GSK Public policy positions

Pharmacovigilance

The Issue

All medicines have risks as well as benefits. The aims of pharmacovigilance[1] are to enhance patient care and safety in relation to the use of medicines; and to support public health programmes by providing reliable, balanced information to ensure that the overall benefits of medicines outweigh the risks.

This paper outlines the well-established and rigorous worldwide system that GSK has in place to monitor and review the safety of our medicines throughout clinical development and following their approval by Regulatory Authorities.

GSK applies consistent pharmacovigilance principles across our entire product portfolio. Throughout this document, the term "product" applies to any GSK marketed or investigational product, and the term "patient" applies to any person receiving such a GSK product.

GSK's Position

– Patient safety is a fundamental principle for GSK. We comply with international regulations governing the reporting, analysis and communication of side effects. We have a governance framework and policies in place to help us detect and act on any side effects and other human safety information that may be associated with our products.

– 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. The GSK Clinical Study Register provides summary results from all GSK sponsored trials (phase I-IV) of marketed medicines completed since the formation of GSK. These summaries include the serious, and other non-serious, side effects reported in the trials. Our trial results are made public regardless of whether they reflect positively or negatively on our medicines.

– We are committed to identifying and managing human safety information to help safeguard those who take our products or take part in our human subject research. All GSK employees and complementary workers across the world are trained on their responsibilities to report human safety information.

– We apply computerised statistical tools to support identification and evaluation of safety information. For example, the identification of new side effects or a change in the nature, frequency or severity of known side effects.

– GSK is committed to continuously evaluating the benefit/risk profile of our products. All products in development are assessed for their benefits vs. risks at milestone reviews. Marketed products 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 (HCPs) and patients to enhance methodologies in this area.

Background

Product Development and Safety Issues

Before evaluation of a potential new product in humans can begin, appropriate 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, data is provided to regulatory authorities, requesting approval to begin evaluating the potential new product in humans. This evaluation is conducted through interventional clinical trials, usually conducted in four main phases and governed by strict regulation.

[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 investigational product's safety usually in a small number of healthy human volunteers (typically between 20 and 100 people) and are designed to determine what happens to the investigational product in the human body.

Phase II: An investigational product that passes Phase I testing then moves on to Phase II, which usually includes the **"**proof of concept" stage. Here, for the first time, it is administered to carefully selected patients suffering from the disease which the product will potentially treat. Generally, 100–300 patients are enrolled in these Phase II studies, although Phase II prophylactic vaccine trials enrol up to several hundred healthy volunteers.

The main aim of these studies is to determine if the investigational product has a beneficial effect on the illness it is intended to target, as well as the amount and frequency of dosing that will achieve the optimal benefits for patients with the fewest side effects.

Phase III: In Phase III studies, the investigational product is given to hundreds - and frequently thousands - of patients. Phase III studies require differing periods of time to complete, depending on the disease being studied.

The principle objectives in Phase III are to demonstrate the safety and effectiveness of the investigational product in the typical patient likely to use it; to confirm effective dosing levels; to identify side effects or reasons why the treatment should not be given to people with another condition (known as 'contraindications'); and to build knowledge of the risks/ benefits of the product by comparing results with those achieved by existing treatments.

Phase IV: Trials of an investigational product may continue after it has been approved for marketing. Phase IV trials may further evaluate the effect of the product for the approved use; assess other potential uses; or yield additional safety data. Regulatory agencies may require these trials to address specific questions.

Other types of clinical research, such as **non-interventional research** (using data collected during the provision of routine healthcare) and analyses of data that is combined from a number of clinical trials (e.g. **meta-analyses**), are increasingly seen as important evidence in the evaluation of the risks and benefits of products.

GSK's Safety Governance Framework

The benefit/risk profile of a GSK product 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), sending communications to HCPs and sometimes carrying out further clinical trials, epidemiological studies, Post Authorization Safety Studies and/or other risk management measures. In certain cases, it may be appropriate to stop clinical trials or to withdraw the medicine from the market.

