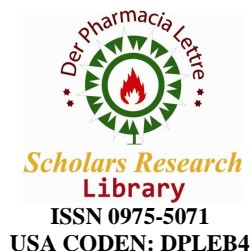




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# Pharmacovigilance and its importance in drug regulation: An Overview

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## ABSTRACT

*The aim of pharmacovigilance is to protect public health by identifying, evaluating and minimizing safety issues to ensure that the overall benefits of medicines outweigh the risks. However, the recent withdrawal from the market of certain medicines has focused 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 ("Adverse Drug Reactions" - ADRs). In drug regulation problems related to the safety and quality of drugs exists in many places. Effective drug regulation is required to ensure the safety, efficacy and quality of drugs, as well as the accuracy and appropriateness of the drug information available to the public. Regulation of drugs encompasses a variety of functions like licensing, inspection of manufacturing facilities and distribution channels, product assessment and registration, adverse drug reaction (ADR) monitoring, QC, control of drug promotion and advertising, and control of clinical drug trials.*

**Keywords:** Pharmacovigilance, Drug regulation, Adverse Drug Reactions, Safety, Efficacy.

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## INTRODUCTION

### What is Pharmacovigilance?

WHO defines pharmacovigilance as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem.

**Brief history of Pharmacovigilance in India**

Even though pharmacovigilance is still in its infancy, it is not new to India. It was not until 1986 that a formal adverse drug reaction (ADR) monitoring system consisting of 12 regional centers, each covering a population of 50 million, was proposed for India [1]. However, nothing much happened until a decade later when in 1997, India joined the World Health Organization (WHO) Adverse Drug Reaction Monitoring Programme based in Uppsala, Sweden. Three centers for ADR monitoring were identified, mainly based in teaching hospitals: a National Pharmacovigilance Centre located in the Department of Pharmacology, All India Institute of Medical Sciences (AIIMS), New Delhi and two WHO special centers in Mumbai (KEM Hospital) and Aligarh (JLN Hospital, Aligarh Muslim University). These centers were to report ADRs to the drug regulatory authority of India. The major role of these centers was to monitor ADRs to medicines marketed in India. This attempt was unsuccessful and hence, again from the 1<sup>st</sup> of January 2005, the WHO-sponsored and World Bank-funded National Pharmacovigilance Program for India was made operational [2]. The National Pharmacovigilance Program established in January 2005, was to be overseen by the National Pharmacovigilance Advisory Committee based in the Central Drugs Standard Control Organization (CDSCO), New Delhi. Two zonal centers-the South-West zonal centre (located in the Department of Clinical Pharmacology, Seth GS Medical College and KEM Hospital, Mumbai) and the North-East zonal centre (located in the Department of Pharmacology, AIIMS, New Delhi), were to collate information from all over the country and send it to the Committee as well as to the Uppsala Monitoring centre in Sweden. Three regional centers would report to the Mumbai center and two to the New Delhi one. Each regional center in turn would have several peripheral centers reporting to it. Presently there are 24 peripheral centers.

The science as it is today had to go through various milestones to reach what it is today. Some of the issues which are important in the historical point of view are: [3]

- Elixir of Sulphanilamide (1937) which resulted in poisoning in children. It was identified that it was a formulation defect which led to improvements in Pharmaceutical regulation.
- Thalidomide tragedy (1961) which resulted in phocomelia (absence of limbs) in the children of mothers who took this apparently 'safe drug', led to National and international collections of ADR reports and resulted in the introduction of yellow card system initiated in the UK in 1964.
- Ethnic susceptibility and drug use issues were raised and early work on Pharmacogenetics began after new clinical syndrome SMON (Sub acute myelo optic neuropathy) reported following use of Clioquinol(1969).
- Realization that spontaneous reporting will not pick up 'events' that are not easily recognized as caused by drugs after the new clinical syndrome, oculomucocutaneous reaction with the use of Practolol (1975) recognized by UK experts led to Prescription event monitoring(PEM).
- One of the most important milestones is the establishment of WHO collaborating center for Drug Monitoring, which is called the Uppsala Monitoring Center (UMC), in 1978, which led to National collaboration enhanced under the WHO programme. This also led to standardizing Adverse Drug Reaction Terminology (ART), WHO-DD (World Health Organization Drug Dictionary) etc., which are updated periodically.

