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Pharmacovigilance Guideline

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ABSTRACT: Pharmacovigilance science has traditionally been a discipline focussed on the postmarketing or post-authorisation period, with due attention directed towards pre-clinical safety data, clinical trials and adverse events. As the biological sciences have evolved, pharmacovigilance has slowly shifted toward earlier, proactive consideration of risks and potential benefits of drugs in the pre- and peri-approval stages of drug development, leading to a maturing of drug safety risk management. Further advances in biology, pharmacology and improvements in computational applications to medicine have led to the development of more complex medicines have also permitted a more thorough assessment of risks and potential benefits even earlier in the development process. Elevated public concern with the safety of more sophisticated medicines, combined with new science, have led pharmaceutical innovators, regulators and healthcare professionals to collaborate to develop guidelines, which drive enhanced pharmacovigilance and safety risk management earlier in drug development.

In this paper, we review international guidelines on pharmacovigilance planning applicable to the pre-approval phases of medicines development and provide author opinion on these guidelines' potential drug safety implications. We discuss the possible evolution of a pharmaceutical industry model to respond to these guidelines; a view on multidisciplinary safety management teams is provided to encourage refinement of safety-signal identification and risk assessment early in drug development and to communicate important safety concerns to internal research efforts, patients, investigators and regulators. We further describe these functions in the context of the complexities of vulnerable populations.

Pharmacovigilance is a pharmacological science related to the detection, assessment, understanding and prevention of adverse effects, particularly long-term and short-term adverse effects of medicines (WHO-Essential Medicines and Health Products, 2002). It has been observed that a medication that is proven efficacious in large patient population often fails to work in some other patients of different ancestry. Ancestral background of the patients are controlled by genetic factors that influence drug response-drug targets, drug-metabolizing enzymes, drug transporters, and genes indirectly affecting drug action can modulate drug toxicity and contribute to its individual variability .

I. CHAPTER 1. INTRODUCTION

1.1. DEFINATION

Pharmcovigilance is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem. WHO established its Programme for International Drug Monitoring in response to the thalidomide disaster detected in 1961 .[1]

The safety monitoring of preparation and use of different types of medicines, they are all equally important from a pharmacovigilance perspective. Herbal medicines is compared and contrasted with that of other medicines currently undertaken in the context of the WHO International Drug Monitoring Programme . While there are regulatory and cultural differences in the preparation and use of different types of medicines, they are all equally important from a pharmacovigilance perspective.[1]

The guidelines were developed with the view that, within current pharmacovigilance systems, monitoring of the safety of medicines should be enhanced and broadened in ways that will allow the successful monitoring of herbal medicines.

1.2. (a) AIMS AND SCOPE [1]

- **Patient care** - To improve patient care and safety in relation to medicine and all medical invention.
- **Public Health** – To improve public health and safety in relation to the use of medicine.
- **Risk benefit assessment** - To contribute to the assessment of benefit, harm, effectiveness and risk of medicine
- **Communication** - To promote understanding, clinical training and effective communication to health professionals and the public.

International Journal of Pharmaceutical Research and Applications
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1.2 . (B) Purpose Of Pharmacovigilance

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related Problems . Recently, its concerns have been widened to include:

• herbals
• traditional and complementary medicines
• blood products
• biologicals
• medical devices
• vaccines.[1]

Many other issues are also of relevance to the science:

• substandard medicines
• medication errors
• lack of efficacy reports
• use of medicines for indications that are not approved and for which there is inadequate scientific basis
• case reports of acute and chronic poisoning
• assessment of drug-related mortality
• abuse and misuse of medicines
• adverse interactions of medicines with chemicals, other medicines, and food.[1]

Pharmacovigilance intended for

Pharmacovigilance and all drug safety issues are relevant for everyone whose life is touched in any way by medical interventions. The document is planned or meant for the following:

- Pharmaceutical industry executives and scientists.
- Professional staff of poison and drug information centres.
- Professional staff in national pharmacovigilance centres
- Policy makers at all levels of healthcare.
- Healthcare practitioners including doctors, nurses and pharmacists.
- Editors of medical and scientific journals.
- Health epidemiologists.
- Health economists.
- Legal advisors in health care.
- Schools of health sciences.
- Consumer groups and patient support groups.[7]

1.3. A SHORT HISTORY OF INVOLVEMENT IN DRUG SAFETY MONITORING BY WHO

According to Article 2 of its constitution , WHO gives an official order or commission to do something from its member states, to develop, establish, and promote international standards with respect to food,biological, pharmaceutical and similar products.

It was not before 1961. It was initiated to address drug safety issues after disaster caused by thalidomide in 1961. Sixteenth World Health Assembly (1963) adopted a resolution (WHA)that state again strongly the need for early action in regard to rapid action or fact of spreading something, especially information on adverse drug reactions and led , later, to creation of the WHO Pilot Research Project for International Drug Monitoring in 1968.

