to regulators, healthcare practitioners and business stakeholders. Enhanced product labelling will be essential for true risk communication and that will require data far more quantitated then possible from spontaneous reporting.

9. Conclusion

GPVP in the 21st century is a process composed of best practices. It could also be considered a systems approach to PV, with IT systems enabling. Pioneers in the drug safety field developed many of those best practices over the past three decades. However, modern computer technology has allowed these individual best practices to be joined in a supportable process. A new pair of state-of-the-art IT systems were recently developed with a PV concept of operations to support this GPVP logic. They support the 'clinical art' of PV, by providing 'soup to nuts' approach, powerful data-mining and query tools, and work environments for case-series management and product preparation.

A similar process was developed in the late 1990s at the US Food and Drug Administration and is supported by the adverse event reporting system (AERS) [figure 2].[6]

The technical tools now available substantial steps forward in identifying alerts from random data. They can be effective in seeing what may be otherwise invisible to the human eye. They also allow for the development of and focus on higher-level processes that are both efficient and effective. These computer systems can make the human more productive and less likely to miss important public health information hidden in 'haystacks' of data. They also provide the needed tools and work environments to analyse the data so that a full assessment can be conducted in an efficient and effective manner.

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