Pharmacovigilance: Current Schedule Y Perspective

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Abstract

Conducting clinical trials for the approval of new drug molecules needs careful safety monitoring procedures in place. Unethical approval of drugs by the pharmaceutical companies just for monetary benefits needs to be restrained. Thus, practice of pharmacovigilance during clinical trials is imperative. The safety of the clinical trial participant is paramount during its conduct. Regular monitoring of the clinical trials, help in keeping a check on the trial activities. If there occurs, an event during the trial, in the form of an injury or death, it needs proper medical management and the trial participant needs to be well compensated financially. A decision regarding continuation or termination of the trial, as the requirement may be, needs to be taken by the Drug Safety Monitoring Board (DSMB). In India, Schedule Y of the Drugs and Cosmetics Act, 1945 pens down the guidelines for the conduct of a clinical trial. Approval from Drug Controller General of India (DCGI) is required prior to the start of the trials in India with strict adherence to Schedule Y. It is regularly updated to include the latest information and new requirements as per the need; in compliance with GCP-ICH guidelines and local conditions. This review discusses the pharmacovigilance practices in India in relation to clinical trials, latest updates and further improvements needed in Schedule Y.

Keywords: Pharmacovigilance, Clinical trials, Schedule Y, India, Safety.

Introduction

New drugs and therapies are regularly needed to improve and fulfil the availability of healthcare needs of the patients and meet the new challenges posed by either growing resistance to already available drugs or to manage new diseases. The gold standard to evaluate a new therapy includes properly planned and conducted clinical trials in all its phases. It becomes the responsibility of all those involved in conducting the clinical trials to make sure that the rights and safety of the participating subjects are protected and the conduct of the trial is as per the recommended guidelines. It is imperative that all clinical trials conducted in India should follow the International Conference of Harmonization-Good Clinical Practices Guidelines (ICH-GCP) and the recently amended Schedule Y of the Drugs and Cosmetics Act. Although it has been seen that there is a further need for improvement in Schedule Y, cheap costs of operation, availability of ICH-GCP trained principal investigators, versatile patient population along with an updated regulatory reforms make India an attractive destination for the conduct of clinical trials. This article summarizes the role of pharmacovigilance in the conduct of clinical trials and the necessary changes that are required in Schedule Y for this.

Clinical Trials

According to Schedule Y rule 122-DAA, a clinical trial is defined as "a systematic study of any 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."[1] Clinical trial usually compares new treatment approaches with a standard one already available in the market. When a new product is studied, it is not known whether it will be useful, harmful or similar to the already available alternative.

The investigators determine both the safety and efficacy of the interventions by measuring individualized outcomes in the participants according to the research protocol prepared by the investigators and approved by regulators and ethics committee (EC). These clinical studies can be sponsored by various agencies like pharmaceutical companies, academic centers providing medical education, voluntary groups, other organizations, etc.[2]

A potential new drug molecule first undergoes pre-clinical evaluation for safety and efficacy before it reaches the clinical evaluation phase. These clinical trials further take about 8-10 years for generating data required for drug approval and marketing. This long duration is attributed to safety and efficacy studies which need to be done carefully and stepwise so as to make sure that the new molecule is not only efficacious but also safe for use among humans.[3]

Phases of Clinical Trials

All new drug molecules have to undergo four phases of clinical trials in India, although Phase I is not mandatory in all cases. Each phase is covered in a sequence following strict guidelines to safeguard not only the health of the subjects of the trial but also for understanding the potential risks of the new drug molecule on the health of the patients who are going to consume them later. For new chemical entities discovered in India, clinical evaluation starts from phase I clinical trial.

These phase I trials are conducted to evaluate the pharmacological and metabolic actions of the molecule on its first use among humans. These trials involve a small group (<100) of healthy volunteers or volunteer subjects with the targeted disease (cancer and HIV patients). For new drug substances discovered in other countries, their Phase I data is required for their approval in India. After submission of this data to the Licensing Authority, permission may be granted to repeat Phase I trials and/ or to conduct Phase II trials directly.

Phase II trials observe the efficacy, dose response relationship, tolerance and adverse effects of the drug. Larger group of subjects (normally 200-300) with the targeted disease are included based upon very-well-defined inclusion and exclusion criteria.

On the other hand, phase III trials are the final step before the drug innovator can apply for marketing authorization. The number of subjects may range from several hundred to several thousand who are followed for a few years (2 to 5 years). Phase III trials mainly focus on the safety and efficacy of the molecule in diverse sub-groups with broader inclusion/ exclusion criteria.[4] After Phase III trials, the drug is approved for marketing.

