

POST MARKETING SURVEILLANCE: A REAL – LIFE EFFECTIVENESS OF ESSENTIAL MEDICINES IN INDIAN POPULATION

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ABSTRACT

The aim of the work is the need of post marketing surveillance in India. The objective in Postmarketing surveillance is to estimate the strength of the association between adverse events (AEs) and drug exposures that vary over time. In premarketing testing, the numbers and types of patients used to demonstrate a drug's efficacy and safety are limited compared with the numbers and types of patients who will eventually be prescribed the drug after it is marketed. Although post-marketing surveillance cannot provide knowledge of the safety or efficacy of drugs at the time of their introduction on the market. Post-marketing surveillance of drug therefore play an important role to discover an undesirable effect that might present at risk. This paper provides you the information of importance of PMS, Guidelines in the other countries, SOP of PMS, Analytical methods of PMS with few direct examples, content of PMS as per DCGI Guidelines and information on the benefit and risk of the drugs.

Keywords: Post marketing surveillance, Drug explosers, Drug's efficacy, PMS, SOP.

INTRODUCTION

Postmarketing surveillance (PMS) is the practice of monitoring the safety of a pharmaceutical drug or medical device after it has been released on the market and is an important part of the science of pharmacovigilance [1].

Post-marketing surveillance (PMS) to assure the efficacy and safety of drugs after they go on the market and to establish proper methods of use of drugs consists of three systems: the ADR collecting and reporting system, the reexamination system, and the reevaluation [2] system.

Adverse Event (AE) is an unanticipated problem involving "risk" to subjects that ultimately results in harm to the subject (impacts on subject's morbidity and mortality) or others. AE reports must be filed with the sponsor and the Institutional Review Board (IRB) when any of the following happens to a subject on a study: Death, Unanticipated "risk" requiring treatment, hospitalization or prolongation of existing hospital stay,

Any suspicious findings that may have relationship to the study, Adverse pregnancy outcome before, during and at the time of delivery, Birth defects or congenital anomaly, Loss of research records that contain identifiable information, Overdose of drug, Unusual frequency or intensity of expected effects described in the informed consent document or trends in one type of AE event toward within a protocol (serious or not), Breach of confidentiality, Unanticipated problems involving risks to "others" (Example: A nurse in a research study is inadvertently stuck by a needle containing a chemotherapeutic agent that is Teratogenic, mutagenic, etc), Abnormal test results that is critical to evaluate the "risk" or "safety" of subjects, Unexpected – any adverse experience that is not identified in nature, severity or frequency in the consent form and is not due to a disease process. [3]

Good Vigilance practice establishes standards for post-marketing safety management related to the collection, evaluation, and assessment of proper use information on the establishment of appropriate safety-related organizations and systems as one of licensing requirements for the marketing authorization holder, development and implementation of relevant SOPs, marketed drugs, etc., and to the implementation of measures for safety assurance. [2]

(i) Difference between PMS and Phase 4

Phase 4 includes all post marketing studies.

- PMS is one type of Phase IV study to obtain additional information about the risks and benefits resulting from long term usage of drug. PMS primarily is a surveillance of safety of new drug.

- Another type of Phase IV study is that is designed to evaluate the marketed drug in specifically designed studies, which have inclusion/exclusion criteria, objectives and end points. The drug is used for the labeled indication in these studies

- Another type of Phase IV study involves evaluation of the drug for a new indication of a marketed drug,

- For Phase 4, EC permission is essential. In addition, DCGI approval also essential.[4]

Not all Phase IV studies are post-marketing surveillance (PMS) studies but every PMS study is a phase IV study. Phase IV is also an important phase of drug development. In particular, the real world effectiveness of a drug as evaluated in an observational, non-interventional trial in a naturalistic setting which complements the efficacy data that emanates from a pre-marketing randomized controlled trial (RCT). True safety profile of a drug is characterized only by continuing safety surveillance through a spontaneous adverse event monitoring system and a post-marketing surveillance/non-interventional study. Surveillance of spontaneously reported adverse events continues as long as a product is marketed. And so Phase IV in that sense never ends. JUST as Phase I is sometimes referred to as the acid test of drug development (where the rubber meets the road), since it is the first time that the drug is being tested in humans, Phase IV may be considered as the real test since for the first time that the drug is tested in the real world. In the real world no patient can be excluded; even pregnant and lactating women, those with hepato-renal dysfunction, on multiple concomitant medications for concomitant clinical conditions must be treated. How the drug performs in such real world conditions is a test of its effectiveness. All studies conducted in a phase IV setting, i.e., after marketing authorization approval per label are called phase IV studies. Of these, those mandated by the regulatory authority to be conducted as observational studies in a naturalistic setting per label are called PMS studies. [5]