It marked the introduction of pharmacovigilance formally into the research and academic world, and its increasing integration into clinical practice by creating the International Society of Pharmacoepidemiology (ISPE) in 1984 and of the European Society of Pharmacovigilance (ESOP – later ISoP – the International Society) in 1992.It implemented active surveillance systems to complement conventional methods of drug monitoring.example

- Record linkage systems in the USA and Canada.
- Case control studies in the USA.
- Prescription event monitoring systems (PEM) in New Zealand, and
- Prescription event monitoring systems (PEM) in the UK.[7]

1.4.

1.5. Pharmacovigilace activities develop gradually as a regulatory activities.

In the early 1980s, in close collaboration with the WHO,the Council for International Organizations of Medical Sciences (CIOMS) launched its programme on drug development and use.

CIOMS provided a forum for policy makers, pharmaceutical manufacturers, government officials and academics to make recommendations on the communication of safety information between regulators and the pharmaceutical industry.

Adoption of many of the recommendations of CIOMS by the International Conference on Harmonization (ICH) in the 1990s has had a notable impact on international drug regulation.[7]

The scope of pharmacovigilance should be extended with growing awareness within last decade beyond detecting new signals of safety concerns. Change in access to all medicinal products and information by

- Globalization,
- consumerism,

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 1 Jan-Feb 2021, pp: 317-329 www.ijprajournal.com ISSN: 2249-7781

- the explosion in free trade and
- communication across borders, and
- increasing use of the Internet

Due to this many safety concerns was arises such as ----

- increasing self-medication practices
- increasing use of traditional medicines
- increasing use of herbal medicines
- increasing use of medicine with other medicine with potential for adverse interactions
- unsafe drug donation practices
- illegal sale of medicines and drugs of abuse over the Internet.

II. CHAPTER 2. SAFETY MONITORING OF MEDICINAL PRODUCTS: GUIDELINES FOR SETTING UP AND RUNNING A PHARMACOVIGILANCE CENTRE

(The Uppsala Monitoring Centre, Uppsala, Sweden, 2000)

2.1. INTRODUCTION

- The principal function of the Uppsala Monitoring Centre is to manage the international

database of ADR reports received from National Centres.

- The UMC has established standardized reporting by all National Centres and has facilitated communication between countries to promote rapid identification of signals.
- A sophisticated Bayesian confidence propagation neural network (BCPNN) programme was created in 1998, which partly automates the signal detection system, and provides earlier alert signals than previous methods.
- The effectiveness of this system depends on:
  - size of the database
  - quality of the reports received from the contributing centres
  - timeliness of such reporting
  - an active and reliable reporting culture within participating countries.
- An international advisory panel of clinical experts determines the validity and clinical importance of the signals generated.
- In recent years the UMC has expanded its role as a communications and training centre and clearing-house for information on drug safety. Through

• mail discussion groups,
• website development,
• newsletters
• annual National Centre meetings,[7]

- The UMC team, in collaboration with the WHO, facilitates and encourages the international collaboration, which was identified in 1972 as being vital for the success of pharmacovigilance.
- The terminologies developed within the WHO programme for coding adverse reactions and medicines have been widely adopted by National Centres, manufacturers and drug regulators.
- In recent years, the introduction of a new terminology known as MedDRA (Medical Dictionary for Drug Regulatory Activities) has replaced the World

Health Organization Adverse Reaction Terminology (WHO-ART) in developed countries.

- WHO-ART remains the mainstay of communicating adverse reactions in most developing countries within the International Programme.
- More effective communication of information is being promoted and encouraged through the WHO International Drug Monitoring Programme and the UMC. They are working towards playing a more pro-active role in working together with countries .
- An example of such a system, as it applies to vaccine safety.[7]

2.2.(A) How To Start A Pharmacovigilance Centre

The development of a pharmacovigilance system is the first and uncertain stage to becoming an established and effective organization. Pharmacovigilance is a process that needs time, vision, dedication, expertise and continuity. The most promising location for a new pharmacovigilance centre may depend on the organisation and development of the healthcare system in the country and other local issues.

A governmental department (health authority, drug regulatory agency) can be a good host for a pharmacovigilance centre. Any department in a hospital or academic environment, working in clinical pharmacology, clinical pharmacy, clinical toxicology or epidemiology, is a suitable starting point for pharmacovigilance .

The reporting of adverse drug reactions may start locally, perhaps in one hospital, then extend to other hospitals and family practices in the region, and progress step by step into a national

International Journal of Pharmaceutical Research and Applications
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activity. In some countries professional bodies such as the national medical association may be a good home for the centre.

When a centre is part of a larger organisation (for example, a poison control unit, a clinical pharmacology department, or a hospital pharmacy) providing administrative continuity, it can get going as long as there is one professional (e.g. a physician or pharmacist) available who is primarily responsible for pharmacovigilance.