Now is the time for the drug to be tested for its adverse effects in the wider population base. This is called the phase IV of the clinical trials where the pharmaceutical company looks for any adverse effects of their newly marketed product in the general population after it has been openly marketed. This exposure tests nearly all possible permutation and combinations of co-morbidity and concomitant medication.

Clinical Trials: Practical Challenges

The biggest barrier in the conduct and completion of a clinical trial is the hesitation in participation in the trials or a high drop rate after participation. The main reason for this is the unawareness of the existence and benefits of well-regulated clinical trials. There is a fear of unfair and unethical practices on the part of pharmaceutical companies and drug regulators. This fear is based on past experiences seen in the form of deaths and permanent injuries caused by new drug molecules during the conduct of clinical trials.

The recent example of a fatal incident which occurred in a Phase I clinical trial subjects enrolled by a French CRO in January, 2016 took the whole world by surprise and suspicion. When the incident was scrutinized, it was concluded that there were many mistakes on the part of researchers. The doses of the new drug were given in too quick a succession; there was a delay in interpretation of the adverse effects seen in the first case and as a result the others continued to receive the same drug for many more days and there were many inadequacies in the approval process as the compound being tested was no more effective than several others from the same family that had already been abandoned on the basis of poor efficacy.[3,5]

In 2010, Central Drugs Standard Control Organization (CDSCO) started clinical trial inspection programs, based on guidance documents for inspection of the sites of conduct of clinical trials, but their implementation remained a major problem. In India, deaths seen in cases such as anticancer drug study in a hospital from Kerala and recruitment of children in a study at a hospital in New Delhi,[6,7] show the inadequacies in the working of the Institutional Review Boards/ Independent Ethics committees. Not only this, many shortcomings have come up in the 59th report of the Parliamentary Standing Committee on Health and

Family Welfare on the part of Indian drug regulatory bodies. All of these are valid concerns and need to be dealt with. Much more is required to be done to prevent the unnecessary approval of clinical trials and new drugs under waiver clauses of the Schedule Y rules.[8]

Around 344 fixed drug combinations (FDCs) were banned recently in India. When two or more individually approved drugs are combined, the combination produced is considered as a 'new' product called FDC and requires approval from DCGI. In actual practice, state drug controller authorities illegally give licenses to such combinations. Once approved by a state drug controller, the FDC can be sold all over the country. It is now that the legal powers of the state drug controller have been curtailed and the sole rights rest with the central drug controller (DCGI) only.[9]

Pharmacovigilance Program of India

When a new drug is exposed to larger masses during marketing, newer and unpredictable adverse effects come into picture. For the monitoring of such developments, Government of India launched the Pharmacovigilance Program of India (PvPI) in July 2010 through CDSCO. The World Health Organization (WHO) defines pharmacovigilance as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem."[10]

The National Coordinating Center (NCC) of PvPI is located at Indian Pharmacopoeia Commission (IPC), Ghaziabad which provides all the technical support to the CDSCO office. Reports that are generated at adverse drug reaction (ADR) monitoring centers (AMC) are sent to the NCC which correlate, assess and then incorporate these reports into the pharmacovigilance database through vigiflow to the WHO's Uppsala Monitoring Center (UMC).[8] In addition, ADRs from clinical trials, vaccination and other programs are also archived in the data bank for comprehensive records.

Regulations related to Adverse Drug Reaction (ADR) Monitoring during Clinical Trials

The Ministry of Health and Family Welfare, Government of India under Schedule Y has made it mandatory for the pharmaceutical companies to have a pharmacovigilance system in place for their marketed products. It has given power to Central Drugs Standard Control Organization (CDSCO) and Drug Controller General of India (DCGI) by expanding them along the lines of United States Food and Drug Administration (USFDA). These organizations have framed their own local regulatory guidelines based on the international principles. Schedule Y defines the requirements for import and manufacture of new drugs, for sale or for use in clinical trials. It gives details of the application process for conducting clinical trials in India and responsibilities of the sponsors, investigators and the Institutional Ethics Committee (IEC).[8]

A clinical trial can only be started after obtaining a written permission from IEC and DCGI. The application utilizes form number 44 accompanied by the documents concerning chemical and pharmaceutical information, data on animal pharmacology (pre-clinical studies), toxicology and clinical pharmacology (human studies) of the drug molecule. Other documents which are submitted with the application are the trial protocols, investigator's brochure, case report forms, informed consent document (ICD), patient information sheet (PIS) and the investigator's undertaking.

