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CHARTING THE COURSE: AN OVERVIEW OF PHARMACOVIGILANCE HISTORY

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Abstract
Pharmacovigilance is a critical component of healthcare systems worldwide, focusing on the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems. This abstract provides a concise overview of pharmacovigilance, its significance, objectives, and key processes. It highlights the role of pharmacovigilance in ensuring the safety and efficacy of pharmaceutical products and its evolving importance in the context of public health. It also emphasises the international collaboration and legal framework that oversee pharmacovigilance efforts, highlighting the ongoing requirement for thorough medication safety monitoring to safeguard patient welfare.

Keywords: Thalidomide disaster, Regulatory agencies, Post-marketing surveillance, Adverse Drug Reactions (ADRs)

Introduction

Under the European Union (EU), pharmacovigilance (PV) is described as the "process and science of monitoring the safety of medicines and taking action to reduce the risks and increase the benefits of medicines". The global PV systems seek to enhance patient safety and quality of life while also keeping an eye on the risks and benefits of drugs. PV activities include data collection and management on medication safety, case report analysis to identify novel "signals," proactive risk control to reduce possible risks related to medication usage, and stakeholder and interaction with patients. The Overview of Product Characteristics, published by the holder of the marketing authorization for any new drug at initial boot into the market, may be modified by CAs (Controlling Authorities) based on newly identified signals thanks to this simple after-marketing surveillance,

which mainly aims to protect the public[1]. The word "pharmacovigilance" are: Pharmakon (Greek) = medicinal substance, and Vigilia (Latin) = to keep watch.

Historical evolution of Pharmacovigilance

1848 -Hannah Greener death caused by Chloroform
1901 -In USA, 13 Children died from contaminated diptheria antitoxin due to which passed Biological Control Act 1902- ensure purity and safety of serum, vaccines, and other products.
1937-Death of more than 100 children due to toxicity of Sulphanilamide.
1938-Federal Food and Drug Cosmetic Act was established and the public system was renovated.
1950-Aplastic Anaemia reported due to Chloramphenicol toxicity.
Durham- Humphrey Amendment of 1951 (FDCA amendment 1951) – separation of drugs in 2 types – drugs 1951could be used without physician assistance (OTC drugs) and drugs needing physicians assistance.
1961-Mc Bride letter about the tragedy of Thalidomide.
19631-6th World Health Congregation recognised significant to rapid action on ADR
1964-The Yellow Card was structured in UK.
1965-European Legislation
1995-WHO Programme for International Drug Monitoring was instituted
1996-Clinical Trial Initiated in India
1997-India attached with WHO ADR Monitoring Programme.
1998-Initiation of Pharmacovigilance in India.
2001-Eudravigilance was funded (EC Directive 65/65)
2002-67th National Pharmacovigilance centre established in India.
2012-New European Legislation Directive (2010/84/EU)
2017-New Eudravigilance Format

In 1747, James Lind conducted a groundbreaking experiment to prove the benefits of lemon juice for scurvy prevention. He divided sailors into different groups and provided The benefits of lemon juice for scurvy prevention them with various dietary supplements. The group receiving lemon juice quickly recovered from scurvy, demonstrating that vitamin C in citrus fruits was a crucial factor in preventing this debilitating disease. Lind's work laid the foundation for the understanding of nutrition and the importance of vitamin C in maintaining health.

Pharmacovigilance began 170 years ago on January 29, 1848, when Hannah Greener, a little girl from the northern region of England, passed away following the administration of a chloroform anaesthesia

prior to the excision of an infected toenails. Chloroform was a more potent and safer anaesthetic, which Sir James Simpson developed and used in clinical practice. Although the circumstances of Hannah's death were looked into in order to comprehend what had happened to her, the cause of her death could not be determined. Most likely, a fatal arrhythmia or a pulmonary aspiration caused her death [3].

A commission to address this issue was formed by The Lancet Journal in response to additional deaths and concerns expressed by physicians and the general public regarding the safety of anaesthesia. The panel urged all English physicians, including those practicing in colonies of organisms, to report any fatalities brought on by anaesthesia. The findings were released in 1893 [4] in The Lancet.On June 30, 1906, the US Federal Food and Drug Act was created, establishing the need that medications be clean and devoid of any impurities. Additionally, this organisation outlawed the use of fraudulent therapeutic indications for medications in 1911 [4].