Whatever the location of the centre, pharmacovigilance is closely linked to drug regulation. Governmental support is needed for national co-ordination. Pharmacovigilance is nobody's individual privilege. Good collaboration, co-ordination, communications and public relations are needed for a coherent development and for the prevention of unnecessary competition or duplication.[7]

2.2(b)Steps to establish a pharmacovigilance centre

1. Make contact with the health specialist and with local,regional groups ,working in clinical medicine , and toxicity outlining importance of project.
2. Design reporting form and start collecting data.
3. Produce printed material to inform health professionals about aims and method of pharmacovigilance.
4. Create the centre : -staff -phone
-accomadation -word processor
-database management - bibligrophy
5. Take care of education of pharmacovigilance staff with regard
6. Establish a database
7. Organize meetings in hospitals , academia and professional associations ,explaining the demands of pharmacovigilance and importance of reporting.
8. Promote the importance of reporting adverse drug reaction through medical journal and other professional
9. Maintain contact with international institutions working in pharmacovigilance e.g. Uppsala Monitoring Centre, Sweden [7]

2.3.National Pharmacovigilance Centres

In collaboration with the UMC the National Centres have achieved a great deal in:

- ✓ collecting and analysing case reports of ADRs
- ✓ distinguishing signals from background 'noise'
- ✓ making regulatory decisions based on strengthened signals
- ✓ alerting prescribers, manufacturers and the public to new risks of adverse reactions

Centres vary considerably in size, resources, support structure, and scope of activities. Collecting spontaneous reports of suspected ADRs remains their core activity.[7]

2.4.REPORTING OF ADVERSE DRUG REACTIONS

SPONTANEOUS REPORTING- regional or country wide syatem for the reportingof suspected adverse drug reactions – is currently the major source of information in pharmacovigilance.

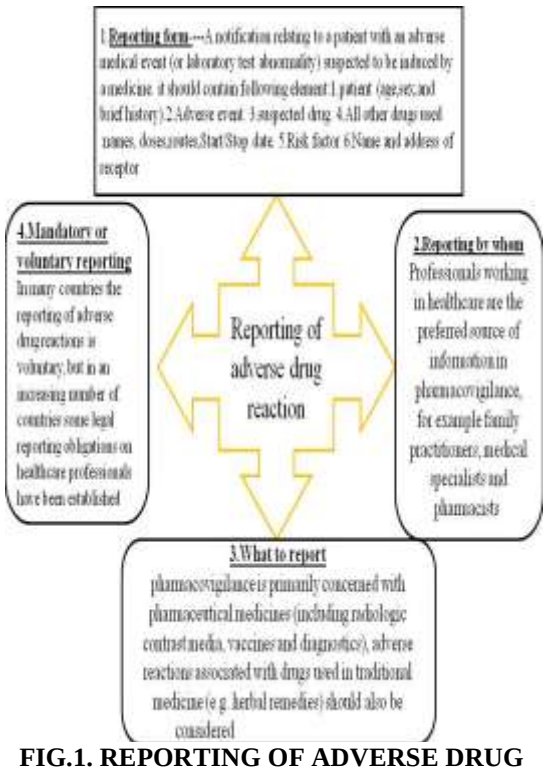

FIG.1. REPORTING OF ADVERSE DRUG REACTION

National Centres have played a significant role in increasing public awareness of drug safety Pharmacovigilance is increasingly seen as more than a regulatory activity, having also a major part to play in clinical practice and the development of public health policy. This development partly contributed in many national and regional centres are housed within hospitals, medical schools or poison and drug information centres, rather than within the confines of a drug regulatory authority.

The scope of activities of National Centres has expanded to include communication of information about benefit, harm, effectiveness and

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risk to practitioners, patients and the public. Major centres in developed countries have established active surveillance programmes using record linkage and prescription event monitoring systems (PEM) to collect epidemiological information on adverse reactions to specific drugs.[7]

2.5.Relation with other parties

1. Regulatory Authority
2. Pharmaceutical companies
3. Professional medical and pharmaceutical associations
4. Centre for international drug monitoring
5. Academia
6. Media and consumer organisation

1. **Regulatory authorities:**With the rapid spread of drug information across the globe, there is a need for routine and rapid communication between National Centres and between national regulatory authorities. Many regulatory authorities in different regions of the world have great relationship to discuss safety data obtained on particular medicines and on the regulatory decisions.

The International Conference for Drug Regulatory Authorities (ICDRA), the Annual meeting of National Pharmacovigilance Centres Participating in the WHO Programme for International Drug Monitoring and other similar conferences facilitate.

2. **Pharmaceutical Companies:**Pharmaceutical industry has prime responsibility for the safety of medicines. Manufacturers are uniquely placed for monitoring the safety of medicines, from the start of drug development and thereafter throughout the lifetime of the drug.

Many companies have developed innovative and efficient monitoring systems that have contributed to the detection of new safety signals. The pharmaceutical industry has made many technological advances in drug developments that have improved the safety of new drugs.

3. **Professional medical and pharmaceutical associations :**The number of staff in the pharmaceutical industry involved in pharmacovigilance isgrowing. This has been in response to the high regulatory standards that have been set at national and international levels and the increasing requirement for post-approval monitoring set by national drug regulatory authorities.

Communication and exchange of information between the industry and regulatory authorities has improved as a result of the regional and international harmonization arrangements that have emerged in recent years. Continuing professional education, patient education, and sponsorship by industry of drug information activities have also contributed to safer use of medicines.

4. **Centre for international drug monitoring:**A new pharmacovigilance centre should make contact with the World Health Organization in Geneva and the WHO Collaborating Centre for International Drug Monitoring (the UMC) in Uppsala, Sweden
5. **Hospitals and Academia**:The efforts of clinical pharmacology and pharmacy departments around the world have resulted in the development of pharmacovigilance as a clinical discipline.