GSK collects information on possible side effects of its products from multiple sources including:

– Clinical trials and clinical trial investigators
– *Ad hoc* (spontaneous) reports from HCPs and patients/consumers
– Regulatory authorities
– Interactive Digital Media, Patient Support Programs and Market Research studies
– Medical and scientific literature
– Newspapers and social media

It is GSK policy that staff are required to immediately report any issues relating to the safety or quality of our products. For each GSK Local Operating Company, the General Manager is accountable for establishing a Pharmacovigilance System to ensure collection and reporting of safety information to the Central Safety Department and the relevant regulatory authorities. The data is recorded on a computerised database for ease of retrieval and analysis and, when necessary, further information is sought from individuals who have reported the potential side effect. GSK reports safety information in an expedited manner for serious safety concerns. We also submit individual case safety reports (ICSRs) and/or periodic safety updates, in accordance with the requirements of regulatory authorities around the world.

Governance Bodies

The governance of our safety processes is managed through the **GSK Human Safety and Product Information (HS&PI) Medical Governance Board.** It provides enterprise-wide oversight of the system of principles, policies and responsibilities that ensure the safety evaluation of our products is operating effectively.

The GSK **Global Safety Board's** remit is to ensure that human safety is addressed proactively throughout the product life-cycle and to review the safety of individual GSK products as may be warranted in light of clinical experience.

At designated milestones during the research and development stage, the GSK **Scientific Review Board** reviews the benefit/risk balance of pharmaceutical medicines, and the protection of patient welfare. Either the Chair of the Scientific Review Board or the Chief Medical Officer may refer these milestone reviews to the Global Safety Board.

There are also business unit Safety Boards focused on consumer healthcare products and vaccines that work collaboratively with the Global Safety Board. A business unit Safety Board may self-refer a matter it has considered for further discussion by the Global Safety Board.

Labelling Committees review and approve the prescribing and/or product information for GSK products as well as updates when appropriate. Labelling committees may refer labelling issues related to significant safety concerns to the Global Safety Board for advice and/or decision making. The Global Safety Board may direct teams to work with labelling committees to create or amend labeling related to safety issues.

Initiatives Aimed at Enhancing Pharmacovigilance

The tools and processes used in pharmacovigilance are continually evolving. Effective use of these tools, along with improved reporting and communication, helps to ensure that human safety information can be better identified in investigational and marketed products. Initiatives to improve the pharmacovigilance framework focus on and include:

- **Improving reporting of human safety information by HCPs, patients and consumers**: 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 shortcoming of this system is the variable nature of reporting, including challenges in ensuring the quality of the reports and obtaining necessary follow-up information. In some instances, the reporter is unable or unwilling to provide sufficient detail to allow for a rigorous evaluation of the reported side effect.

  GSK is an active participant in industry initiatives to improve current practices, such as the WEB-RADR project whereby a mobile app will enable patients and HCPs to report suspected side effects to national European Union regulators. It is also investigating the potential for publicly available social media data for identifying drug safety issues (https://web-radr.eu/).

- **Improving education of medical students and HCPs in the developing world**: Training modules explain the role and responsibilities of HCPs in identifying and evaluating side effects and other human safety information, and subsequently preparing and submitting reports of high quality.

- **Ensuring compliance with the Identification of Medical Products (IDMP) Project**: IDMP is a set of international data standards for the unique identification of medicines. The standards allow for identification of a product, where individual components are sourced and where it is marketed, enabling consistent analysis of safety issues across products and manufacturers.

- **Using novel technologies**: Using novel technologies such as real-life / real-time databases allowing companies and regulators to access 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.

- **Pregnancy registries**: There is a need to monitor the safety of medicines in pregnancy both for the mother and for the child. One common solution is the creation of national or international pregnancy registries to gather information on medicines received by a mother during pregnancy, together with the health outcome for the mother and baby.

GSK supports all of these approaches to ensure that the benefits of our products continue to outweigh their risks. We are committed to collaborating with industry colleagues, regulators, healthcare providers, patients, consumers and patient advocacy groups and other interested parties to continually improve the science of benefit/risk evaluation and pharmacovigilance. We also invite continued dialogue with these stakeholders to improve communication about our products.

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