(ii) According to PMS Guidelines of Japan

Standard operating procedures for post-marketing surveillance

1. The following standard operating procedures for post-marketing safety management must be prepared.
2. Procedures for collection of safety management information
3. Procedures for drafting of safety assurance measures based on examination of safety management information and the results thereof

4. Procedures for implementation of safety assurance measures
5. Procedures for reporting from safety management supervisors to general marketing compliance officer
6. Procedures for early post-marketing surveillance
7. Procedures for in-house inspections
8. Procedures for education and training Procedures for retention of records
9. Procedures for contacts with quality assurance supervisors and other supervisors engaged in work related to marketing of prescription drugs and highly controlled medical devices
10. Other procedures necessary for properly and smoothly implementing safety assurance measures of post-marketing surveillance[2]

(iii) According to European Commission Volume 9A

Analytical methods for Post-marketing safety surveillance

The common types of post-marketing surveillance are passive and active surveillance, stimulated reporting, comparative observational studies, targeted clinical investigations, and other descriptive studies.

a) Active surveillance

Active surveillance is defined within the European Commission Volume 9A to be the ongoing, proactive monitoring of product use and potential adverse events (AEs) "to ascertain more completely the number of adverse events in a given population via a continuous organised process." One objective of active surveillance is to detect safety issues early in the post-marketing environment that were not identified during development, such as rare events or latent onset. Active surveillance can also quantify the effects of misuse or overdose. Another objective is to characterize drug use patterns, including profiles of prescribers and patients, indications, and dosing and discontinuation. Active surveillance can include the regular, periodic and stimulated collection of case reports from healthcare providers or facilities, such as sentinel sites. The use of sentinel sites may involve the review of medical records or patient and/or physician interviews for complete and accurate date on reported adverse events. This method may allow for a focus on patient subgroups that would not be available in a passive reporting system, and is most efficient when employed in the surveillance of products frequently used in an institutional setting. However, the use of sentinel sites is limited by small sample size, selection bias, and expense. Additional methods for active surveillance include prescription monitoring, patient registries, and database and/or electronic medical record research

b) Passive surveillance

Passive surveillance primarily includes the analysis of spontaneous adverse event reports. Sources for reports include regulatory systems such as MedWatch in the US. Passive surveillance often involves assembling a series of cases to examine specific types of events, such as overdose and product re-challenge. This method of safety surveillance is limited by incomplete reporting information (which can impede determination of causality), potential underreporting of events, and unknown parameters for calculation of incidence (denominator and numerator). A component of passive surveillance is data mining looking for disproportionality patterns

Comparative observational studies

Comparative observational studies can be analytic, such as case-control studies, or descriptive, including cross-sectional surveys and cohort studies. Observational studies do not recruit participants into a controlled environment, as in a random-controlled trial, but instead observe the outcome of interest (e.g., a specific adverse or other drug event) in a population that already takes the drug compared to a population that does not. Case control studies that compare individuals with the outcome of interest to a matched sample of the population without the outcome of interest and ascertain exposures. These studies are commonly used to identify side effects rather than evaluate treatment effectiveness, and may be used to calculate relative risk, but usually cannot be used to calculate absolute risk. Cross-sectional surveys examine a

"snapshot" in time to quantify prevalence of an outcome of interest, such as a disease, within a defined population. These studies can be used to calculate both absolute and relative risk. Cohort studies compare data from an exposed-population to an unexposed-population in order to analyze predictive risk factors for an outcome of interest. In cohort studies, participant exposure is self-determined and not controlled or assigned by the study. Cohort studies may be conducted retrospectively or prospectively