A number of medical institutions have developed adverse reaction and medication error surveillance systems in their clinics, wards and emergency rooms. Case-control studies and other pharmacoepidemiological methods have increasingly been used to estimate the harm associated with medicines once they have been marketed.

The expansion of scientific knowledge in drug safety is attributable to greater awareness and academic interest in this field.

Academic centres of pharmacology and pharmacy have played an important role through teaching, training, research, policy development, clinical research, ethics committees (institutional review boards) and the clinical services they provide.

In many medical institutions, particularly in thedeveloped world, ADR monitoring is recognized as an essential quality assurance activity.

6. **Media and consumer organization:** For general public relations and as part of the risk management strategy whenever an acute drug problem arises. Special attention may be needed to explain to journalists the limitations of pharmacovigilance data

PRACTIALITIES IN THE ORGANISATION OF A PHARMACOVIGILANCE CENTRE

1**. Staff**

2**. Useful equipment** (includes)

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 1 Jan-Feb 2021, pp: 317-329 www.ijprajournal.com ISSN: 2249-7781

- Multiconnection telephone
- Computer
- Printer
- Fax
- Email

3. **continuity**
4. **advisory committee** : to support the pharmacovigilance centre with regard to quality of the procedures in
- Data collection and assessment
- Interpretation of the data
- Publication information

5**. Information**
6.**communication**
7.**poison control and drug information centres**

2.6.(a)Assessement of case reports

- **Quality of documentation**: (e.g. completeness and integrity of data, quality of diagnosis, follow-up)
- **Coding**: Drug names should be registered in a systematic way, for example by using the WHO Drug Dictionary (which is based on the INN nomenclature and the ATC classification).
- **Relevance**: with regard to the detection of new reactions, drug regulation, or scientific or educational value
- **Identification of duplicate report**: Certain characteristics of a case (sex, age or date of birth, dates of drug exposure, etc.) may be used to identify duplicate reporting.
- **Casuality assessement of imputation**: Various approaches have been developed for the structured determination of the likelihood of a causal relationship between drug exposure and adverse events,

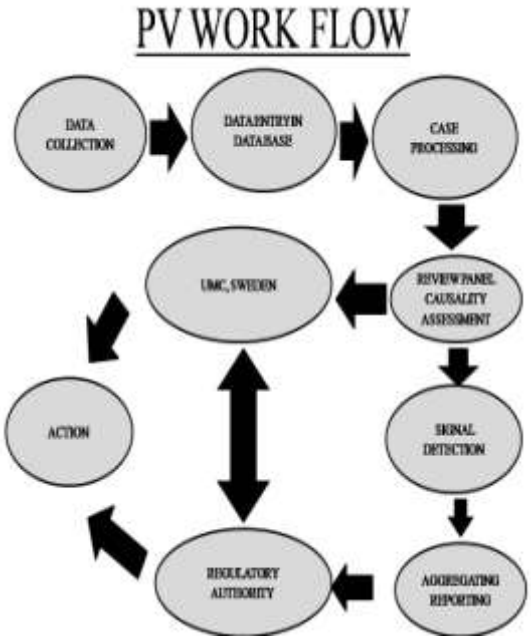

FIG.2. PV WORK FLOW

2.6.(b)Uses of data

Data collected in pharmacovigilance can be used in a variety of ways.

1. **Hypothesis generation and strengthening**: early detection of hypotheses or signals (see Glossary) with regard to possible adverse reactions.
2. **Drug regulation:** After approval of a medicinal product, all available domestic and international safety information is continuously monitored by the drug regulatory authority and the pharmaceutical company concerned.
3. **Information:** the dissemination of information of current importance or interest to healthcare practitioners, an adverse drug reactions bulletin or a column in medical and pharmaceutical journals may be very helpful.
4. **Education and feedback:** Continuous pre- and postgraduate education of healthcare professionals is an important aspect of pharmacovigilance. Appropriate educational activities will improve knowledge and awareness of adverse drug reactions and stimulate reporting.
5. **Limitations regarding the use of the data:** Usually case reports of suspected adverse reactions may be influenced by all sorts of bias. The interpretation of pharmacovigilance data may be difficult. Often signals are unsubstantiated and require further study for

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 1 Jan-Feb 2021, pp: 317-329 www.ijprajournal.com ISSN: 2249-7781

confirmation or refutation (hypothesis testing) and for the assessment of the reaction frequency, for example, as needed for drug regulatory decision-making.[7]

III. CHAPTER 3 .WORLD HEALTH ORGANIZATION(GENEVA) PHARMACOVIGILANCE GUIDELINE FOR WHO GUIDELINES ON SAFETY MONITORING OF HERBAL MEDICINES IN PHARMACOVIGILANCE SYSTEMS:

A/c to WHO; The importance of pharmacovigilance: safety monitoring of medicinal products.

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects of drugs or any other possible drug-related problems.