There are additional requirements for studies in special population groups like children, pregnant/ nursing women, elderly patients, patients suffering from renal/ hepatic failure and those on specific concomitant medications. The protocol must be reviewed properly before approval by an IEC with a minimum of seven member team including a basic medical scientist (preferably pharmacologist), a clinician, a legal expert, a social scientist and lastly a lay person from the community, along with representation of both genders and member without any affiliation with the institution. More members can be co-opted based on protocol to opine but these invites do not have a vote.

No permission is, however, required for the trials for academic purposes in respect of approved drug formulation for any new indication or new route of administration or new dose or new dosage form.[8]

In 2005, amended Schedule Y came into picture which clearly specified reporting timelines for serious adverse events (SAEs) for sponsors and investigators. An SAE is any untoward medical occurrence at any dose which results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/ incapacity or is a congenital anomaly/ birth defect. Secondly, its Appendix XI gives a list of data elements required for reporting of the SAE and provides general reporting structure for such events. Thirdly, it enlists requirements of post-marketing surveillance which include the requirement of furnishing Periodic Safety Update Reports (PSUR) and also describe the frequency, structure, contents of PSURs. According to Schedule Y, PSURs of a new drug are required to be submitted to the office of the DCGI every six months for

the first two years and then annually for the next two years. Fourth, it provides legal support to Indian Good Clinical Practices (GCP), making reporting requirements legally binding. Thus, amended Schedule Y started a new era of time-bound pharmacovigilance practices in India.[11]

Adverse drug reactions should be mentioned in the source documents of the clinical trial based on the World Health Organization Adverse Reaction Terminology (WHO-ART). This helps in better categorization and evaluation of the data obtained.[12] The source documents should also contain detailed description of the precautions needed during drug intake.

To assess the progress of a clinical trial, establishment of an independent advisory committee (Data Safety Monitoring Boards) by the sponsor of a study was recommended by the Indian GCP guidelines. The main purpose of the committee is to review the data on the safety and efficacy of the trial drug and to recommend to the sponsor whether to continue, modify or stop a trial in between. This is to ensure the integrity and validity of the trial data. But there has been little progress in this regard due to very few studies initiated on product development in India.[13]

Changes Recently Introduced in Schedule Y

Over the recent years, new trends have come up in the conduct of clinical trials. This has brought up new challenges to the drug regulators in ensuring that the rights of the trial subjects and health of the patients are kept protected. For the approval of conduct of clinical trials in humans, the regulatory bodies evaluate the animal data for safety and efficacy of new chemical entities.[14]

Potential participants are provided detailed information about a clinical study with the help of ICD. This helps them in deciding whether they want to enroll themselves for the trial or even continue to participate in a study or not, if they are already enrolled. This informed consent is needed to protect the rights of the participants and therefore should be able to provide complete information to help them understand the risks/ benefits/ alternatives of the intended study. In general, a participant must sign an ICD before participating in a study. This makes sure that the participants are given complete information on risks/ benefits/ alternatives of the study and that they understand those completely. Regulations in India now require taking an audio-video consent to make sure that the consent is actually taken and archived for reference. Introduction of an audio-video consent and other required conditions has been incorporated in accordance with the amendments in Schedule Y. However, recently some relaxation has been provided in the audio-visual recording process. Now, taking an audio-visual consent shall only be mandatory for cases where vulnerable population is involved and the trial involves a new chemical entity or a new molecular entity, as mentioned in DCGI approval letter.

For clinical trials of anti-HIV and anti-leprosy drugs, only audio recording of the informed consent process shall be mandatory. Inspite of such detailing, there is a lack of clear understanding of what falls under vulnerable population.[15]

An ICD must inform about the possibility of failure of the investigational product in providing the intended therapeutic effect and also mention that in case of a placebo-controlled trial, the placebo shall not have any therapeutic effect. It should also mention that the subject shall be provided with free medical management (for as long as required) in case of any injury during the conduct of the clinical trial. In case of death or injury, the sponsor shall also provide financial compensation. The format of ICD has been amended to include address, qualification, and occupation, annual income of the subject and name and address of his / her nominee. It is now mandatory for the investigator to hand over a copy of duly filled ICD to the subject or his/ her attendant.[16]

Just signing the informed consent document and giving consent is not a contract forever. Participants can withdraw themselves from a study any time, even if the study is still incomplete.[16,17] this regulation is to comply with autonomy of the study participant and to maintain voluntariness for participation which can be withdrawn anytime. Efforts for maintaining strict ethical standards during the conduct of a clinical trial and the launch of PvPI are expected to maximize the potential of the country in clinical research.