- Some of the important issues which followed were ICH guidelines, European Pharmacovigilance, US, EU and Japan work on harmonized drug regulation, ADR Signal analysis project etc., etc.,

The above issues are recommended for drug safety and monitoring in drug regulation, i.e. Pharmacovigilance plays an important role in drug regulation in medicine world.

### **Pharmacovigilance in drug regulation**

Pharmacovigilance and all drug safety issues are relevant for everyone whose life is touched in any way by medical interventions. Robust drug regulatory arrangements provide the foundation for a national ethos of drug safety, and for public confidence in medicines. The issues, with which drug regulatory authorities have to contend besides the approval of new medicines, include:

- clinical trials
- safety of complementary and traditional medicines, vaccines and biological medicines
- Developing lines of communication between all parties with an interest in drug safety and ensuring that they are open and able to function efficiently, particularly at times of crisis.

Pharmacovigilance programmes need strong links with regulators to ensure that authorities are well briefed on safety issues in everyday practice that may be relevant to future regulatory action. Regulators understand that pharmacovigilance plays a specialized and pivotal role in ensuring ongoing safety of medicinal products. Pharmacovigilance programmes need to be adequately supported to achieve their objectives.

A new medicine must pass three hurdles before its approval by the national drug regulatory authority. Sufficient evidence is required to show the new drug to be

- Of good quality,
- Effective, and
- Safe for the purpose or purposes for which it is proposed.

Whereas the first two criteria must be met before any consideration can be given to approval, the issue of safety is less certain. Safety is not absolute, and it can be judged only in relation to efficacy, requiring judgement on the part of the regulators in deciding on acceptable limits of safety. There is a possibility that rare yet serious adverse events (such as those occurring with a frequency of, say, and one in five thousand) will not be detected in the pre-registration development of the drug. For example, fatal blood dyscrasia occurring in 1 in 5,000 patients treated with a new drug is only likely to be recognized after 15,000 patients have been treated and observed, provided that the background incidence of such a reaction is zero or a causal association with the drug is clear.

### **Clinical trial regulation**

In recent years there has been a substantial increase in the number of clinical trials in developed and developing countries. Clinical trials in the United States of America alone nearly doubled

between 1990 and 1998[4]. With sequencing of the human genome, clinical research in potential new drug therapies is likely to increase even further.

There is also a growing alliance between academia and the pharmaceutical and biotechnology industries. This has given rise to serious and widespread concern over ethical and scientific issues such as: [5-8]

- The potential for conflict of interest
- Unethical patient recruitment practices
- Inadequacy of informed consent
- lack of capacity to ensure on-going monitoring of clinical trials and adherence to principles of sound and ethical clinical practice
- Poor reporting and management of adverse events.

For drug regulators, the changing trends over recent years in the conduct of clinical trials present special and urgent challenges, particularly in ensuring that the rights and health of patients and their communities are protected. In their approval of clinical trials, regulatory bodies look at safety and efficacy of new products under investigation. They must also pay attention to the general standards of care and safety of study subjects, in conjunction with the appropriate institutional review boards (IRBs). Medicines those are required for diseases such as tuberculosis, malaria, HIV/AIDS and meningococcus, meningitis, and those which may have a questionable or uncertain effectiveness - safety profile, require careful surveillance when first introduced on a large scale into communities [9].

The increasing complexity of clinical trials presents further challenges to regulators [10]. Study designs often require large cohorts of participants. In many instances trials are carried out at various sites in several countries. Local ethics committees and drug regulators are not always aware of patients' and investigators' experiences at other international sites. Responsibility for ensuring proper conduct of the clinical trial may, in such circumstances, be divided between the parties. Information requested by ethics committees and regulators may be difficult to obtain in a short time. Regulators and ethics committees do not always have the capacity to carry out these functions effectively. This may have serious implications for the safety of patients.