It include:

- biologicals
- blood products
- traditional and complementary medicines
- herbals
- vaccines
- medical devices

3.1.Aims of pharmacovigilance

- identification of risk factors
- detection of increases in frequency of (known) adverse reactions
- estimation of the quantitative aspects of benefit/risk, and analysis
- to improve the prescription, dispensing, provision and regulation of medicines.
- early detection
- safe and proper use of effective medicines [1]

3.2.Pharmacovigilance operate

There is no difference in principle between the safety monitoring of herbal medicines and that of other medicines.

Under the WHO International Drug Monitoring Programme the competent health authorities are responsible for the collection, processing and evaluation of case reports of suspected adverse reactions supplied by health-care professionals. Programme currently comprises a network of more than 70 national pharmacovigilance centres that operate independently, but whose functions are coordinated and facilitated by WHO and UMC. UMC manages the global WHO database to which all case reports received by the national pharmacovigilance centres are sent. UMC uses the global WHO database to identify/detect signals of new adverse reactions from the cumulative data and to communicate risk assessments back to the national pharmacovigilance centres and to others concerned with drug safety.

3.3.Regulation, quality assurance and control

Regulation

Regulatory status of a particular herbal product may differ in different countries. The national regulatory framework usually also includes involved qualified providers and distributors of respective substances. National regulatory information on herbal medicines is not fully shared among national regulatory authorities, and is often not shared between national regulatory authorities and national safety monitoring/pharmacovigilance centres. All new medicines are introduced to the market as prescription medicines, and a significant volume of post-marketing safety data from spontaneous reporting will have been realized over time.

Quality assurance and control

It measures, such as national quality specification and standards for herbal materials, good manufacturing practices (GMP) for herbal medicines, labeling ,and licensing schemes for manufacturing ,imports and marketing, should be in place in every country where herbal medicines are regulated. These measures are vital for ensuring the safety and efficacy of herbal medicines. Requirements and methods for quality control of finished herbal products, particularly for mixture herbal products, are far more complex than for other pharmaceuticals.[1]

3.4. Safety monitoring of herbal medicines

Sources of reports

Reports from health-care professionals: adverse drug reaction reporting systems in the post-marketing safety surveillance setting depend primarily on voluntary reporting by health-care professionals, preferably those directly associated with the care of the patient/consumer. A substantial proportion of herbal medicines are non-prescription medicines, and many come directly into this category without prior post-marketing safety monitoring as prescription medicines.

Manufacturers Consumers may report directly to companies or their representatives. However, there

International Journal of Pharmaceutical Research and Applications
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are reasons other than concern about an adverse effect that might prompt a consumer to contact a company. These include legal concerns and, most frequently, requests for further information about the product.

Reports from consumers Consumer reports on adverse reactions should be accepted as a serious source of information, which can contribute to the identification of signals for unknown effects of herbal medicines.

Reports from other sources:

- National poisons centres.
- Drug information centres
- Consumer organizations
- Clinical trials and studies

Herbal products targeted for safety monitoring

Who should report and to whom

Following should provide reports

Health professionals who are providers of herbal medicines including physicians, pharmacists and nurses, should report to the national pharmacovigilance centre.

Patients/consumers should normally report to their physicians or providers of herbal medicines. They may also report directly to the national pharmacovigilance centre, consumer organizations or manufacturers.

Manufacturers should report directly to the national pharmacovigilance centre or national regulatory authority.

What information should be requested?

Any suspected adverse reaction associated with the use of a herbal medicines should be reported. A case report should contain information on the following elements:

♦ **where it is permitted** by the country health information privacy code, and with appropriate confidentiality, some form of identification of the patient/consumer in order to avoid duplications and facilitate follow-up

♦ **age, sex and a brief medical history of the consumer/patient**

♦ **details of suspected herbal product(s) if known:** species name (Latin binomial name and common vernacular name of medicinal plant) and/or brand or ingredient name(s), including the part of medicinal plant used, preparation methods; manufacturer, country of origin, batch number, expiry date and provider

♦ **administration details**: dose and quantity supplied, dosage form, route, start/stop dates

♦ **indication or for use reason**

♦ **adverse reaction data:** date of onset (or duration from first administration to onset of event), description with symptoms and signs, severity and seriousness, results of clinical investigations and tests, course and outcome, and dechallenge/rechallenge with the same product, where appropriate

♦ **risk factors**, e.g. age, impaired renal function, previous exposure to the herbal medicine(s) concerned, previous allergies, drug misuse or abuse, the social use of drugs

♦ **name and address of reporter** (to be considered confidential and to be used only for data verification, completion and case follow-up).

How to report

For health-care providers already included in a national pharmacovigilance system, a familiar form will facilitate reporting; the introduction of a second type of reporting form may cause confusion. It is desirable to use a standard printed or electronic reporting form and to ensure that forms are widely available. It should also be acceptable to receive reports by telephone, letter or e-mail. If possible, a sample of the herbal product and its packaging should be submitted with the report. Educational materials, including a list of simple terminology that can be understood by all parties, should be developed to inform and assist those not familiar with reporting.

