Pharmacovigilance During Pre-Approval Phases -Comparison of ICH E2E, CIOMS VI, FDA, EMEA/CHMP and CDSCO Risk Management Guidelines

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Abstract: To compare Pharmacovigilance planning ICH-E2E, managing safety information from clinical trials (CIOMS-VI), FDA, EMEA/CHMP) and CDSCO risk management guidelines involved in Pharmacovigilance during the pre-approval phases and to find out the differences and similarities between the guidelines (Safety parameters). Systematic search was conducted using different search engines such as Google, Pub med, Web MD, Cochrane, Medline and PLOS-ONE to identify and download the various regulatory guidelines. Safety parameters assessed across regulatory body guidelines were selected for comparison. The similarities and differences between safety parameters of the said regulatory bodies were presented in appropriate manner and opinion was provided on drug safety implications. CIOMS's Serious Adverse Event (SAE) reporting form is known as Universal SAE reporting form. The purpose of Investigational new drug annual report (IND AR) of FDA is to submit the progress report while that of annual safety report (ASR) of EMEA is to provide a benefit-risk evaluation for the clinical trial concerned. ICH has produced harmonized toxicity guidelines and same have been implemented by FDA and EMEA. Various forms and guidelines required for reporting safety parameters during preapproval phases are harmonized. Animal toxicity studies required by CDSCO are longer in duration when compared to FDA and EMEA.

Key Words: —*Pharmacovigilance risk management, Pre-marketing Pharmacovigilance, FDA, CDSCO, ICH E2E.*

I. Introduction

The aim of pharmacovigilance and the regulator agencies to fortify patients from undesired effects by identifying drug hazards, quantifying risk benefit ratio, clarifying predisposing factors and discredit invalid safety signals.1 In Pharmacovigilance the usual focus was on post marketing surveillance, nowadays it has changed to pre-approval phases; monitoring safety parameters and analyzing safety data, adverse events and clinical trials. Its improved drug safety risk management.2

Each regulatory authority has their own legislation to abet industry in planning risk management activities throughout life cycle of a drug development. Regulatory authorities generate guidelines to ensure minimum risk and maximum safety and efficacy.

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1.1 Materials and Methos

This study mainly involves the comparison of safety parameters of the ICH E2E, CIOMS VI, FDA, EMEA/CHMP and CDSCO risk management guidelines involved in pharmacovigilance during the pre-approval phases. This is a comparative study, where the effort has been made to study, compare and provide recommendations on the harmonization of the regulatory frame work for the approval of drugs in various countries.

Sources of data have been referred includes guidelines and guidance documents issued by regulatory authorities, websites of various regulatory agencies and organizations and peer reviewed publications and articles on safety parameters in clinical trials. The steps involved in methodology are identification and download of guidelines, selection of safety parameters to be compared, comparison of guidelines (safety parameters) and presentation of results.

II. Results And Discussion

2.1 Pre-Approval Pharmacovigilance Advantages and Disadvantages

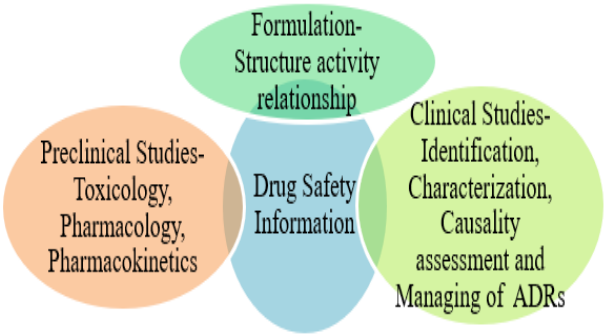

Fig.1. Marketing Pharmacovigilance

Pre-approval pharmacovigilance is mainly focused on drug safety information gathered during formulation, preclinical and clinical phases of a drug. Structure activity relationship determines biological and toxicological properties of a drug. Preclinical studies conducting in rodents and non-rodents reveal pharmacology, pharmacokinetics and toxicological properties of a drug. The toxicological studies conducting in animals include reproductive toxicology, carcinogenicity, mutagenicity, genotoxicity and toxicokinetic.