According to Schedule Y amendment, all unexpected SAEs from their site of origin must be reported by the investigator to the Chairman, Institutional Ethics Committee (IEC), licensing authority (DCGI) and the sponsor *within 24 hours* now instead of seven working days permitted earlier. This would mean that, now fewer numbers of patients will stay exposed to the drug in the situation of a serious safety issue.

In case of expected SAEs, reporting time is *fourteen days* for *detailed report* by PI to Chairman, IEC. Similarly in case of occurrence of a SAE, sponsor has to send a detailed report to the licensing authority, Chairman, IEC and Head of the institution where the trial is being

conducted within fourteen days (CIOMS/ SUSAR format). This ensures at least two independent and different levels of evaluation of SAE and compiled report, which may be able to explain the event in a better light. Finally the IEC looks at the SAE evaluation and forms an independent, unbiased opinion regarding causality (relationship of the event with study drug) and then reports to DCGI.

Prior to the amendments, ethics committee was required to send its report of an SAE to the licensing authority in twenty one calendar days but now it needs to do so within thirty days to the expert committee constituted by the regulator (DCGI). This helps the expert committee at DCGI office to look at the evidence for causality (relationship) independently as well to take into consideration the analysis of evidence done at site by IEC.

The independent expert committee constituted by the licensing authority examines all the death cases for arriving at the cause of death and quantum of compensation and report within thirty days to the licensing authority (Rule 122 DAB). In case of SAEs excluding death, the licensing authority decides the quantum of compensation within three months of receiving the report using a standard formula approved for this purpose which takes into consideration the base amount (Rs. 8 lakh), age of the patient and risk factor (as standardized by the notification). Then the sponsor needs to pay the compensation within 30 days of order of DCGI to the nominee as recorded in IEC document.[16]

Free medical management is provided as long as required or till it is established that the injury is not related to the clinical trial, whichever is earlier. Sponsor needs to give an undertaking for this and in case the sponsor fails to provide the said compensation the present trial can be suspended/ cancelled or PI can be barred from conducting any trials in the future.

Rule 122 DD makes it mandatory to have registration of the Ethics Committees done at office of DCGI. This registration is valid for a period of only three years.[16] Rule 122 DAC has been inserted, which allows inspectors (authorized by the CDSCO) to inspect the premises of sponsors, their subsidiaries, agents, sub-contractors and clinical trial sites. The IEC need to maintain all records and allow the officers authorized by CDSCO, to inspect them as and when required, after confirming the identity of Inspectors and keeps a copy of the authority letter carried by inspectors. This also needs to be recorded and a copy of inspection report filed under appropriate head. Now even the IEC need to get NABH certification, though optional at this point of time but would become mandatory at a later stage. This is a great leap to check wrong practices and allow transparency and fairness in the working of EC.

Another great regulation is exemption of DCGI approval for the conduct of clinical trial intended for academic purposes in respect of approved drug formulation shall be required for any new indication or new route of administration or new dose or new dosage form where, (a) the trial is approved by the Ethics Committee; and (b) subject to the provisions of sub-rule 5, the data generated is not intended for submission to the licensing authority. IEC must keep a provision of internal audit with prior intimation to PI. This will train to PI to handle inspection.

The Ethics Committee shall, however, inform the licensing authority about the cases approved by it and also about cases where there could be an overlap between the clinical trial for academic and regulatory purposes and where the said authority does not convey its comments to the Ethics Committee within a period of thirty days from the date of receipt of communication from the Ethics Committee, it shall be presumed that no permission from the licensing authority is required. This will give research a quantum leap in the country.

It has been decided that if a drug has been withdrawn from the markets of at least two countries due to safety and efficacy issues, then the continued marketing of that drug in India would be scrutinized for appropriate action. For the approval of a new drug, waiver of a clinical trial is allowed only in cases of national emergency, epidemics and for orphan drugs for rare diseases and for drugs indicated for diseases for which there is no treatment available.

All sponsors/ clinical trial PI and support staff have been advised to provide ancillary care to patients for other illnesses occurring during the trial at the same hospital or trial site as required.