Targeted clinical investigations include large-streamlined trials (LSTs) and randomized controlled trials (RCTs)

These studies compare outcomes of interest in an exposed population to an un-exposed population. . Double-blind RCTs are considered the "gold standard" of research; however, they can be the most costly and time-consuming to conduct and may not be representative of actual using populations [6]

(iv) Post marketing surveillance in USA

Physicians and patients expect that when medications are prescribed correctly for labeled indications and are used as directed, these medications generally will have beneficial effects and will not cause significant harm. This confidence in pharmaceutical products reflects trust in the effectiveness and integrity of the drug approval and monitoring process.

However, the current approval process for drugs and biological agents in the United States has come under intense scrutiny, most notably because of concerns about influence from industry. For instance, since adoption of the 1992 Prescription Drug User Fee Act, which augmented the budget of the Food and Drug Administration (FDA) by charging "user fees" to pharmaceutical firms, the FDA has received approximately \$825 million in fees from drug and biologic manufacturers from fiscal years 1993 through 2001. During that time, median approval times for standard ("Nonpriority") drugs decreased from 27 months in 1993 to 14 months in 2001, but as an inevitable consequence of faster approvals, drug recalls following approval increased from 1.56% for 1993-1996 to 5.35% for 1997-2001. In addition, an investigation of 18 FDA expert advisory panels revealed that more than half of the members of these panels had direct financial interests in the drug or topic they were evaluating and for which they were making recommendations. [7]

Examples of post marketing surveillance

1. Postmarketing surveillance for Angiotensin-Converting Enzyme Inhibitor Use During the First Trimester of Pregnancy -- United States, Canada, and Israel, 1987-1995

Angiotensin-converting enzyme inhibitors (ACEIs) are effective antihypertensive drugs, but use of ACEIs during the second and third trimesters of pregnancy has been associated with a pattern of defects known as ACEI fetopathy. The predominant feature of the fetopathy is renal tubular dysplasia. Other associated conditions include hypocalvaria, intrauterine growth retardation (IUGR), and patent ductus arteriosus (PDA). These features may be related to fetal hypotension secondary to ACEI-induced decreases in fetal angiotensin or increased bradykinin . Although no adverse fetal effects have been linked to first trimester use of ACEIs, there has been no systematic evaluation of births to women with such exposures. To determine whether features of ACEI fetopathy occurred after first trimester exposure, in 1992 the Organization of Teratology Information Services (OTIS) in North America initiated the ACEI Registry; two members of the European Network of Teratology Information Services agreed to participate. This report presents findings from the ACEI Registry, which indicate that the infants of 66 women who self-reported first trimester only exposure to ACEI showed no evidence of renal tubular dysplasia.

Among the 48 live births, three cases of IUGR were documented. One infant with IUGR was from twins delivered at 36 weeks' gestation; the other two were full-term. Another child had a PDA that required surgical ligation at age 18 months. That infant was born at 40 weeks' gestation to a woman who discontinued therapy with an ACEI at 71/2 weeks gestation. She also was treated with digoxin throughout her pregnancy and with warfarin sodium for the first 5 weeks

followed by heparin throughout the remainder of her pregnancy. There were no children with renal tubular dysplasia who had been exposed to ACEIs exclusively during the first trimester. [8].

2. A qualitative study to determine best methods for post-marketing surveillance in usual rheumatology care in Ontario

To determine best methods for post-marketing surveillance (PMS) in usual rheumatology care in Ontario with an emphasis on low cost and sustainable procedures.

Recommendations for PMS in rheumatology care in Ontario include

Use of paper CRF's with fax back to the data management centre, a very brief clinical form to be completed biannually, methods to address the heterogeneity of the Ontario population (e.g. language), centralized consent, and provision of a range of low cost incentives that participating rheumatologists can choose from to best fit their needs.

