

Pharmacovigilance

The Issue

All medicines have potential risks as well as benefits. The aim of pharmacovigilance¹ is to protect public health by identifying, evaluating and minimizing safety issues to ensure that the overall benefits of medicines outweigh the risks.

Historically post-marketing processes have relied primarily on the voluntary reporting of side effects. However, the recent withdrawal from the market of certain medicines has focussed attention on pharmacovigilance approaches; raised concerns about improving the existing pharmacovigilance framework; and highlighted the need to ensure consistency among international regulations governing the reporting of side effects (aka "Adverse Drug Reactions" - ADRs).

This paper outlines the stages involved in monitoring and reviewing the safety of a medicine before and after approval by Regulatory Authorities; explains the well-established and rigorous, world-wide system that GSK has in place to monitor the safety of potential new medicines during clinical development and for approved medicines; and highlights where GSK believes better regulation and pharmacovigilance approaches could improve the current pharmacovigilance framework.

GSK's Position

- Patient safety is the fundamental principle for GSK, ahead of commercial or other interests. We conduct our clinical trials according to high standards of ethics and safety, and we are committed to transparency on the benefits and risks of all our medicines in all communications with patients, prescribers, payers and regulators.
- GSK is committed to continuously evaluating the benefit/risk profile of our medicines. We are leaders in the field of signal detection (identifying possible side effects associated with our medicines) and evaluation methodology including the use of computerised systems (Online Signal Management Bioinformatics Awards June 2005). We also have policies and a governance framework in place to help us detect and act on any side effects that may be associated with our medicines.
- GSK is an industry leader in a number of areas of emerging science which can be applied to characterise risk and benefit, for example, "pharmacogenetics" - the study of the genetic variations between individuals that may pre-dispose people to respond differently to medicines. We are in regular dialogue with industry Regulators (e.g. FDA, EMEA) about how this and other monitoring mechanisms might be applied during the development, registration and pharmacovigilance of medicines.

¹ The WHO defines pharmacovigilance as "the science and activities relating to the detection, monitoring, assessment, understanding and prevention of adverse effects or any other drug related problems (WHO).

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- The science of pharmacovigilance is continually evolving, providing new ways of enhancing the pharmacovigilance framework to the benefit of industry, regulators, healthcare professionals and most importantly patients. To enhance pharmacovigilance GSK would recommend that:
 - Regulators consider safety and efficacy together. Separating them would prove counterproductive. Every medicine involves a combination of benefit and risk, and decisions on the use of a medicine must be made in that context.
 - Initiatives are undertaken to increase the quantity and quality of the reporting of possible side effects of medicines from healthcare professionals and patients
 - There is a focus on the development of electronic patient records and active safety surveillance systems which would permit “real time” access to anonymised data sets for the detection and evaluation of possible side effects.
 - Pregnancy registries are established by health care systems to enable the rapid collection and evaluation of data related to possible adverse events, including birth defects.
 - Research is undertaken to establish the most effective ways to minimise the risks of medicines including effective ways of communicating the benefits and risks of medicines to healthcare professionals and patients.
 - There is increased harmonisation of pharmacovigilance rules through the rapid and consistent implementation of ICH guidelines by the EU, US and Japan.
 - An EU Pharmacovigilance Regulation is introduced to streamline and simplify pharmacovigilance reporting requirements in Europe.

BACKGROUND

Product Development and Safety Issues

Before evaluation of a potential new medicine in humans can begin, extensive preclinical (or laboratory research) must be conducted. This research typically involves years of experiments including animals and human cells. If this stage of testing is successful, these data are provided to regulatory authorities, requesting approval to begin evaluating the potential new medicine in humans. This evaluation is done through clinical trials and is usually conducted in three main phases. Each phase addresses different questions that determine if the testing of the “Investigational Medicinal Product” (IMP) can proceed to the next phase.

Phase I: Phase I studies are primarily concerned with assessing the IMP's safety in a small number of healthy human volunteers (typically between 20 and 100 people) and are designed to determine what happens to the IMP in the human body.

Phase II: An IMP that passes the Phase I testing hurdle then moves on to Phase II, the “proof of concept” stage. Here for the first time, the IMP will be administered to carefully selected patients suffering from the disease which the IMP will potentially treat. Generally 100 – 300 patients are enrolled in these Phase II studies. The aim of the studies is to determine if the IMP treats the illness it is intended for, as well the amount and frequency of drug dosing necessary to achieve the optimal benefits for patients with the smallest number of side effects.

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Phase III: Phase III clinical testing is the most expensive and time consuming part of the development process. In these studies, the IMP is administered to hundreds and frequently thousands of patients throughout the world. Phase III studies require differing periods of time to complete depending on the disease being studied. Results of anti-infective studies can be obtained in a period of 30 days or less, but Phase III studies in chronic diseases may require years.

Phase IV: Trials of a medicine may continue even after it has been approved for marketing. Known as Phase IV trials, they may further evaluate the effect of the medicine for the approved use, assess other potential uses, or yield additional safety data. Regulatory agencies may require these trials to address specific questions.