Diethyl glycol was the solvent of sulfanilamide elixir, which caused 107 deaths in the United States in 1937. Although the manufacturing businesses were unaware of the solvent's toxicity at the time, it was believed to be the root cause of deaths [3, 5, 6]. As a result, in 1938 the Federal Food, Drug and Cosmetic Act was created with the intention of updating the public health system. In fact, the new system included the ability to perform factory inspections and anticipated that pharmaceutical safety should be shown prior to market approval [7]. Acetylsalicylic acid (ASA) was proposed by Douthwaite as a possible cause of melena in 1938 [8]. Different results were found in the investigation of ASA's gastrointestinal toxicity.

In 1950, a pivotal medical breakthrough occurred when the first instances of aplastic anemia resulting from the toxic effects of chloramphenicol came to light. This discovery represented a crucial milestone in the field of medicine, establishing a clear connection between the antibiotic chloramphenicol and the rare yet life-threatening blood disorder called aplastic anemia. This revelation brought about heightened awareness of ADRs and underscored the imperative for more secure pharmaceutical practices.

However, In 1955, a significant medical breakthrough occurred when it was definitively established that acetylsalicylic acid (ASA), commonly known as aspirin, could potentially cause gastrointestinal diseases. This pivotal discovery marked a crucial turning point in the history of medicine, shedding light on the adverse effects associated with this widely used pain-relief medication. The research findings not only confirmed the link between ASA and gastrointestinal disorders but also paved the way for significant changes in clinical practice.

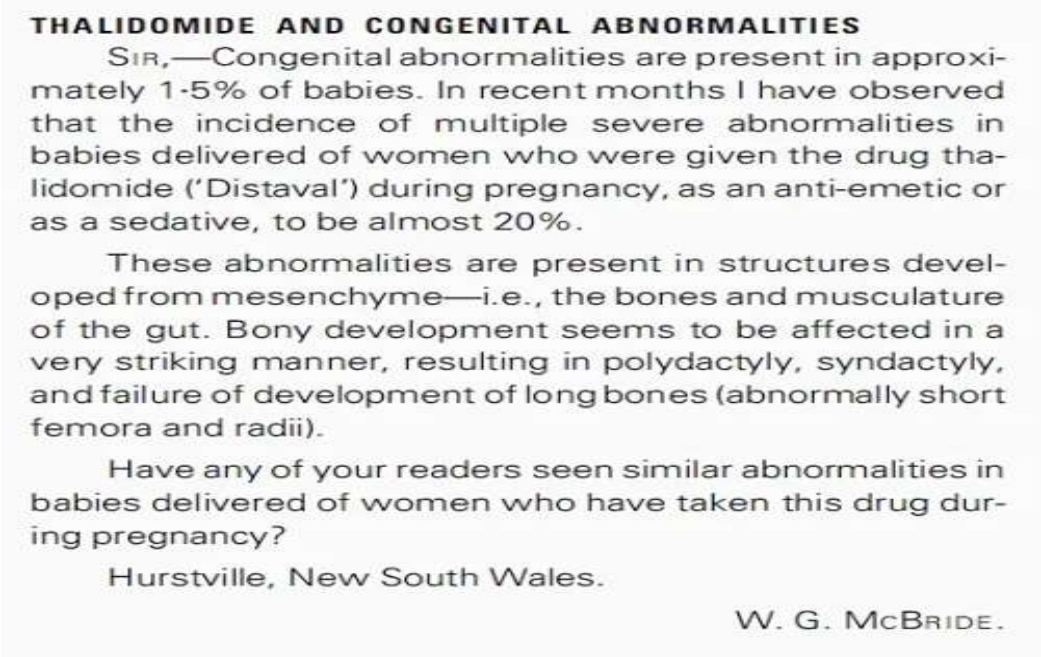
As a direct consequence of this discovery, ASA is now considered contraindicated for individuals who have pre-existing gastrointestinal ulcers. This contraindication serves as a crucial guideline for healthcare providers when making treatment decisions for their patients. It underscores the

importance of considering individual patient histories and risk factors when prescribing medications, especially ASA.

The recognition of ASA's potential to cause gastrointestinal harm has led to increased awareness of the need for safer pharmaceutical practices. Physicians and healthcare professionals now exercise greater caution when prescribing ASA, particularly to patients with a history of gastrointestinal ulcers. Additionally, patients are advised to be aware of the potential risks associated with ASA and to communicate any existing conditions to their healthcare providers.

The landmark discovery in 1955 linking ASA to gastrointestinal diseases has had a profound impact on medical practice. It has significantly influenced the contraindication of ASA in patients with gastrointestinal ulcers, emphasizing the importance of individualized patient care and safer pharmaceutical practices. This discovery serves as a powerful reminder of the ever-evolving field of medicine and the ongoing commitment to patient safety.