Safety monitoring during clinical trials is now recognized as one of the major concerns for new drug development. This is currently being addressed by a CIOMS working group. Three main topics are being addressed:

- 1) the collection of adverse experience information
- 2) assessment/monitoring of clinical data
- 3) Reporting/communication of clinical data.

A standardized reporting system for safety concerns arising during clinical trials might serve as a helpful tool for regulatory agencies, and for ethics committees (institutional review boards), provided there were full exchange of information between them and the investigators and sponsors. Expedited electronic submission of safety reports in ICH countries has facilitated the reporting process to some extent; however, routine review of safety information requires

considerable resources, expertise, support and commitment from those involved. Once research into new drugs is in the post-marketing stage (Phase IV studies) safety may be monitored to comply with the conditions of registration, particularly when there are unresolved concerns. This may lead to improved and more rapid changes in labelling or even withdrawal of a new drug from the market [11]. Routine application of principles of good clinical practice that ensure patient safety and strict compliance with prescribed regulatory requirements would substantially improve standards of clinical trials [12].

### **Post-marketing safety monitoring**

It is now generally accepted that part of the process of evaluating drug safety needs to happen in the post-marketing (approval) phase, if important innovations are not to be lost in an unduly restrictive regulatory net. Judgement as to whether and how this might happen lies with the regulators. The stronger the national system of pharmacovigilance and ADR reporting, the more likely it is that reasonable regulatory decisions will be made for the early release of new drugs with the promise of therapeutic advances. Legislation governing the regulatory process in most countries allows for conditions to be placed on approvals, such as a requirement that there should be detailed pharmacovigilance in the early years after a drug's release. Careful safety monitoring is not confined, however, to new drugs or to significant therapeutic advances. It has an important role to play in the introduction of generic medicines, and in review of the safety profile of older medicines already available, where new safety issues may have arisen. While spontaneous reporting remains a cornerstone of pharmacovigilance in the regulatory environment, and is indispensable for signal detection, the need for more active surveillance has also become increasingly clear. Without information on utilization and on the extent of consumption, spontaneous reports do not make it possible to determine the frequency of an ADR attributable to a product, or its safety in relation to a comparator [13]. More systematic and robust epidemiological methods that take into account the limitations of spontaneous reporting are required to address these important safety questions. They need to be incorporated into post-marketing surveillance programmes. There are other aspects of drug safety that have been rather neglected until now, which should be included in monitoring latent and long-term effects of medicines.

These include:

- detection of drug interactions
- measuring the environmental burden of medicines used in large populations
- assessing the contribution of 'inactive' ingredients (excipients) to the safety profile
- systems for comparing safety profiles of similar medicines
- Surveillance of the adverse effects on human health of drug residues in animals, e.g. antibiotics and hormones.

A more difficult question is whether pharmacovigilance has resulted in inappropriate removal from the market of potentially useful medicines as a result of misplaced fears or false signals. The CIOMS report [14] on benefit-risk assessment of medicines after marketing has contributed to a more systematic approach to determining the merit of available medicines. Systematic medical and prescription record linkage, with drug utilization studies, would contribute to greater accuracy. This is a responsibility that falls outside the strict traditional terms of reference of national pharmacovigilance centers.

**Promotional activities**

The safety of medicines in the development stage is increasingly affected by the constraints placed by sponsors on the study plan, laboratory programme and the open sharing of information as the research agenda is negotiated with clinical collaborators [15]. There is growing public concerns that close collaboration between academia and the pharmaceutical industry may adversely affect medical practice and clinical research [4, 16 & 17]. A worrying development for drug safety is 'direct to consumer' advertizing by pharmaceutical manufacturers, other sellers of medicines and parties with a vested interest. Spending on this activity has doubled in the USA over the past four years [6]. While it may improve patients' understanding and is in keeping with the need to improve access to drug information, lack of reliability and accuracy may compromise patient care and safety. Even where direct advertizing of prescription medicines to consumers is illegal, the Internet provides a medium that makes communication possible across borders. This may make national regulations about advertizing ineffective. Websites now make it possible to buy and sell prescription drugs such as benzodiazepines without controls. These developments in communication all have an impact on the safety of medicine [18].

