GSK Public policy positions

Pharmacovigilance

The Issue

All medicines have risks as well as benefits. The aim of pharmacovigilance[1] is to protect public health by identifying, evaluating, managing and minimising 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; and explains the well-established and rigorous, worldwide system that GSK has in place to monitor the safety of potential new medicines during clinical development and for approved medicines.

GSK's Position

– Patient safety is a fundamental principle for GSK.

– We conduct our clinical trials according to high standards of ethics and safety and support 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.

– We 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.

– We apply 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).

– GSK is committed to continuously evaluating the benefit/risk profile of our medicines. All medicines in development are assessed for their benefits vs. risks at milestone reviews. Marketed medicines are regularly assessed throughout their lifecycles. We are committed to transparency in our evaluation and communication of these benefits and risks with patients, prescribers, payers and regulators.

– The science of pharmacovigilance is continuously evolving and GSK is actively involved in working with industry, regulators, healthcare professionals and patients to enhance methodologies in this area.

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.

[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".

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 dose and frequency of dosing necessary to achieve the optimal benefits for patients with the least side effects.

Phase III: Phase III clinical testing is the most complex and lengthy 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 last for periods depending on the disease being studied. Results of anti-infective studies can be obtained in 30 days or less, but Phase III studies in chronic diseases may require years.

Post-marketing Trials

Phase IV: Trials of a medicine may continue even after it has been approved for marketing. Known as Phase IV trials, these 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 collects information on possible side effects of medicines from several sources including:

– Ad hoc reports from health professionals and patients
– Clinical trials and clinical trial investigators
– Patient Support Programs and Market Research studies
– Regulatory authorities
– Medical and scientific literature
– Newspapers and social media

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

Each GSK Country Manager is responsible for the collection of safety information and reporting the information to the 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, reported as soon as possible after such concerns are identified.

The benefit/risk profile of a GSK medicine is assessed throughout its lifecycle using a benefit/risk framework and appropriate analyses. When information is found that changes the benefit/risk balance in a negative direction, action is taken to characterise, communicate and minimise the risk. Proposed actions are discussed with regulatory authorities and can include modifying the prescribing information (which includes the patient information leaflet), 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 Global Safety Board chaired by the Chief Medical Officer. The Safety Board's mission is to ensure that human safety is addressed proactively throughout product development and to review the safety of GSK products on the market 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.

Enhancing Pharmacovigilance

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

- Improved reporting of ADRs by HCPs: 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 healthcare 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.
- Real-life / real-time databases: Pharmacovigilance will be enhanced by using novel technologies to allow companies and regulators to access larger and larger electronic health record information from anonymised data to help identify a potential association between a side effect and a particular medicine or combination of medicines The Innovation in Medical Evidence Development and Surveillance (IMEDS) program is an example of a public-private partnership created to advance the science and tools necessary to support post-market evidence generation on regulated products, including safety surveillance and evaluations, and to facilitate utilisation of a robust electronic healthcare data platform for generating better evidence on regulated products in the post-market settings. GSK is participating in this project. http://www.reaganudall.org/our-work/safety-and-better-evidence/imeds-program/
- 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 can be conducted through collaborative approaches (industry, regulators, patients and academia). One such example is the Innovative Medicines Initiative project PROTECT (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium). This is a collaborative European project aimed at addressing the limitations of current methods in the field of pharmacoepidemiology and pharmacovigilance. The EMA is the coordinator of PROTECT and GSK is the deputy coordinator of PROTECT. They manage a multi-national consortium of 33 partners including academics, regulators, SMEs and EFPIA companies. http://www.imi-protect.eu/
- Pregnancy registries: There is a need to monitor the safety of medicines in pregnancy both for the mother and for the offspring. One common solution is the creation of, national or international pregnancy registries to gather information on medicines given during pregnancy together with the health outcome for the mother and baby.

GSK uses all of these approaches to monitor our patients' well-being and ensure that the benefits of our products continue to outweigh their risks. We are committed to collaborating with our industry colleagues, regulators, healthcare providers, patients and other interested parties to continually improve the science of benefit/risk evaluation and pharmacovigilance, as well as inviting more dialogue with all of these collaborators to improve communication about our medicines.

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