2.2 Advantages

- Pharmacovigilance during the phases of clinical trials ensures safety of drugs and monitoring and analyzing adverse events of the subject with respect to investigational drug and other concomitant medications.
- During clinical trials we will identify ADRs related to pharmacological action of the drug and how tolerant it is for the subject and their plasma drug concentration.
- It also helps in creation of drug's safety profile.
- Clinical trials help in decision making by regulatory authorities post analysis of safety and efficacy data of the drug collected and its tolerance in its subject. Thus, ensuring marketability of the drug.
- Due to effective pharmacovigilance during preapproval phases, some drugs do not get approval for market authorization. Example for a drug that shows ADRs during clinical trial and did not get approval is Ralfinamide. (Sponsor: Newron & Sweden AB, Use: Chronic neuropathic low back pain, ADR occurred: Retinopathy and liver toxicity, MOA: Inhibition of Na channels, including NaV 1.7, N-type Ca+ channels and NMDA receptors).

2.3 Disadvantages:

- Adverse drug reactions associated with chronic use of medications, Delayed ADRs and rare ADRs were difficult to find out during premarketing pharmacovigilance.
- It's difficult to detect drug-drug and drug-food during premarketing pharmacovigilance.
- The populations have not been studied in the pre-approval phase includes children, elderly, pregnant or lactating women, patient with relevant co-morbidities such as hepatic and renal failure, patients with disease severity different from that studied in clinical trials, populations with pertinent genetic polymorphism, patients of different hereditary and ethnic origins.

2.4 Comparison of SAE Reporting Form Templates

Each regulatory authority has their own SAE reporting form templates to report the serious adverse events to concerned regulatory bodies. This comparison includes three regulatory bodies namely FDA which is related to United States, CIOMS which is a centralized regulatory body and CDSCO which applies to India. FDA, CIOMS and CDSCO recommends 'form FDA 3500A' (Annexure I), 'CIOMS I form' (Annexure II) and Schedule Y's SAE reporting form (Annexure III) respectively for reporting SAEs during clinical trial.

- Each SAE reports must contain some specific details of respective patient, which includes subject initials, date of birth, gender etc. Country is more specific to CIOMS and height and weight are more specific to Schedule Y.
- Adverse event information present in SAE reports include start date of onset of reaction, stop date, duration of reaction, outcome attributed to AE, description of reaction, relevant tests or laboratory data including dates etc. Schedule Y covers dechallenge and rechallenge information in this section. Schedule Y specifies information on recovery.

- Suspect product information comprises name, dose, route of administration & indication for use of suspect product, therapy dates, dechallenge and rechallenge information. FDA more specifies expiry date of the medication.
- Name of concomitant medicinal products and their date of therapy are included in SAE reporting forms. Relevant histories such as diagnostics and allergies are confined to CIOMS.
- Suspect medical device information is included only in FDA's SAE reporting form, hence reaction occurred due to medical device can be reported through it. The FDA's SAE reporting form is the only SAE reporting form which covers the suspect medical device information such as brand name, manufacture name and address, model, expiry date, if implanted give date, if explanted give date, concomitant medical products and therapy dates. It also has column for use by user facility or importer and for manufacture of medical device.
- FDA's SAE reporting form is the only one which covers details of initial reporter such as name, address phone number and occupation of initial reporter.
- Both FDA and CIOMS has separate column for manufactures which include name, address, contact number, report source, data received by manufacture, type of report etc. Schedule Y does not have this section.
- Only SAE reporting form of Schedule Y has details of investigator such as name, address, telephone number, profession, date of reporting event to ethic committee & licensing authority and signature of the investigator.
- For reporting SAE of medical devices, EMEA has separate form for submission to regulatory agency.
- The FDA' SAE reporting form has separate sections to report SAE of medical device.
- For schedule Y and CIOMS, the same form is being used for both purposes.