Results

- 100% of participants have access to a fax machine, while 86% have access to the internet
- 64% of participants felt that using paper CRF's as opposed to electronic CRF's would work best in their office environment
- Most participants see their RA patients at least twice a year therefore a biannual patient assessment would be acceptable
- 100% of participants felt comfortable collecting informed consent
 - However, it was suggested that a second consent should be collected by program staff, despite the cost, to ensure all patients have been consented fully, without bias or coercion, leading to a standardized method of obtaining informed consent
- The greatest perceived barrier to patient recruitment was language
 - All participants felt that full participation of the widest possible range of patients was vital to PMS and warrants the cost of translation
- Low cost incentives for participation in PMS were discussed and those identified include:
 - the ability to use PMS activities for Continuing Professional Development credits,
 - feedback on patient and practice characteristics,
 - full assistance with ethics submissions and maintenance, and
 - the ability to align the data collected through PMS with the requirements for Individual Clinical Review, the publicly funded procedure for approval of biologics and other therapies in Ontario.
- Current dislikes with clinical trials and PMS studies were discussed and those identified include:
 - screening process
 - excessive paperwork
 - lack of manpower
 - monitor visits [9]

3. Postmarketing surveillance of safety and effectiveness of Etanercept in Japanese patients with Rheumatoid arthritis

Patients with early moderate RA were less likely to experience SAEs and were more likely to achieve remission compared with patients with more severe disease. The safety and effectiveness of Etanercept was demonstrated in Japanese patients in one of the largest observational trials conducted thus far in RA patients treated with biologics .

Results

A total of 13,894 patients treated with Etanercept completed the 24-week study (Table 1). The majority of patients were women (n = 11,314; 81.4%). Mean \pm SD patient age was 58.1 \pm 13.1 years; most patients (78.3%) were aged \geq 50 years (more than one half were aged \geq 60 years), and the mean \pm SD patient weight was 53.2 \pm 10.1 kg. About 40% of patients had a disease duration of \geq 10 years. Concomitant use of DMARDs/ biologics was 74.0% (n = 10,276) and that of Methotrexate was 55.9% (n = 7768). The most commonly used Etanercept dose regimen (76.1%; n = 10,578) was 50 mg per week (i.e., 25 mg twice weekly). Previous use of glucocorticoid was

83.4% (n = 11587) and previous use of Infliximab was 13.5% (n = 1878). Additionally, 57.1% of patients had Comorbidities, including 877 patients (6.3%) with a medical history of tuberculosis.

Significant differences were observed between men and women in most demographic characteristics, including age, weight, disease duration, Steinbrocker stage and class, history of concomitant medical conditions, Comorbidities, concomitant use of Methotrexate, and prior glucocorticoid use.

A total of 11,615 (83.6%) patients completed 24 weeks of therapy, with 2309 patients (16.6%) discontinuing during the 24-week period.

Reasons for stopping treatment were AEs (7.6%, n = 1049), lack of treatment effectiveness (2.6%, n = 368), refusal of treatment for economic reasons (1.5%, n = 212), moved to another hospital (1.6%, n = 222), and other (3.3%, n = 458). [10]

History of Pharmacovigilance in India

It was not until 1986 that a formal adverse drug reaction (ADR) monitoring system consisting of 12 regional centres, each covering a population of 50 million, was proposed for India. In 1997, India joined hands with the World Health Organization (WHO) Adverse Drug Reaction Monitoring Programme based in Uppsala, Sweden.

Three centres 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 centres in Mumbai (KEM Hospital) and Aligarh (JLN Hospital, Aligarh Muslim University).
- These centres were to report ADRs to the drug regulatory authority of India. The major role of these centres was to monitor ADRs to medicines which are marketed in India.
- However, they hardly functioned as information about the need to report ADRs and about the functions of these monitoring centres were yet to reach the prescribers and there was lack of funding from the government. This attempt was unsuccessful and hence, again from the 1st of January 2005, the WHO-sponsored 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 centres—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 centres would report to the Mumbai centre and two to the New Delhi centre. Each regional centre in turn would have several peripheral centres reporting to it. Presently there are 24 peripheral centres.

Post marketing surveillance

Subsequent to approval of the product, new drugs should be closely monitored for their clinical safety once they are marketed. The applicants shall furnish Periodic Safety Update Reports (PSURs) in order to-

- Report all the relevant new information from appropriate sources;
- Relate these data to patient exposure;
- Summarize the market authorization status in different countries and any significant variations related to safety; and
- Indicate whether changes should be made to product information in order to optimize the use of the product.