All these issues suggest the need for more thorough monitoring of drug safety and scrutiny of advertizing. Resources and expertise are necessary to ensure that promotional materials contain accurate and balanced information, and that practices are ethical. Self-regulation by industry is unlikely to be sufficient in many countries. Regional or international collaboration in the implementation of a regulatory code of practice for advertizing medicinal products, overseen by an impartial advisory body, would help in this regard [19]. Misrepresentation and lack of full disclosure may have equally important and potentially serious safety implications. A joint editorial, which outlines the rationale for this policy, states that this action is a response to the industry's increasingly tight control over research, results and, in many cases, whether and how results are made public [20].

**International harmonization of drug regulatory requirements**

Harmonization of various elements of drug regulatory activities has been undertaken in the last decade by various intergovernmental organizations at regional and inter-regional levels. Harmonization activities related to drug regulation are being pursued in all WHO regions. The ICH initiative, which started in 1990, is an inter-regional venture covering seventeen high-income countries. The guidelines produced by these groups of specialists drawn from the regulatory authorities and pharmaceutical companies of ICH members represent the latest thinking and are having an impact on all countries [21, 22]. WHO has observer status in all ICH activities. Discussions are in progress to consider the implications of the ICH process and globalization of its guidelines. This includes describing the benefits of the process and explaining concerns about extending its influence to non-ICH countries. If ICH moves into the field of pharmacovigilance, the group should be encouraged to capitalize on the work already carried out by WHO in this area. All ICH countries should be encouraged to participate more actively in the WHO Programme for International Drug Monitoring.

**Promoting communication in the field of drug safety**

Society has a great concern about coping with the dangers of modern life. Medicinal products are among the technological advances that have provided society with great benefits and added risks. Knowledge of the public perception of these risks is essential if they are to be managed



effectively. How safe is safe enough? Which risks are acceptable? These are two critical questions that providers of medicines need to consider when communicating with patients and the public. Recognizing that there is variance between expert views of risk and public perception, there is a need to analyse and understand the differences much more thoroughly. It is not sufficient for the experts to be satisfied with the evidence for safety. The pharmaceutical industry, governments and healthcare providers must build public trust through effective risk communications. This can be achieved only once the public mindset is examined and understood [23, 24].

Some regulatory authorities are increasing the transparency with which they conduct their affairs. However, many authorities continue to be constrained by real or notional secrecy provisions, intended to protect the intellectual property rights of pharmaceutical manufacturers. The problem with secrecy is that it creates an environment of distrust and misunderstanding. It is now expected of regulators that they should deal with drug regulation, including drug safety issues, with a new commitment to openness, including patients and their representatives in the process. In this regard, considerable progress has been made in many countries, notably in the regulation of drugs for HIV/AIDS and cancer.

There has been a tendency for drug safety issues to be dealt with in a way that protects the interests of pharmaceutical manufacturers in the first instance [25]. National pharmacovigilance centers, provided they have the necessary expertise and resources, are especially well placed to collect, evaluate and make recommendations on drug safety, free of other constraining influences. The greatest challenge for National Centers, as it is for drug regulatory authorities, is to promote and maintain effective and open communication of information regarding the benefit, harm, effectiveness and risk of medicines, including the uncertainty of knowledge in this area, with the public and the health professions. The 1998 Erice Declaration on Communicating Drug Safety Information called for a united effort on the part of all interested parties in establishing a new culture of transparency, equity and accountability in the communication of drug safety information. Much has already been accomplished internationally in achieving this. Since Erice, many regulatory authorities have extended their communication activities, developed websites and newsletters, and have actively engaged with the media to provide the public with updated safety information.