GSK's Safety Governance Framework

GSK receives information on possible side effects of medicines from several sources including:

- Unsolicited reports from health professionals and patients
- Clinical trials and clinical trial investigators
- Regulatory authorities
- Medical and scientific literature
- Newspapers and other media

It is GSK policy that staff are required to report immediately any issues relating to the safety or quality of our medicines.

According to the type of product (pharmaceutical, vaccine or consumer healthcare product) the information is sent to one of three Central Safety Departments. Each GSK country manager is responsible for the collection of safety information and reporting the information to the relevant Central Safety Department. When necessary, further information is sought from individuals who have reported the potential side effect and the data is recorded on a computerised database for ease of retrieval and analysis. Where appropriate safety information is reported to regulatory authorities in periodic safety updates or for serious safety concerns as soon as possible after such concerns are identified.

Information that changes the benefit/risk profile of a GSK medicine will result in certain actions to characterise, communicate and minimise the risk. Proposed actions are discussed with regulatory authorities and can include modifying the prescribing information, communications to physicians and other healthcare providers and sometimes carrying out further clinical trials. In certain cases it may be appropriate to stop clinical trials or to withdraw the medicine from the market.

GSK operates a worldwide Safety Board Chaired by the Chief Medical Officer. The Safety Boards' mission is to ensure that human safety is addressed proactively throughout product development and to review the safety of GSK Products as may be warranted in light of clinical experience. GSK also has Global Labelling Committees that review and approve the prescribing information for all GSK medicines and ensure that this is updated when appropriate.

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GSK is a leader in:

- Applying computerised statistical tools to facilitate the evaluation of safety information through, for example, the identification of unexpected adverse events that are being reported on a disproportionate basis (safety signals).
- Evaluating and applying pharmacogenetics² to enhance the risks and benefits of our medicines for patients. As part of our efforts, we collect blood samples for potential DNA analysis in the majority of our Phase I, II and III drug development trials (with ethics committee review and informed patient consent). GSK is in regular dialogue with Regulators (e.g. US FDA, EMEA and Japan's Ministry of Health, Labour and Welfare) regarding how PGx data should be interpreted and applied on a case by case basis during the development, licensing and post marketing phase of a medicine.
- Supporting the public disclosure of the results (including safety information) from GSK sponsored clinical trials. In 2004 we launched the GSK Clinical Study Register which provides summary results from all GSK sponsored trials (phase I-IV) of marketed medicines completed since the formation of GSK. These summaries include all the serious adverse events and common adverse events reported in the trials.

Proposal for Enhancing Pharmacovigilance

Data Collection and Evaluation

The tools and processes used in pharmacovigilance are continually evolving. Effective use of these tools, along with improved reporting and communication tools, helps to ensure that potential and actual side effects can be better identified in investigational and marketed medicines. GSK recommends that initiatives to improve the pharmacovigilance framework should include:

- *Improved reporting:* Collection of data on rare side effects through company or regulatory agency databases serves as an important starting point for possible further action. However, one of the shortcomings of this system is the variable nature of reporting and the quality of reports received. One of the chief difficulties with side effect reporting is ensuring the quality of the databases, and obtaining any necessary follow-up information. Resources are often expended in contacting health care professionals regarding aspects of a report they have filed. In some instances, the reporter is unable or unwilling to provide sufficient detail to allow for a rigorous evaluation of the reported event. GSK would therefore support initiatives aimed at improving pharmacovigilance through improved education of medical students and physicians regarding the quality of ADR reporting. Training modules could explain the role and responsibilities of healthcare professionals in reporting ADRs; how to identify and evaluate an ADR; and how to prepare and submit reports of high quality.

² The goal of PGx is to provide information which could help identify a subcategory of patients who are more likely to respond negatively ("safety" PGx) or positively ("efficacy" PGx) to certain medicines, PGx could enable better prediction of likely outcomes and influence a medicine's benefit-to-risk ratio for a subgroup of patients.

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- *Real-life / real-time databases:* Pharmacovigilance could be enhanced by using novel technologies to allow companies and regulators to access anonymised data obtained from the use of medicines in clinical practice. For example, information captured systematically in electronic patient records could help identify a potential association between a side effect and a *particular medicine* or combination of medicines, by facilitating a comparison of side effects between patients who have and have not taken the medicine(s). The incidence of side effects associated with the *natural history of diseases* would also be of value in helping evaluate more effectively whether a side effect is more likely to have been caused by the medicine or whether it is more likely to have been caused by another treatment or the disease.
- *Research into Risk Management Methodologies:* Risk Management is defined as a set of pharmacovigilance activities and interventions designed to identify, characterise and prevent or minimise risks relating to medicinal products, including risk communication and the assessment of the effectiveness of risk minimisation interventions. It is important that research is undertaken to establish the most effective ways to minimise the risks of medicines including effective ways of communicating the risks and benefits of medicines to healthcare professionals and patients. This research could be conducted through collaborative approaches (industry, regulators, patients and academia). An ideal framework to conduct this research is the proposed European Technology Platform on Innovative medicines
- *Pregnancy registries:* Rare side effects that occur in a particular sub-group of the patient population are particularly challenging to detect because of the low number of patients and the low incidence of the side effect. In this regard, pregnancy registries could be established by public health systems that require information on medicines given during pregnancy to be recorded together with the health outcome for the mother and baby.