Table.1. Comparison of SAE reporting form templates

COMPONENTS	FDA	CIOMS	SCHEDULE Y
Patient Details	1. Patient identifier 2. Age at time of event or DOB 3. Sex 4. Weight (lbs or kgs)	1. Patient initials 2. DOB and age 3. Sex 4. Country	1. Patient initials & other relevant identifier (hospital/OPD record number etc.) 2. Age and/or date of birth 3. Gender 4. Weight 5. Height
Adverse event	1. Column for AE and/or product problem 2. Outcomes attributed to AE (Death, Life-threatening, hospitalization, required intervention to prevent permanent impairment-devices, Disability or permanent damage, Congenital anomaly, other serious) 3. Date of event (dd/mm/yyyy) 4. date of this report 5. Describe event or problem 6. Relevant tests/laboratory data, including dates 7. Other relevant history including preexisting medical conditions	1. Reaction onset date 2. Describe reactions including relevant tests/lab data 3. Check all appropriate to adverse reaction (Patient died, Involved or prolonged inpatient hospitalization, Involved persistence or significant disability or incapacity, Life threatening)	1. Full description of reaction(s) including body site and severity, as well as the criterion (or criteria) for regarding the report as serious. 2. In addition to a description of the reported signs and symptoms, whenever possible, describe a specific diagnosis for the reaction 3. Start date (and time) of onset of reaction 4. Stop date (and time) or duration of reaction 5. Dechallenge and rechallenge information 6. Setting (e.g., hospital, out-patient clinic, home, nursing home) 7. Information on recovery and any squeal; results of specific tests and/or treatment that may have been conducted 8. For a fatal outcome, cause of death and a comment on its possible relationship to the suspected reaction; Any post-mortem findings.
			9. Other information: anything relevant to facilitate assessment of the case, such as medical history including allergy, drug or alcohol abuse; family history; findings from special investigations etc.
Suspect product	1. Name (give labeled strength &Mfr. labeler) 2. Dose, Frequency &Route used 3. Therapy dated 4. Diagnosis for use 5. Event abated after use stopped or dose reduced? 6. lot 7. Exp Date 8. Event reappeared after reintroduction	1. Suspect drug (include generic name) 2. Daily doses 3. Route of administration 4. Indication for use 5. Therapy dates 6. Therapy duration 7. Did reaction abate after stopping drug? 8. Did reaction reappear after reintroduction?	1. Generic name of the drug 2. Indication(s) for which suspect drug was prescribed or tested 3. Dosage form and strength 4. Daily dose and regimen (specify units - e.g., mg, ml, mg/kg) 5. Route of administration 6. Starting date and time of day 7. Stopping date and time, or duration of treatment
Concomitant Drugs	1. Concomitant medical products and therapy dates	1. Concomitant drugs and date of administration (Exclude those used to treat reaction) 2. Other relevant history (Diagnostics, allergies etc)	1. Provide the same information for concomitant drugs (including nonprescription/OTC drugs) and non-drug therapies, as for the suspected drug(s).
All manufacturers	1. Contact office - name & address 2. Phone no: 3. Report source 4. Date received by manufacturer 5. If IND give protocol	1. Name and address of manufacturer 2. MFR Control no: 3. Date received by manufacturer 4. Report source 5. Date of this report 6. Report type	

2.5 Comparison of Annual Report on Investigational New Drug of FDA And EMEA

A report created annually on the assessment and analysis of the yearly trend shown during clinical trial activities is known as annual report of investigational new drug. Yearly submission by the sponsor is required on safety information gathered for the period reported and this report will be reviewed by the ethics committee and the concerned authority. The annual safety report helps to describe all new safety information for clinical trials and to assess safety of subjects included.[3]

Annual report of FDA is known as IND annual report (IND AR) and of European Union is known as annual safety report (ASR).[3,4] The sponsor should submit annual reports within 60 days of Development International Birth Date and data lock point.[3,4]

- EU Directive 2001/20/EC and 21CFR 312.33 sets out guidance on various process which includes collection, verification, analysis, coding and decoding formalities of AE/ ADRs derived from clinical trials on the investigational drug for human use for ASR and IND AR respectively.
- The purpose of IND AR is to submit the progress report of ongoing clinical trial; while for ASR, a precise description on safety analysis and conclusive findings providing a concise description creates an impact on the population considered for clinical trial and risk benefit analysis.
- The annual report needs to be submitted by the sponsor within sixty days of the data lock point (DIBD) to EMEA and within sixty days of the anniversary date that the IND went into effect to FDA.
- In addition to the expedited reporting, sponsors shall submit, ASR once a year throughout the clinical trial or on request a safety report to EMEA, member state and to the Ethics Committee taking into account all new available drug safety information gathered for the period reported. Also sponsor shall submit IND AR to FDA once a year throughout the clinical trial.
- For short term trials end of study report for all trials within 1 yr of end for IND AR whereas Safety report within 90 days for ASR.
- Serious, associated and expected ADR are reported in both IND AR and ASR but SUSAR is reported only in ASR.
- Results of non-clinical researchers or any other instances of the investigating drug that are likely to affect the subjects and summary of AE are required by both. The IND AR require list of deaths and dropouts but ASR require proposed measures to minimize risk and rationale for updates of study documents and procedures