Under no circumstances an investigator is allowed to participate in more than three trials at a time. This ensures proper working and using the available resources judiciously and definitely improves quality of data generated as well. This condition has however been removed by recent amendment. But the IEC needs to make a conscious decision at the time of trial approval that the PI will be able to conduct the study properly and has adequate support staff for conducting the study. A useful tip for IEC members is to record the number of trials the PI is conducting (Approved but not started/Study Closed out/ Enrollment completed/Follow up phase in progress). Remember the golden rule “Duty can be delegated but not abdicated by the PI”

Changes required in Schedule Y

Considering the slowdown in the global clinical trials, the Indian pharmaceutical industry is seen having a huge potential in generic drugs business but there are no definite Indian guidelines for the safety reporting of their clinical trials (BA/ BE studies). Although according to certain new guidelines all BA/ BE study protocols need to be reviewed and approved by a registered Institutional Ethics Committee (preferably), there is a need for approval for protocol amendments and change of BA/ BE study centers and revision of the existing SOPs and other study BA/ BE documents but the BA/ BE centers are experiencing a tough time due to lack of clarity on many aspects of these amendments. Therefore, it is of utmost importance that the Indian regulators make things more clear regarding the conduct of the BA/ BE studies.[11,18]

Indian guidelines (Schedule Y) are silent on the issue of criteria for causality assessment for reporting of SAEs. As a result, many reports are generated where clear causal relationship between the drug and the SAE is missing, which burdens the regulators with increased number of cases due for review. This risks the overall quality of work and waste of time and manpower. Thus, there is a need for revision of the Indian reporting criteria incorporating the causality assessment as an important aspect for reporting of SAEs.

There are certain SAEs that can be exempted from immediate reporting.[19] These include events which occur very commonly in the study group even in the absence of exposure to the drug, e.g., sedation caused by anti-histaminic drugs, etc. These events should be specified in the protocol itself by the sponsor. According to ICH E6 4.11.1, "all SAEs should be reported immediately to the sponsor except for those SAEs that the protocol identifies as not needing immediate reporting." This helps in reducing the burden of evaluating unnecessary information and makes the process faster and efficient. The present Schedule Y needs revision to incorporate all such provisions.[11]

According to Schedule Y, there are no variations in the reporting time lines for unexpected deaths or life-threatening events suspected to be occurring due to a study medication. This is in contrast to both ICH E2A and 21 CFR 312.32, where such reporting is done within seven calendar days.[20,21] Therefore, Schedule Y needs to be modified and definition and standards for expedited reporting need to be added.

Schedule Y does not elaborate on safety reporting requirements for multinational trials being conducted on foreign sites. Therefore, in the event of SAEs occurring on a foreign site, the procedures and timeframes for reporting those to Indian regulators are undefined. On the other hand, for a multinational study being conducted in India, the sponsor will report any life-threatening SAE originating from Indian site to USFDA within seven working days,[20] whereas the Indian regulators will come to know about it in fourteen days, i.e., seven days later.[11] This needs serious consideration.

Pregnancies occurring in the trial subjects during their participation in clinical trials present a unique situation. Any such event should be followed to either termination or to term. Most of the sponsors outside India report pregnancy in a pregnancy report form, which is separate from standard SAE form and all such pregnancies are followed up till their outcome. On the other hand in India, there are no guidelines on pregnancy-reporting requirements. This creates confusion over whether to report pregnancy or not and how. Therefore, Indian guidelines need to be updated incorporating detailed pregnancy reporting process.[11,22]

Impact of the Recent Changes in Schedule Y

These changes affect the completion time of clinical trials, as it takes a long time to get required approvals from concerned authorities. Further, the cost of conduct of a trial per patient also increases as the investigators have to devote more time and effort to fulfill the criteria regarding maintenance of records for the purpose of evaluation and auditing. The mandatory requirement for compensation of the trial subjects in case of injury/ death adds to the cost of the conduct of a trial. Ensuring quality and compliance according to good clinical practices (GCP) require efforts and money and also consumes time which further eats money. Exemption of academic trials from approval is a big boost. The working of IEC and its procedures have become more robust.

Conclusion

Pharmacovigilance programs like PvPI need strong associations with the drug regulators to make sure that they are well aware about the safety issues in everyday practice. Regulators need to understand that pharmacovigilance plays a pivotal role in ensuring the safety of medicinal products undergoing clinical trials. Therefore, pharmacovigilance programs need to be adequately supported to achieve this objectives.[14] In modern era, where India plays an active role in global multinational clinical trials, Schedule Y needs to be revised in tune with international norms. Harmonization among different guidelines would help in overcoming any confusion over reporting of the SAEs originating from global or Indian sites to the Indian regulators.[8,11] A

balance is needed to generate quality data with minimum harassment to sponsor and principal investigator and adequate safety procedures (medical management and financial compensation) in place for the study subjects. These all components will ensure that there is no misuse by the sponsor, principal investigator and even patient support groups/ advocates. Schedule Y is one of the most stringent regulations for trials in the world today. All for the good cause of getting data safely from Indian population and there is scope for improvement.

Conflict of Interest: None

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