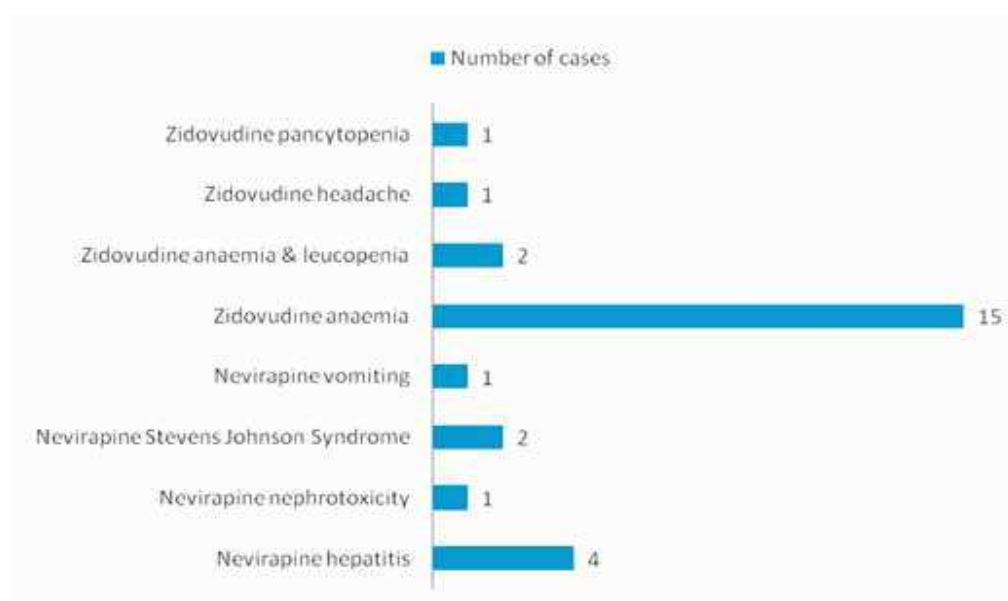
#### **Reports received from the National AIDS Programme (Pharmacovigilance Centre Suriname) [26]**

Adverse drug reactions from the National AIDS Programme in September 2006 to complete the data collected the ADRs reported in the Programme retrospectively to 2002. The primary therapy is Zidovudine (AZT) – Lamivudine (3TC) – Nevirapine (NVP). Most of the patients treated receive this combination. Between 2002 and 2008, more than a thousand patients received ARVs. The reported ADRs are almost equally distributed between men (64) and women (68). 132 ADRs as a consequence of ARVs, are reported between 2002 and 2008 to the National AIDS Programme are collected. 110 of these 132 ADRs resulted in drug substitution, 17 led to other actions (reduction of doses, additional medication for relieve of the adverse drug reaction) and 5 times the ADR resulted in discontinuation of the medicines.

In the years between 2002 and 2008, adverse drug reactions led to at least 79 referrals to medical specialists and to 45 hospitalizations. For 19 of 45 hospitalizations, Zidovudine was the immediate cause, among which 15 for anaemia and 2 for anaemia in combination with leucopenia.

**Table 1: Reported adverse drug reactions by ARV from 2002 to 2009**

Anti retroviral	Number of toxicities	%
Abacavir	3	2.3
Zidovudine	63	47.7
Stavudine	21	15.9
Didanosine	1	0.7
Efavirenz	4	3.0
Indinavir	7	5.3
Lopinavir	2	1.5
Nelfinavir	1	0.8
Nevirapine	29	22.0
Saquinavir	1	0.8
<b>Total</b>	<b>132</b>	<b>100</b>



**Figure 1: ADRs resulting in hospitalization**

### Communication with health professionals

A further strategy for integrating pharmacovigilance into clinical practice is the creation of open lines of communication and broader collaboration between health professionals and National Centres. For this to happen, National or regional centres need to be situated so that two-way communication between health practitioners and professional staff of the centre is easy. Drug information and poison centres are ideal locations for this purpose, since many poisoning reports and drug information queries are in fact ADRs [27].



Academic departments and university hospitals have proved effective places for national and regional pharmacovigilance centres for a number of reasons.

These include the following:

- (i) Pharmacovigilance can readily be linked with experimental and clinical pharmacology, and epidemiology in that environment
- (ii) The location makes peer review of adverse reaction reports easier and more efficient, and it provides ready access to hospital specialists in university departments. From such a base, an advisory panel for the National Centre with scientific and medical experts can be created
- (iii) The information obtained from spontaneous reports can be incorporated into undergraduate and postgraduate teaching in the health sciences
- (iv) Health professionals are likely to feel confident in reporting problems and therapeutic dilemmas to an academic unit with which they are familiar and that they know will consider their reports thoroughly and expertly
- (v) Effective medical education strategies such as academic detailing [28], feedback on individual cases, reminders and soliciting the support of acknowledged experts are most readily achievable under these circumstances [29].