Use of a standardized classification and identification for(2) transmitting reports to UMC is desirable. Coding of adverse events/adverse reactions to herbal medicines should be compatible with that for other medicines. UMC therefore proposes the use of the WHO Drug Dictionary (WHO-DD) as it has been developed to store structured, classified information on the names of herbal products and their ingredients in the same way as similar information on other medicines.

Other reporting issues

Under no circumstances should information obtained during pharmacovigilance activities be divulged for commercial purposes. The identity of both the patient and the reporter should remain confidential unless their written permission to reveal this information is obtained.

Data management

- **Data quality**. Strenuous efforts should be made to ensure that there are quality controls on data processing and that the data elements

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 1 Jan-Feb 2021, pp: 317-329 www.ijprajournal.com ISSN: 2249-7781

of reports are as complete and accurate as possible. Mechanisms to check for duplications should be instituted.

- **Data storage.** Computer databases should be managed to as high a standard as possible to facilitate access to and use of the data. Software should be selected with expert advice so that analytical needs can be met.
- **Data analysis.** Programmes should be developed to provide for regular analyses and data output appropriate for local needs.
- **Analysis of the global WHO database.** The global WHO database managed by UMC is being improved on the basis of the proposed "Database management and classification for coding of herbal medicines", of which the previously mentioned HATC is one part (Annex 6). Data-mining techniques that have proved effective on the very large numbers of reports for other medicines will be used for signal detection on reports for herbal medicines. The success of these techniques depends on the volume and quality of data submitted by national pharmacovigilance centres.
- **Support on technical and data management** is available from the WHO Collaborating Centre for International Drug Monitoring, UMC.

DATABASE SAFETY

FIG. 3. DATABASE SAFETY

Communication

Effective communication of the results of monitoring is also essential so that pharmacovigilance activities can have a positive impact on the health of the people. Communication should be established at many different levels, for example, between

- the national pharmacovigilance centre and consumers
- the national pharmacovigilance centre and the regulatory authority
- the national pharmacovigilance centre and such centres in other countries, within the region or in other regions
- the national pharmacovigilance centre and health professionals
- the national pharmacovigilance centre and providers of herbal medicines
- the national pharmacovigilance centre and UMC
- the national pharmacovigilance centre and the mass media.
- health professionals and providers of herbal medicines, and consumers and patients.[1]

IV. CHAPTER 4. PHARMACOVIGILANCE PROGRAMME IN INDIA (PVIP)

It was launched in July 2010, initiated by government of INDIA, with the AIIMS,Delhi as the **National coordination Centre** for monitoring Adverse Drug Reaction.

The National Coordination Centre was shifted from the **AIIMS**,New DELHI to the **Indian Pharmacoepia Commission** (IPC), Ghaziabad, Uttar Pradesh on 15th April 2011, for better implementation of Program.

4.1. HISTORY:

- The origin of pharmacovigilance in India goes back to 1986, when a formal adverse drug reaction (ADR) monitoring system consisting of 12 regional centers, each covering a population of 50 million, was proposed for India.
- However, nothing much happened until a decade later when in 1997,
- India joined the WHO Adverse Drug Reaction Monitoring Programme based in Uppsala, Sweden. This attempt was unsuccessful and hence, from 1January 2005, the WHOsponsored and World Bank-funded National Pharmacovigilance Program for India was made operational.
- 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

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Pharmacology, Seth GS Medical College and KEM Hospital, Mumbai) and the NorthEast 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.

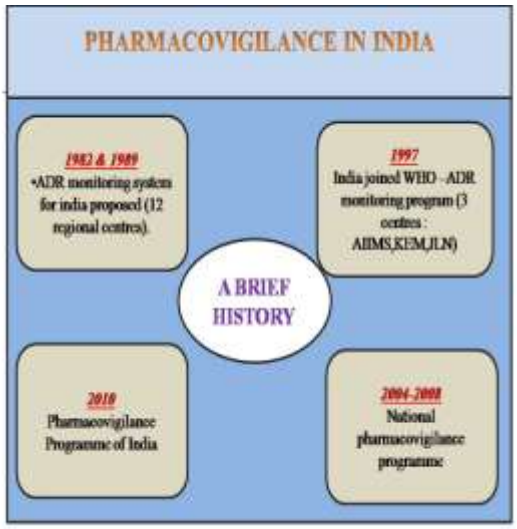

FIG.4 HISTORY OF PvPI

4.2(a). GOAL:

Safeguard the health of the Indian population by ensuring that the benefits of use of medicine outweigh the risks associated with its use.