Table.2.Comparison of US IND annual report (IND AR) and EU annual safety report (ASR)

	IND AR	ASR
Purpose	Progress report	Benefit-Risk assessment
Timing	IND Anniversary date (Within 60 days)	Date of 1st authorization of a clinical trial of IMP by authority in member state. The sponsor should submit annual reports within 60 days of the data lock point.
Frequency	Annual	Annual, or on request
Recipients	FDA	EMEA, Member States, Ethics Committees
Content	Study data and summary information	Benefit-risk assessment; Supporting tables
Short term trials	End of study report for all trials within 1 yr of end	Safety report within 90 days
AEs included	All serious ± Associated ± Expected	SUSARs; Serious, Associated; ± Expected
Format and Summary Content	Tabular summary of most frequent and most serious AEs by body system. Summary of all IND expedited reports for the period. Lists of deaths and dropouts. List of completed non-clinical studies and result summary.	Concise global analysis; benefit-risk evaluation; implications for trial subjects; proposed measures to minimize risk; rationale for updates of study documents and procedures; supporting results of non-clinical studies; other considerations

2.6 Comparison of DSUR, The Us Ind Annual Report, And the Eu Annual Safety Report:[3,4,5]

The DSUR (development safety update report) is an annual summary of safety information for an investigational drug

- DSUR, IND-AR, and ASR are used to ensure safety of the subjects in the clinical trials which has same purpose and also have numerous similarities along with some differences to achieve same purpose.[6]
- Major advantage of the DSUR is, it provides cumulative information of investigational medicinal products and it help drug regulatory authority in

decision making in marketing the drug.

- In IND AR all serious and non-serious adverse event information during clinical trial was included whereas for DSUR and ASR only Serious information is included.
- Serious adverse event listings, IB and nonclinical information are included in DSUR, IND AR and ASR.
- Both DSUR and IND AR contain death and AE dropout listing of trial subjects, literature and marketing developments of clinical trial but ASR do not have this information.
- In additional to IND AR and DSUR, ASR includes PK-PD, Manufacturing, Microbiology, Investigation Plan and Phase I Protocol Changes and it is the major disadvantage of DSUR.
- DSUR and ASR have separate sections for Summary of Important Risks and IND AR does not cover this information. The sponsor should submit the first DSUR to the regulatory authority before completing one year.

Table.3. Comparison of DSUR, The US IND annual report, and The EU Annual safety report

	DSUR	IND-AR	ASR
Scope - the extent of the area	Molecule	Indication (IND)	Molecule
Time Period Covered – Information included in the report.	Cumulative mostly	Annual mostly	Annual
Data Lock Point - reporting period	DIBD	IND anniversary date	DIBD
AE Summaries – Summaries of adverse event that occurred during the reporting time of a clinical trial.	Serious	Non-Serious and Serious	Serious
Serious AE Listings - Summaries of serious adverse event that occurred during the reporting time of a clinical trial.	Yes	Yes	Yes
Death Listings – List of patients who died during reporting time of a clinical trial	Yes	Yes	No
AE Dropout Listings – List of patients who dropout from the trial due to adverse event.	Yes	Yes	No
PK-PD, Manufacturing, Microbiology, Investigation Plan, Phase I Protocol Changes	No	Yes	No
Investigator Brochure	Yes	Yes	Yes
Non-Clinical Results	Yes	Yes	Yes
Literature, Marketing Developments	Yes	Yes	No
Summary of Important Risks	Yes	No	Yes
Specifications	ICH E2F	21 CFR 312.33	EU Directive 2001/20/EC

2.7 Comparison of Duration of Toxicity Studies of FDA & EMEA And CDSCO

In drug development, a pre-clinical study plays a major role in getting the approval from the regulatory agency to conduct clinical trials. Data collected from the pre-clinical studies act as the main tool for regulatory authorities to analyze safety of the drug. The main aim of toxicity studies is to determine product's ultimate safety profile.