### **Risk and crisis management**

The importance of an efficient system for dealing with drug safety risks and crises has become increasingly evident in recent years. Drug safety issues tend rapidly to take on international significance. The speed with which information spreads in the modern world means that drug safety concerns are no longer confined to individual countries. Often the media and general public are informed at the same time as, or even before, the national regulatory authority.

Many national authorities have identified the need for developing an organizational plan for managing risks and for communication and action during crises [30]. Regulators themselves often react under duress in a drug safety crisis within a legislative or administrative framework that is inadequate or excessively restrictive. There should be clear yet flexible operating procedures so that their response is not delayed, unnecessarily complicated, or unduly cautious (undue caution may result in removal of a product from the market even when there may be no justification and a more thoughtful and less drastic response would be appropriate). In such circumstances, the greater the disparity in safety information between the pre-registration evaluation and the real situation in practice, the greater is the likelihood that the regulatory response will be inappropriate. When crises arise, the regulatory authority has powers to suspend registration, impose special conditions, or severely restrict use to certain patients or prescribers.

### **Pharmacovigilance and the national drug regulatory authority**

The limitations of pre-marketing drug safety data are well-recognized [31]. They are aggravated by increasing pressure on drug regulators from the pharmaceutical industry to shorten the review time for new medicines. Registration approval of a new drug is likely to be followed by robust marketing and rapid exposures of thousands even millions of patients to it [32]. The implications for drug safety of this evolving situation need to be addressed.

Pharmacovigilance has become an essential component of drug regulation [33]. For the foreseeable future in developing countries, this is likely to take the conventional form of

spontaneous monitoring, even though it is a far from perfect system. Within the national drug regulatory authority post-marketing surveillance is normally understood to serve a distinct function, separate from the process of evaluation and approval of new medicines. Post-marketing surveillance draws on its own special sources of information, infrastructure and expertise, although there is good reason for these systems and resources to be shared with other disciplines. For example, it is necessary that in the proper conduct of pharmacovigilance there should be access to the information on which the original determination of risk and harm was made. Pre-registration files, including the advice and opinions of the original evaluators of the data, are required if a balanced and clinically relevant decision is to be made. In many countries pharmacovigilance and drug regulatory approvals are linked by an ADR advisory committee appointed by, and directly reporting to, the national regulatory authority [34, 35]. The committee consists, amongst others, of independent experts in clinical medicine, epidemiology, paediatrics, toxicology and clinical pharmacology. Such an arrangement inspires confidence amongst health personnel and it can be expected to make a substantial contribution to public health.

### **Herbal and Traditional Medicines**

The use of herbal and traditional medicines raises concerns in relation to their safety [36, 37]. There is wide misconception that 'natural' means 'safe'. There is the common belief that long use of a medicine, based on tradition, assures both its efficacy and safety. There are examples of traditional and herbal medicines being adulterated or contaminated with allopathic medicines, chemicals such as corticosteroids, non-steroidal anti-inflammatory agents and heavy metals. Many traditional medicines are manufactured for global use and they have moved beyond the traditional and cultural framework for which they were originally intended. Self-medication further aggravates the risk to patients. When traditional and herbal medicines are used in conjunction with other medicines there is the potential of serious adverse drug interactions.

As with other products intended for human use (medicines, dietary supplements and foods), herbal medicines should be incorporated within a regulatory framework. These products should be governed by standards of safety, quality and efficacy that are equivalent to those required for other pharmaceutical products. The regulatory status of herbal products differs significantly from country to country. Currently less than 70 countries regulate herbal medicines and few countries have systems in place for the regulation of traditional health practitioners. These disparities in regulation between countries have serious implications for international access to and distribution of such products. For instance, in one country a herbal product may be obtainable only on prescription and from an authorized pharmacy, whereas in another country, it may be obtainable from a health food shop, or even, as has become common practice, by mail order or Internet. For all these reasons, inclusion of herbal and traditional medicines in national pharmacovigilance programmes has become important and inevitable. Healthcare providers, including traditional health practitioners, regulators, manufacturers and the public share a responsibility for their informed and safe use. The World Health Organization has produced guidelines for assessment of the safety, efficacy and quality of herbal medicines [38].