Indian guidelines

In the Drugs and Cosmetics Rules, 2005 (hereinafter referred to as said rules), (1) in Part X-A, after rule 122-DA, the following shall be inserted, namely:-

122-DAA, Definition of Clinical trial.- For the purpose of this Part, "Clinical trial" means a systematic study of new drug(s) in human subject(s) to generate data for discovering and/or verifying the clinical, pharmacological (including pharmacodynamic and pharmacokinetic) and/or adverse effects with the objective of determining safety and / or efficacy of the new drug."

With the latest amendment (dated 20th Jan 2005) to the Schedule Y of Drugs and Cosmetic Act 1945, the reporting of adverse events from clinical trials has become clearer and unambiguous. There is of course a quantum leap between the old and the new version and the serious intentions of the Drug Controller General of India (DCGI) regarding stricter compliance are clearly palpable. According to the amended Schedule Y, the responsibilities of the sponsors safety reporting are given in clause 2; which are as follows:-

Any unexpected serious adverse event (SAE) (as defined in GCP Guidelines) occurring during a clinical trial should be communicated promptly (within 14 calendar days) by the Sponsor to the Licensing Authority and to the other Investigator(s) participating in the study.

Whereas the responsibilities of the Investigator(s) safety reporting are given in clause 3, which are as follows:

"Investigator(s) shall report all serious and unexpected adverse events to the Sponsor within 24 hours and to the Ethics Committee that accorded approval to the study protocol within 7 working days of their occurrence".

The differences between both the versions, w.r.t sponsors' reporting obligations are summarized in the following:

New Schedule Y: All "unexpected SAEs" within 14 calendar days would be communicated to the local regulatory authority & other participating investigators".

Old Schedule Y: "Any unusual, unexpected or serious adverse reaction to be communicated promptly to the local regulatory authority".

ADR monitoring and Pharmacovigilance activities in India

The National Pharmacovigilance Advisory Committee (NPAC) monitors the performance of various zonal, regional, and peripheral centers and performs the functions of "Review Committee" for this program. The NPAC also recommends possible regulatory measures based on pharmacovigilance data received from various centers. The Zonal Pharmacovigilance Centre (ZPC) and Regional Pharmacovigilance Centre (RPC) have also been established. The Central Drugs Standard Control Organization (CDSCO) is initiating a countrywide pharmacovigilance program under the Family Welfare, and Government of India. The National Pharmacovigilance Centre at CDSCO shall coordinate the program. The National Centre will operate under the supervision of the NPAC to recommend procedures and guidelines for regulatory interventions.

The National Pharmacovigilance Program will have the following milestones:

- Short-term objectives: To foster a culture of notification.
- Medium-term objectives: To engage several healthcare professionals and Non-Government Organizations (NGOs) in the drug monitoring and information dissemination processes.
- Long-term objectives: To achieve such operational efficiencies that would make Indian National Pharmacovigilance Program a benchmark for global drug monitoring endeavors.

Periodic Safety Update Reports shall be expected to be submitted every 6 months for the first 2 years of marketing in India, and annually for the subsequent 2 years. In addition, training programs and interaction meetings shall be held every 6 months after the initial training.