- In the United States, as an alternative to 2-week study, they reduced it to a single-dose toxicity study which could support single-dose human trials. If the clinical trial is conducted for 14 days toxicity study should also be conducted for the same period.
- Clinical trials of duration 3 months can be initiated, provided there is data availability of 3-month rodent and non -rodent study respectively, along with chronic rodent and non-rodent study made available.
- In the EU, a 6-month study in non- rodent is acceptable.
- In the US, Repeated-dose toxicity studies in rodent and non-rodent species were conducted for 2 weeks which supports any clinical trial which is also for 2 weeks. One must conduct repeated dose toxicity study if the clinical trials are of longer durations.
- But in the EU, 6-month rodent and 6-month non-rodent studies are acceptable for to support dosing for longer than 6 months in clinical trials.
- In India, for up to 2 weeks clinical use, the repeated dose toxicity studies should be conducted for minimum 4 weeks in rodents & 4 weeks in non-rodents, but in US minimum duration of 2 weeks in rodents & 2 weeks in non-rodents is acceptable.
- And in India for up to 4 weeks clinical use, the toxicity studies should be minimum 12 weeks in rodents & 12 weeks in non-rodents, but in US minimum duration of 4 weeks in rodents & 4 weeks in non-rodents is acceptable.
- And in India for over 1-month clinical use, the toxicity studies should be minimum duration of 24 weeks in rodents & 24 weeks in non-rodents, but in US at least equivalent duration to the clinical study is acceptable. Chronic toxicity testing, 6 months' duration in rodents and 9 months' duration in non-

rodents testing is acceptable in US. But In the EU, 6-month study in non-rodents is accepted.

- In India minimum 28 days/4 weeks male fertility toxicity studies are acceptable but in US only 2 week's male fertility toxicity studies[7] are acceptable for a long-term study. A two-week-testing was considered to be inadequate to obtain a confident fertility data.
- For inclusion of women of childbearing potential (WCBP) in clinical trials,
  - In the EU, Prior to Phase I trials assessment of embryo-fetal development should be completed and female fertility studies prior to Phase III clinical trials.[7]

In the US, the inclusion of WCBP is allowed only in carefully monitored studies without reproductive toxicity studies provided appropriate precautions are taken to minimize the risk.[7]

Table.4. Comparison of duration of toxicity studies of FDA & EMEA and CDSCO

	Duration of Clinical Trials	Minimum Duration of Repeated Dose Toxicity Studies	
		Rodents	Non-Rodents
FDA, EMEA	Single Dose	2-4 Weeks	2 Weeks
	Up to 2 Weeks	2-4 Weeks	2 Weeks
	Up to 1 Month	1 Month	1 Month
	Up to 3 Months	3 Months	3 Months
	Up to 6 Months	6 Months	6 Months
	> 6 Months	6 Months	Chronic
CDSCO	Single dose or several doses in one day, up to 1 week	2 weeks	2 weeks
	>1 week but up to 2 week	4 weeks	4 weeks
	> 2 weeks but up to 4 weeks	12 weeks	12 weeks
	Over 1 month	24 weeks	24 weeks

III. Conclusion

- Information collected and analyzed from each country's regulatory system for medicinal products and the countries have similar requirements for registration of medicinal products and are directing their effort to harmonize their requirements with the ICH guidelines.
- For reporting SAE of medical devices, EMEA has separate form for submission to regulatory agency, SAE reporting form of FDA has the separate sections to report SAE for medical device. For CDSCO and CIOMS, the same form is being used for both purposes. CIOMS's SAE reporting form is known as Universal SAE reporting form.
- The purpose of IND AR of FDA is to submit the progress report while that of ASR of EMEA is to provide a benefit-risk evaluation for the clinical trial concerned.
- According to draft guidelines of FDA and EMEA, DSUR is allowed to be use in place of their annual reports. The DSUR by ICH is intended to harmonize the annual safety reports required in the US and Europe.
- In animal toxicity studies of FDA & EMEA, minimum duration is two weeks and maximum duration is upto six weeks. For FDA & EMEA, the duration of toxicity study is same as the duration of clinical trials and for CDSCO, the duration of toxicity study is double as that of clinical trials. ICH has produced harmonized toxicity guidelines like carcinogenicity, genotoxicity & reprotoxicity and same safety guidelines have been implemented by FDA and EMEA.
- Safety parameters assessed by various regulatory bodies are same but templates and data elements might differ. So, the possibility of complete harmonization may be an unrealistic goal due to differences in requirements and regulations of different countries.

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