New systematic approaches for monitoring the safety of plant-derived medicinal products are being developed [39]. A number of national pharmacovigilance centres are now monitoring the safety of traditional medicines. For that to succeed, the collaboration and support of consumers,

traditional health practitioners, providers of traditional and herbal medicines and other experts is necessary.

### **Vaccines and biological medicines**

For several reasons, vaccines and biologicals require modified systems of safety monitoring. They are often administered to healthy children. This applies particularly to vaccines used within a national immunization programme. In many countries, those exposed to a particular vaccine represent the entire birth cohort and therefore a sizeable part of the entire population. People's expectations of safety are high, and they are reluctant to countenance even a small risk of adverse events.

It is essential that there should be adequate safety surveillance supporting immunization programmes. The skills and infrastructure to deal with genuine adverse events are essential in preventing or managing misplaced fear caused by false or unproven signals from patients and health workers that might adversely affect immunization cover. For example, concerns about the safety of whole-cell Pertussis resulted in dramatic reductions in vaccines coverage and a resurgence of Pertussis in many countries [40].

The difficulties in monitoring and dealing with vaccine safety are complicated by the problems inherent in determining the causal link between an adverse event following immunization and a vaccine [41, 42]. For example, information on dechallenge and rechallenge is often missing, and vaccines are given to most of the country's birth cohort at an age when coincidental disease is likely. Several vaccines are likely to be administered concurrently. However, the responsibility of the regulatory authority is by no means limited to the safety of vaccines used in immunization programmes. The efficient regulation of these products is crucial in order to avoid potential harm to the public as a result of substandard manufacture or improper transportation and storage of imported vaccines and biologicals.

In recent years, the safety of biological products and blood products has come under public scrutiny [43]. Concerns about the safety of medicinal products of animal origin have been raised in connection with variant Creutzfeldt-Jacob disease (vCJD), and with contamination of blood and blood products by infectious organisms such as HIV and hepatitis B [44]. The quality of screening and sterilization procedures and appropriate selection of donors are linked to the risks of contamination. Such safety issues related to the use of plasma-derived medicinal products should fall under the aegis of pharmacovigilance programmes. For that to happen, pharmacovigilance centres would have to consider the special issues related to safety of these products. New vaccines for pandemic diseases such as HIV/AIDS and malaria are in the later phases of development. Clinical trials in large patient populations are being considered for testing the efficacy and safety of these vaccines. Special ethical, legal and regulatory challenges are raised in the conduct of such clinical trials, especially the implications vaccines may have for the epidemiology of disease and the possible direct and indirect risks of harm associated with the introduction of vaccines into large communities.

### **Pharmacovigilance of biosimilars**

Unlike traditional generic pharmaceuticals, biosimilars (also called 'follow-on biopharmaceuticals' in the USA) aim to copy a complex recombinant, three dimensional protein

structure with high molecular weight. Small changes in the manufacturing process can alter the product's effect and safety. According to the guidelines of the European Agency for the Evaluation of Medicinal products (EMA), extensive comparability testing will be required to demonstrate that the biosimilar has a comparable profile in terms of quality, safety and efficacy as the reference product. Various analytical assays are available to compare physicochemical and biological properties between production batches of a potentially similar biopharmaceutical (comparability) and in comparison with a reference product (similarity). It is important to recognize the limits of existing assays so that the results can be accurately interpreted for market authorization. Clinical trials and post-authorization pharmacovigilance are essential to guarantee the product's safety and efficacy over time. Pharmacovigilance, as part of a comprehensive risk management programme, will need to include regular testing for consistent manufacturing of the drug.