1. To develop and implement Pharmacovigilance system in India
2. To enroll, initially, all MCI approved medical colleges in the program covering north, south, east and west of India.
3. To encourage healthcare professionals in reporting of adverse reaction to drugs, vaccines, medical devices and biological products
4. Collection of case reports and data
5. To expand the pharmacovigilance programme to all hospitals (govt. & private) and centers of public health programs located across India.
6. To develop and implement electronic reporting system (e-reporting).
7. To develop reporting culture amongst healthcare professionals.
8. To make ADR reporting mandatory for healthcare professionals. [3]

4.2.(b) .OBJECTIVE:

- To monitor ADR in Indian Population.
- To create awareness between health care professionals about the importance of ADR.
- Support the CDSCO for formulating the safety regulated decisions of medicine.
- Create a national centre of excellence with global drug safety monitoring standards.
- To monitor benefit risk profile of medicine.
- Generate independent,evidence bases on te safety of medicines.
- Communicate findings with all key stakeholders.[3]

4.3.Current Status of Adverse Drug Reactions Monitoring Centres under Pharmacovigilance Programme of India

- ✓ Indian Pharmacopoeia Commission (IPC),is functioning as National Coordination Centre (NCC) for Pharmacovigilance Programme of India (PvPI) since 15th April 2011 under the aegis of Ministry of Health & Family Welfare, Government of India.
- ✓ Major functions of NCC are to collect, collate and analyze Adverse Drug Reactions (ADRs) data to arrive at an inference to recommend regulatory interventions to Central Drugs Standard Control Organization (CDSCO), besides communicating risks to healthcare professionals and the public.
- ✓ NCC provides the logistic support and manpower to AMCs for their smooth functioning and reporting the ADRs[3]

Procedure for the Selection of AMC

'Letter of Intent' is required to be submitted by the Head of the Institutions to participate in this nationwide programme to monitor drug safety.NCC communicates the AMC details to WHO-Uppsala Monitoring Centre (UMC), Sweden to obtain VigiFlow (WHO-UMC owned online software) login details to upload ADRs.[3]

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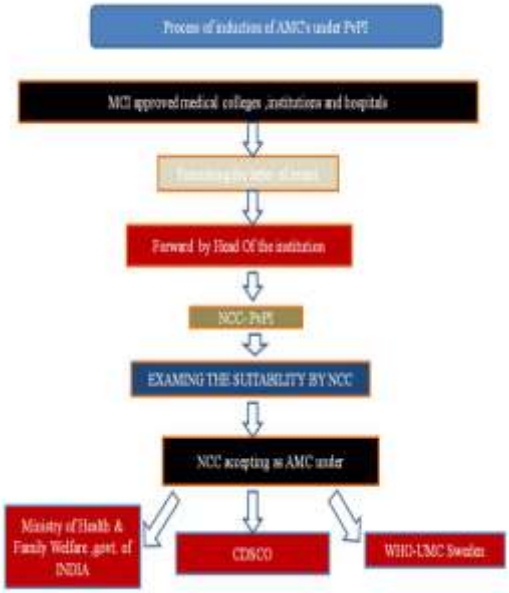

FIG. 5 PROCESS OF INDUCTION OF AMCs UNDER PvPI

FIG.6 VIGIFLOW SAFETY

4.4.Roles and Responsibilities of Personnel at AMCs

Each AMC under PvPI is assigned with a coordinator (department of pharmacology), and a Technical Associate responsible for its functioning. Their roles and responsibilities are:

- ✓ Technical associate appointed is responsible for the collection and follow up of ADR reports, which have to be reported to the AMC coordinator, all the scrutinized and signed ADRs reports should be entered in VigiFlow. Every report has to be sent for the central assessment at NCC.
- ✓ Centre coordinator is responsible for sending the monthly reports of their AMC to NCC.
- ✓ Designated Coordinator is responsible for the proper functioning of respective AMC andcollection, checking completeness for a valid case, causality assessment and scrutinizing the ADRs reports as per SOPs
- ✓ Feedback to all healthcare professionals involved in reporting, to be sent by the AMC Coordinators. [3]

Status of AMCs

- At present ninety AMCs are established under different zonal offices of CDSCO. .CDSCO provides administrative and technical support to the AMCs in their respective zone for the smooth functioning and reporting ADRs to NCC.
- At present one hundred and fifty AMCs are functioning. All these AMCs are engaged to monitor and report ADRs to NCC via VigiFlow, a webbased Individual Case Safety Reports (ICSRs) management system that is specially designed for use by the authorized national centres in the WHO Programme for International Drug Monitoring.[3]

FIG.7. CDSCO offices with different zonal offices

4.5.Regional Resource Centre for Training & Technical Support

- To provide training and technical support to the newly inducted AMCs, four Training and Technical Support Centres at regional level were identified by NCC.
- These include Post Graduate Institute of Medical Education and Research, Chandigarh

International Journal of Pharmaceutical Research and Applications
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(North), JSS Medical College, Mysore (South), Institute of Post Graduate Medical Education and Research, Kolkata (East), Seth GS Medical College and KEM Hospital, Mumbai (West).[3]

- **Roles and Responsibilities** of these centres as follows:
- To provide basic concepts, terminologies and SOPs in Pharmacovigilance
- To provide hands on training and filling the ADRs and data entry in VigiFlow
- Interaction with the AMCs in their respective region on regular basis to resolve the technical issues[3]

FIG.8 AMCs Network under PvPI

4.6. PvPI : Recent developments and future perspectives

Collabaration with adverse events following immunization

NCC-PvPI is assisting with adverse events following immunization (AEFI) at Immunization Technical Support Unit (ITSU) which has been set up by MoHFW with Public Health Foundation of India to ensure the vaccine safety.[5]

Collabartion with CDSCO

In India, PvPI is closely working with CDSCO, drug regulatory authority of India. CDSCO understands that pharmacovigilance plays a specialized and pivotal role in ensuring ongoing safety of medicinal products in India and it seeks inputs from NCC before taking any kind of regulatory decisions. NCC-PvPI is working in close coordination with CDSCO zonal offices also for technical, administrative, and logistics matters related to PvPI.