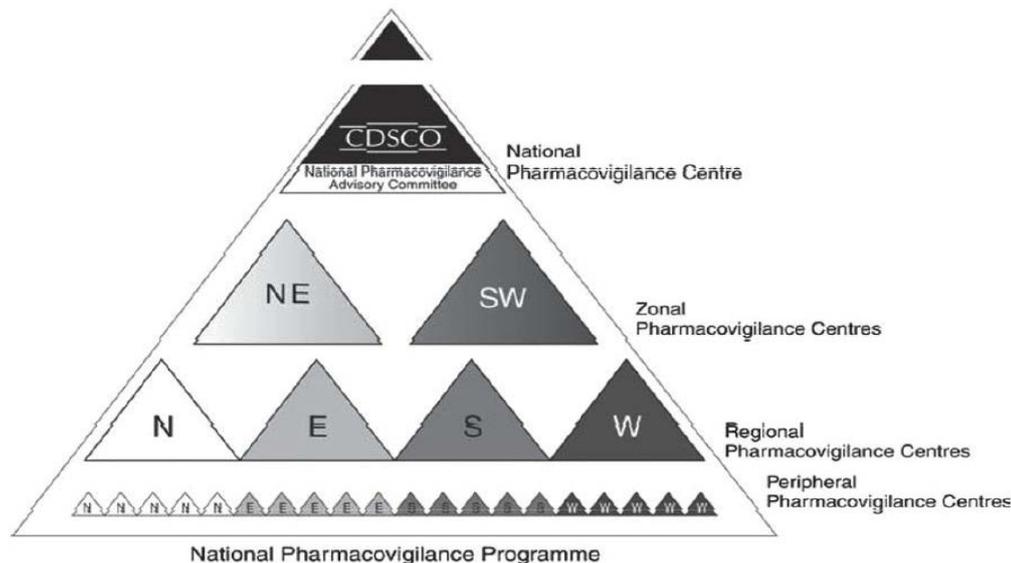


Fig. 2: Hierarchical structure of the proposed centers in India

All data generated (including reporting forms) will be stored and preserved for the purpose of archiving for a minimum period of 5 years at the ZPCs. The reporting of seemingly insignificant or common adverse reactions would be important because it may highlight a widespread prescribing problem.[11]

Examples

1. **Post- marketing Study to assess the safety, tolerability of effectiveness of fungisome: An Indian Liposomal Amphotericin B preparation**

This postmarketing study documents the safety, tolerability, effectiveness and cost advantage of indigenously developed liposomal Amphotericin B in the treatment of systemic fungal infections and febrile neutropenia in actual clinical practice.

RESULTS

Data were available for 109/144 patients from 35/40 physicians. Fungisome™ was administered at 1-3 mg/kg/day for 7-76 days. No serious adverse events related to the drug were observed in the study. Mild infusion-related adverse events were reported in 40

(36%), moderate in 11 (10%) of patients and severe in 2 (1.8%). None of the adverse events were certain to Fungisome™ exposure, 12 (11%) were probable, 28 (25%) were possible, and 13 (11.9%) were unlikely. Of the 91 assessable patients (received at least eight doses of Fungisome™) for efficacy complete response was observed in 67 (73.6%), 16 (17.5%) had partial responses, and 8 (8.7%) of patients had no response. The acquisition cost per day and per course treatment of different fungal infections ranged from (approximately) Rs 4500-8000 and 0.9 -2.1 lakh respectively. [12]

2. A Post-Marketing Surveillance Study of Tolperisone [MYOTOP-150]: It's Use in the General Clinical Practice in India

The present observational study demonstrates that the therapy with Tolperisone is an effective and well tolerated strategy in patients with diseases or conditions which are associated with spasticity or muscle spasm. Data was collected for 165 patients, with a mean age of $43.88 \pm$ (SD) 11.27 years [Range: 15 to 72 years]. At the baseline, the mean \pm SD of the score on the 7-point Likert scale was 4.96 ± 1.01 . After treatment with tolperisone, the mean score was 1.87 ± 0.91 , with a significant reduction of 3.08 ± 1.14 ; $p < 0.0001$. After therapy, 42.04% of the patients reported "no problem". In 88.02% of the patients who were treated, the physicians rated the treatment with tolperisone as excellent, very good or good. Side-effects were observed in 7.88% of the patients. [13]

3. Olmesartan Medoxomil Evaluated for Safety and Efficacy in Indian Patients with Essential Hypertension :A Real World Observational Postmarketing Surveillance

To assess the efficacy and safety of once daily Olmesartan medoxomil 20 mg in Indian patients with stage 1 essential hypertension.

Our findings reiterated that Olmesartan medoxomil 20 mg once daily is not only effective in achieving the desired BP in a significant number of patients, it also shows excellent tolerability and hence compliance. Olmesartan is a valuable option for treatment of essential hypertension in adult Indian patients.