In 1961, thalidomide was a commonly prescribed medication for treating nausea in expectant mothers during the late 1950s and early 1960s. The 1960s saw the discovery that hundreds of children receiving thalidomide had serious birth abnormalities. At that time, thalidomide was illegal in most countries, yet it was shown to be an effective treatment for leprosy and later multiple myeloma. Pregnant leprosy patients treated with thalidomide have continued to develop deformities in rural parts of the world without significant medical surveillance programmes. A deeper comprehension of molecular targets is being attained through research on the mechanisms of action of thalidomide. Better knowledge of these molecular targets could lead to the development of safer medications. The thalidomide incident was a game-changer for toxicity testing because it forced domestic and international regulatory bodies to create organised protocols for testing thalidomide; additionally, using thalidomide as a tool in the field of developmental biology revealed crucial information about the biochemical pathways involved in limb development. It is fitting to review the lessons from the 1960s thalidomide disaster in honour of the community of Toxicology's 50th celebration, which also happens to be the fiftieth anniversary of thalidomide's removal from the market. In a letter to the editor of the Lancet Journal, Australian physician Dr. McBride proposed a link between thalidomide and congenital malformations in infants.Indeed, he noted that among pregnant women who had taken thalidomide, the incidence of congenital abnormalities in newborns (1.5%) had risen to as high as 20%[10].



THALIDOMIDE AND CONGENITAL ABNORMALITIES

SIR,—Congenital abnormalities are present in approximately 1-5% of babies. In recent months I have observed that the incidence of multiple severe abnormalities in babies delivered of women who were given the drug thalidomide ('Distaval') during pregnancy, as an anti-emetic or as a sedative, to be almost 20%.

These abnormalities are present in structures developed from mesenchyme—i.e., the bones and musculature of the gut. Bony development seems to be affected in a very striking manner, resulting in polydactyly, syndactyly, and failure of development of long bones (abnormally short femora and radii).

Have any of your readers seen similar abnormalities in babies delivered of women who have taken this drug during pregnancy?

Hurstville, New South Wales.

W. G. MCBRIDE.

Simultaneously, during a German Paediatric Convention, Dr. Lenz proposed a link between thalidomide and abnormalities, and his suspicion was reported in the German journal Welttam Sonnatag [11]. A retrospective research conducted in 1973 revealed a link between thalidomide consumption during pregnancy and congenital abnormalities in newborns [12].The USA did not observe the thalidomide catastrophe since Dr. Kelsey expressed serious concerns regarding the drug's safety during pregnancy [5]. The thalidomide catastrophe exposed a number of crucial concerns and difficulties, including the validity of animal testing, the actions of the pharmaceutical corporation, and the significance of drug monitoring following commercialization. This tragedy specifically modifies the pharmacovigilance system by making the unplanned reporting of adverse medication reactions structured, regulated, and methodical. Everything required to create an impromptu reporting and demonstrate a causal connection between the medication and the adverse event was already there in this letter [13].

The "Yellow card" (YC) was established in the United Kingdom in 1964. YC is a particular form used to get an unplanned report on medication toxicity [14].

The United States (1962) enacted an amendment mandating the submission of safety and effectiveness data for pharmaceuticals prior to premarketing approval. This modification requires that teratogenicity tests on three separate animals be included in the safety data[5].

In 1963, during the 16th World Health Congress, the importance of taking rapid action on Adverse Drug Reactions (ADRs) was officially recognized. This acknowledgment highlighted the need to promptly address and monitor adverse effects of medications to enhance patient safety and improve

the regulation of pharmaceuticals. It marked a significant step towards prioritizing drug safety and public health on a global scale.

The thalidomide tragedy in Europe in 1965 sparked the creation of European legislation, resulting in the EC Regulation 65/65 [15]. The Boston Collaborative Drug Surveillance Programme began with a pilot study in 1966. It was the first organisation to use in-hospital monitoring to perform epidemiologic studies to measure the possible side effects of medications, and it played a crucial part in the creation and use of techniques in drug epidemiology[16].

Ten countries—Australia, the United Kingdom, the United States, Germany, Canada, Ireland, Sweden, Denmark, New Zealand, and the Netherlands—participated in the WHO Programme for International Drug Monitoring when it was established in 1968. Italy took part in this initiative back in 1975[17]. Between 1968 and 1982, a number of studies were carried out on observed adverse medication responses [3]. Following funding, the European Society of Pharmacovigilance (ESoP) became the isop in 1992. This society was founded with the purpose of advancing pharmacovigilance and improving all facets of the appropriate and safe use of medications [18].