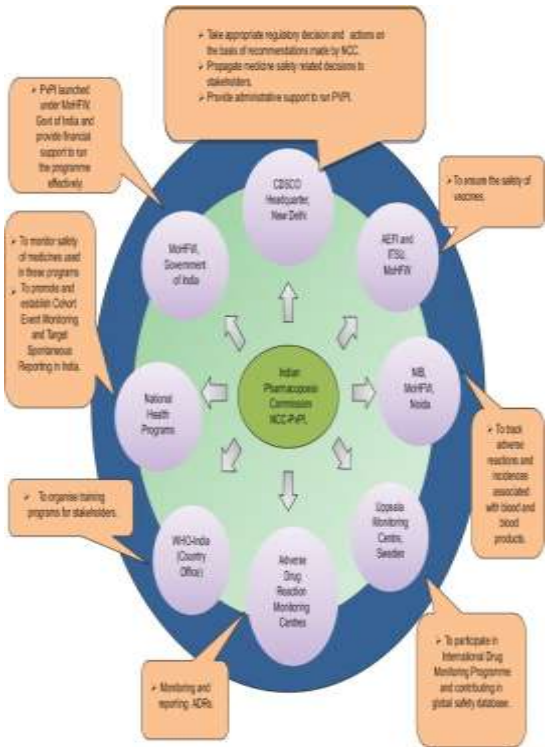

FIG .9 Role of NCC in collaboration with other national and international organizations

EDUCATION AND TRAINING ON PHARMACOVIGILANCE AT REGIONAL TRAINING CENTRE

A primary objective of NCC-PvPI is to promote the safest use of medicines through contributing to appropriate education in pharmacovigilance and training activities across the country.[5]

COMMUNICATION

NCC is committed to communicate the findings of PvPI to stakeholders and public with respect to importance of ADRs and reporting them, information about benefit-harm and effectiveness-risk, rational use of medicines, etc. A variety of methods for PvPI communication is used by NCC as follows.[5]

Website

The websites of CDSCO (www.cdsco.nic.in) and NCC (www.ipc.gov.in) are important tools for communication to the

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Volume 6, Issue 1 Jan-Feb 2021, pp: 317-329 www.ijprajournal.com ISSN: 2249-7781

stakeholders and public seeking specific information. PvPI documents on these websites can be searched by navigating from the home page. Examples of documents on these websites include list of AMCs, how, what, and where to report ADRs, newsletters, training module, guidance document, etc.

Media

Since medicines safety communications with healthcare professionals, patients, and the general public must be focused on joint responsibility for safe and rational therapy, NCC communicates the findings in national newspapers, electronic media, etc., on regular basis.

Newsletter

PvPI Newsletter is unique among healthcare professionals because it focuses on the ADRs-related informations. Three issues per year guides how to take a leading role in monitoring, reporting, and preventing ADRs. It is available in a convenient electronic format and printed version is circulated to AMCs, corporate hospitals, academic institutions, health departments, etc.[5]

FUTURE PERSPECTIVE

NCC has mandated the RTCs to organize advance level training for the personnel's of all AMCs under their respective regions and one CME in pharmacovigilance at an AMC under their region to increase the awareness of healthcare professionals about the ADR reporting. In near future, all Medical Council of India approved institutions will be enrolled under the PvPI. As IPC was recognized as the WHO Collaborating Center for medicines and vaccine safety in the South East Asia region during 38th Annual Meeting of National Pharmacovigilance Centers participating in the WHO program for international drug monitoring, plan to initiate, and coordinate with countries in South East Asia region for potential signals from the built safety database. [5]

V. CONCLUSION

India is now considered to be a hub for clinical research. The DCGI has shown its commitment to ensure safe use of drugs by establishing the National Pharmacovigilance Program. More and more clinical trials are now being conducted in India and business process outsourcing (BPOs) based in India are now also undertaking pharmacovigilance projects from MNCs. Healthcare professionals, consumer groups, NGOs and hospitals should appreciate that there is now a system in place to collect and analyze adverse event data. They should start reporting adverse events actively and participate in the National Pharmacovigilance Program to help ensure that people in India receive safe drugs. With the help and proper coordination of all stakeholders, we can definitely build a worldclass pharmacovigilance system in India.

ADRs reporting through PvPI improved with the measures such as education, training, and provision of technical assistance. The PvPI is a vital knowledge databases for Indian drug regulation. The CDSCO has notified important safety label changes for carbamazepine and piperacillin + tazobactam in the year 2015. The PvPI plans to expand its scope of activities to widen its reach to other healthcare professionals and to strengthen measures for capacity building.

At present, teaching and corporate hospitals have been identified as AMCs under PvPI. In future Pharmacy institutions may be enrolled in PvPI to enhance ADRs reporting. NCC is closely working with the AMCs to coordinate with nearby Pharmacy institution in reporting of ADRs.

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