RESULTS

There were significant changes in mean sitting systolic and diastolic blood pressure, the primary end point of the study. From baseline visit to the end of the surveillance visit-7 (week 8), a mean change of -18.7 (147.86 to 129.16; $p < 0.0001$; 95% CI) in sitting SBP and a mean change of -14.47 (95.99 to 81.56; $p < 0.0001$; 95% CI) in sitting DBP respectively was observed with olmesartan 20 mg once daily. The response rate at the end of study was 81.82% and 70.18% for SBP and DBP respectively, in stage 1 hypertensive patients without diabetes mellitus. It was 73.38% and 65.47% respectively for SBP and DBP in patients with diabetes. [14]

Table 1: General content of PMS as per DCGI guidelines

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3	List of appendices
4	List of abbreviations
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	i. Investigational sites
	ii. Laboratory(ies)
6	Introduction
	i. Background information
	ii. Mechanism of Action
	ii. Pharmacokinetics
	v. Previous clinical experience
7	Rationale
8	Objectives
9	Study design
	i. Study Endpoints
	a. Primary Study Endpoints
	b. Secondary Study Endpoints
	ii. Design summary
	ii. Patients numbers
	v. Study duration
	v. Patients commitment to the study
	vi. End of study
10	Study population
	i. Inclusion Criteria
	ii. Exclusion Criteria
11	Study methodology
	i. Recruitment Of Study Patients
	ii. Study Visits/Assesments
	a. Sreening/base line visits
	b. Visit 2: End Of Study Investigator Questionnaire
	ii. Study specific suppliers
	v. Unsheduled visits
	v. Patient withdrawal Criteria
12	Study treatments
	i. Identification of Investigational medicinal product
	ii. Treatment allocation
	ii. Dosage instructions
	v. Packaging, labeling, storage
	v. Accountability of Study medication
	vi. Disposal of unused Study medication
	ii. Concomitant therapies
	ii. Prohibited therapies
13	Safety assessments
	i. Adverse Events

-
- a. Adverse Event Definition
 - b. Information to be Collected on Adverse Events
 - c. Procedure for Reporting Adverse Events
 - d. Procedure for Reporting serious Adverse Events
 - e. Reporting to regulatory authorities
 - f. Folloents w up of Patients experiencing Adverse Events upon completion of / withdrawal of study
 - g. Procedures for Patients experiencing onset of serious Adverse Events upon completion of / withdrawal of study
 - h. Treating Overdose
 - i. Pregnancy
 - ii. Clinical laboratory Investigations
 - ii. Vital signs , physical findings and other observations related to safety
- 14 **Statistical consideration**
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 - ii. Date to be analysed
 - ii. Demographics
 - v. Statistical methods for End of Study Investigator questionnaire analyses
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 - a. Adverse Events
 - b. Laboratory data
 - c. Vital signs
 - d. Other variables related to safety
 - e. Patients who are withdrawal from study
 - ri. Interim analyses
- 15 **Quality control and quality assurance audit**
- i. Monitoring
 - ii. Source Document verification
 - ii. Audit
 - v. RB policy on fraud in Clinical Studies
- 16 **Ethics**
- i. Ethical committee / institutional review board review
 - ii. Patient Information and concent
 - ii. Informing general practitioner
- 17 **Regulatory requirements**
- i. Competent authority authorizations
 - ii. Curriculum vitae
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- i. Case report form
 - ii. Retention of essential documentation
 - ii. Protocol amendments
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- 20 **Compensation and indemnity**
- i. Compensation
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- 21 **Reporting, publication and presentation**
- 22 **Investigator responsibilities**
- i. Pre- study
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CONCLUSION

Postmarketing surveillance (PMS) is the practice of monitoring the safety of a pharmaceutical drug or medical device after it has been released on the market and is an important part of the science of pharmacovigilance. This review outlines the PMS importance , Procedure concerning PMS study , SOP for PMS, Current Indian guidelines,

ADR Monitoring in pharmacovigilance in india. Since it is the first time that the drug is being tested in humans, Phase IV may be considered as the real test since for the first time that the drug is tested in the real world. True safety profile of a drug is characterized only by continuing safety surveillance through a spontaneous adverse event monitoring system and a post-marketing surveillance/non-interventional study. Surveillance of spontaneously reported adverse events continues as long as a product is marketed. And so Phase IV in that sense never ends.

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