In 1996, a significant event took place when a clinical trial was initiated in India. This marked the beginning of research and testing of medical interventions or drugs within the Indian population. Clinical trials are essential for evaluating the safety and efficacy of treatments and contributed to India's growing role in global medical research and pharmaceutical development.

In 1997, India became affiliated with the World Health Organization (WHO) Adverse Drug Reaction (ADR) Monitoring Programme. This affiliation signified India's commitment to monitoring and reporting adverse drug reactions, contributing to the global effort to ensure drug safety and the effectiveness of medications used in the country. It also facilitated the sharing of information and best practices in drug safety on an international level. [23]

In 1998, India initiated pharmacovigilance, a systematic process for monitoring and assessing the safety of medications in clinical use. This marked a significant step in enhancing drug safety within the country, allowing for the identification and management of adverse drug reactions and promoting the responsible and effective use of pharmaceuticals. Pharmacovigilance programs help safeguard public health by ensuring the continuous monitoring and reporting of potential medication-related risks.[[24]

EudraVigilance received funding in 2001. It is the authorised European databases for tracking and evaluating reports of possible side effects to medications that are being investigated in European clinical studies or that have been approved for sale[20].

In 2002, India established its 67th National Pharmacovigilance Center, further expanding its efforts to monitor and assess the safety of medications. These centers play a crucial role in systematically

collecting, analyzing, and reporting adverse drug reactions, enhancing drug safety, and protecting public health by ensuring the responsible and safe use of pharmaceuticals across the country.[25]

New legislation were [21]:

1. Refinement of the definition of adverse drug reactions (ADRs).
2. Enhanced participation of patients and citizens in pharmacovigilance initiatives.
3. Reinforcement of the Eudravigilance database, which compiles reports of suspected adverse reactions from all European Union (EU) member states.
4. Augmentation of transparency and prompt dissemination of crucial information concerning pharmacovigilance concerns.
5. Mandate for "additional monitoring" of products listed by the European Medicines Agency (EMA).
6. Authority to impose additional safety and/or efficacy studies as a requirement for marketing authorization approval.
7. Establishment of the Pharmacovigilance Risk Assessment Committee (PRAC) within the EMA.

In particular, the most relevant change consists in the new definition of ADR: “A response to a medicinal product which is noxious and unintended”. In fact, with this definition were covering any adverse event following the use of a medicine, also medication errors and uses outside the terms of the marketing authorization, including the misuse and abuse of the medicinal product.

Furthermore, the new legislation set-up measures to facilitate the performance of PV, called the Good Pharmacovigilance Practices (GVP). The guideline on GVP is divided into two categories: modules covering major Pharmacovigilance processes and product- or population-specific considerations. This last category is available for vaccines and biological medicinal products. In this guideline there are also special chapters dedicated to special areas, namely pregnancy and breast-feeding (P III) and geriatric population (P V) [22].

The updated EudraVigilance format was introduced in November 2017. To help marketing authorizations meet their Pharmacovigilance requirements, they will have a greater connection to the EudraVigilance database. According to Council Implementing Regulation (EU) N. 520/20121, these responsibilities include ongoing surveillance of EudraVigilance data and the reporting of recognised signals to the the agency and national regulatory agencies[19].

Special issues in Pharmacovigilance

Drug Name	**Year Removed**	**Reason Removed**
Diethylstilbesterol (DES)	1971	Vaginal tumours in girls and young women
Phenformin	1978	Lactic Acidosis

Phenolphthalein	1997	Carcinogenicity
Troglitazone	2000	Hepatotoxicity
Rofecoxib	2004	Risk of Myocardial Infarction
Rosiglitazone	2010	Increase risk of heart attack and deaths

Signals recommended by PvPI to CDSCO for inclusion in Prescribing Information Leaflets of concerned pharmaceutical products:

S. No.	Suspected Drugs	Adverse Drug Reactions
1	Aceclofenac	Fixed Drug Eruption
2	Ibuprofen	Fixed Drug Eruption
3	Oral Itraconazole	Symmetrical Drug Related- Intertriginous and Flexural Exanthema
4	Covishield	Guillian – Barre Syndrome

PILs Changes recommended by the PvPI to CDSCO:

S. No.	Suspected Drugs	Adverse Drug Reactions
1	Cotrimoxazole	Fixed Drug Eruption
2	Teneligliptin	Bullous Pemphigoid
3	Fludrocortisone	Hypokalemia
4	Piperacillin + Tazobactam	Blurred Vision

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