As patents of first generation biopharmaceuticals derived from recombinant DNA are expiring, the development of 'biosimilars' is increasing. Follow-on biopharmaceuticals aim to copy complex recombinant, three-dimensional proteins with high molecular weight. Their market authorization procedure cannot be based on traditional generics of pharmaceuticals, as the activities of biopharmaceuticals depend on a multitude of factors [45, 46].

Guaranteeing consistency in the production of these agents has already proved difficult [47]. Incidences such as the increased occurrence of pure red cell aplasia (PRCA) cases in 1998 demonstrated how one small change in the manufacturing process can alter the product's characteristics [48]. Such complexity means that requirements for marketing authorization of biosimilar products cannot be the same as for lowmolecular weight generic drugs. Therefore, preliminary guidelines for pre- and postmarket authorization of biosimilar products from the European Agency for the Evaluation of Medicinal Products (EMA) demand extensive testing to ensure that the biosimilar has a similar quality, safety and efficacy profile as its reference product [49]. Various analytical tests are available to analyse the physicochemical properties (such as weight, density and stability) and biological properties (such as activity and immunogenicity) of biosimilars. These assays are necessary to test the similarity and comparability of a biosimilar against the innovator drug, regulations and the safe use of biosimilars in practice.

Although close Pharmacovigilance is a voluntary post-marketing process, it will be in the interest of the manufacturer to guarantee the quality, safety and efficacy of the biosimilar over time. The EMA guidelines state that a comprehensive pharmacovigilance plan should be sent to the authorities together with the data package and such a plan should be established at the time of approval of the product [50]. The manufacturing process must be carefully monitored to ensure comparability between production batches. If a difference in the manufactured product is detected, additional investigations may be necessary, which may include clinical proof of unchanged safety and efficacy profile. It will also be essential to define 'who' and 'when' at the right place and time to do 'what' and 'how'. This is especially important for the risk management component of the programme that needs to guarantee immediate reaction in case of rising numbers of patient disorders with suspected relation to the biosimilar product.

WHO and other international agencies, nongovernmental organizations and donor agencies provide support for countries to supplement national efforts. However, despite the efforts made,

less than 20% of WHO Member States are thought to have a well developed drug regulation system. Those which do are industrialized countries. Of the remaining Member States, about 50% implement drug regulation at varying levels of development and operational capacity. The remaining 30% either have no DRA in place, or have only a very limited capacity which barely functions at all [51]. WHO has never undertaken a systematic assessment to identify the reasons for ineffective drug regulation and determine why so few Member States have succeeded in establishing effective drug regulation. Guaranteeing the safety, efficacy and quality of drugs available to the public is the main goal of drug regulation, and encompasses a variety of functions. Key functions include licensing of premises, persons and practices; inspection of manufacturing facilities and distribution channels; product assessment and registration (marketing authorization); adverse drug reaction (ADR) monitoring; QC; control of drug promotion and advertising. Each of these functions targets a different aspect of pharmaceutical activities, but all of them must be undertaken simultaneously to ensure effective consumer protection.

### CONCLUSION

In conclusion Pharmacovigilance plays an important role in drug regulation for protect public health by identifying, evaluating and minimizing safety issues to ensure that the overall benefits of medicines outweigh the risks. That is to monitoring the post marketing surveillance, drug safety, efficacy and quality of drugs, as well as the accuracy and appropriateness of the drug information available to the public for to reduce the adverse drug reactions. The limitations of pre-marketing drug safety data are well-recognized. Pharmacovigilance and the national drug regulatory authorities are aggravated by increasing pressure on drug regulators from the pharmaceutical industry to shorten the review time for new medicines. Registration approval of a new drug is likely to be followed by robust marketing and rapid exposures of thousands even millions of patients to it. The implications for drug safety of this evolving situation need to be addressed. Pharmacovigilance has become an essential component of drug regulation. For the foreseeable future in developing countries, this is likely to take the conventional form of spontaneous monitoring, even though it is a far from perfect system. Many developing countries do not have rudimentary systems in place for the purpose, and even where pharmacovigilance systems do exist, active support and participation among health professionals, regulators and administrators is likely to be lacking. Underreporting of ADRs by healthcare professionals remains a major problem in all countries.

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