International Harmonisation

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) was established in 1990. It brings together the regulatory authorities of Europe, Japan and the United States, and experts from the pharmaceutical industry via its three regional trade associations, plus key observers (including the WHO).

The ICH's main purpose is to recommend ways of achieving greater harmonisation in the interpretation and application of technical guidelines and requirements for product registration. Over 45 guidelines on a range of activities have been adopted since the ICH's creation.

Increased international harmonisation of pharmacovigilance rules is very important. It is critical that the rules are consistently implemented into national or regional frameworks. Inconsistencies can result in resources being used to meet complex regulations rather than being used to enhance the risks and benefits of medicines for patients. More importantly regulations and their harmonisation should be based on the scientific evidence available and where necessary further research should be conducted.

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For example, research into the effectiveness of risk minimization methodologies should be undertaken to inform the effective incorporation of the recently published guidance ICH E2E on pharmacovigilance planning into national legislation within the EU, US, and Japan.

Pharmacovigilance in Europe

The divergence of rules in different EU Member States makes it impossible for a pharmaceutical company to have a single pharmacovigilance system throughout Europe. This ties up resources that could be better focused on the evaluation of drug safety and risk management to the benefit of public health.

Under current rules, medicines are authorized under different approval procedures (e.g. national, mutual recognition and centralized authorization). This leads to a number of different processes running parallel within the EU framework. For example:

- There are different labelling requirements. As a result, medicines authorized under a national system might well be labelled in a way that could make it difficult for a physician to understand and compare the risk/benefit profile of that product with a product that is centrally authorized. This cannot be in the best interests of public health.
- There are different expedited reporting requirements depending on approval procedure and country of origin of the reports. For example *all* serious ADRs from within the EU but only serious *unexpected* reactions from outside the EU need be reported. Pharmacovigilance should not be affected by national borders.
- Pharmaceutical companies are required to submit all serious unexpected drug reactions to each individual Member State. This amounts to an unnecessary duplication of work. It would be far more efficient and logical to report all serious cases to a single point in the EU (or better still, to report all cases to a single point)

GSK's main recommendation for addressing this inconsistent and inefficient system of reporting within Europe would be the adoption of a Council Regulation on Pharmacovigilance ('PV Regulation').

- A PV Regulation should contain clear and concise provisions that would simplify, strengthen and provide legal certainty to the EU legislative framework for pharmacovigilance. A Regulation is directly applicable and legally binding on all interested parties in all EU Member States, and would therefore eliminate burdensome national discrepancies throughout an enlarged European Union. The PV Regulation should:
 - Contain a single set of simplified rules for expedited and periodic reporting of ADRs in the EU and provide for a single reporting point for ADRs within the broader European Economic Area (ie. the 25 EU Member States plus Norway, Iceland and Liechtenstein).
 - Remove the "unexpected/expected" concept, and require the reporting of all serious cases when electronic reporting is implemented (or potentially all cases, following a feasibility study/pilot).

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- Contain clear and flexible provisions regarding EU Qualified Persons ('QPs') responsible for pharmacovigilance that allow individual companies to appoint the number of QPs best suited to their respective organizations.
- Eliminate personal liability for QPs in order to ensure the availability of highly qualified professionals willing to perform the function of QP
- Provide for consistent standards for inspections of company pharmacovigilance departments by the EMEA and EU Member State authorities

Pharmacovigilance in the United States

In recent years, Federal lawmakers have responded to public concerns regarding product safety with several oversight hearings and legislative proposals. The most prominent proposals have been to require greater clinical data transparency and to expand the FDA's post-market surveillance powers.

In September 2007, in conjunction with the reauthorization of the Prescription Drug User Fee Act (PDUFA), the US Government enacted significant new laws relating to drug safety. This legislation, entitled the FDA Amendments Act (FDAAA) includes provisions in the areas of:

- Expanded post-marketing authorities for FDA, particularly in the area of requiring post-marketing studies and clinical trials.
- Establishment of a Risk Evaluation and Mitigation Strategy (REMS) infrastructure that will allow FDA to require additional communication and reporting around drug safety, as well as possible restrictions on distribution and use.
- Clinical Trial Registration and Results Database.
- Active Safety Surveillance, using anonymized data from large health care databases.

FDAAA also authorizes significant new user fee funding to be directed toward drug safety efforts.

GSK recognises and shares the FDA's goal of creating a more effective pharmacovigilance framework through its ongoing efforts, as well as through the implementation of the provisions within FDAAA, and we will continue to work with the Agency toward that goal.

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