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Regulatory Challenges in Clinical Trials: Strategies to Overcome Commonly Observed Deficiencies

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Apart from the regular clinical trials, bioavailability/bioequivalence studies are conducted to assess the safety and efficacy of generic drugs, comparing it with a reference listed drug. Clinical trial data is mandatory for further approval of the drug, for it to enter the market. These investigations are strictly regulated by various global and national regulatory authorities. The global clinical trials market is expected to register a Compound Annual Growth Rate (CAGR) of nearly 4.5% during the forecast period, 2018 to 2023. A major challenge for them to achieve the forecasted growth is meeting the increased level of compliance to the regulations. In recent times the research Organizations have been issued an increased number of warning letters with stringent procedures and even subsequent closure of the organizations. This case study conducted by the review of warning letters and other observations pointed out by two major global regulatory authorities, the FDA and EMA and the critical areas were identified. Recommendations were made for the major areas which were critical and repetitive. It was concluded that consistent methods are required to improve the quality of studies to effectively eliminate the challenges in mere future and contribute for the betterment of the drugs' market.

Keywords: World Health Organization, Food and Drug Administration, Clinical Research Organizations, Quality Management System, clinical trials, regulatory authorities, warning letters, medical devices, drugs, biomedical research

The concept of clinical trial is relatively recent which stemmed in part from the availability of more effective treatment modalities in recent years. The main stimulus arose from the recognition of the possibility that by chance a patient's spontaneous improvement could coincide with the administration of the drug. Clinical trials are part of drug development aiming towards marketing authorization are designed logically and progressively with a continuous expanding process under controlled laboratory conditions. Such prospective biomedical or behavioral research studies on human participants are designed to answer specific questions about biomedical or behavioral interventions, including new treatments (such as, novel vaccines, drugs, dietary choices, dietary supplements, and medical devices) and known interventions that warrant further study and comparison. Clinical trials generate data on safety and efficacy. These are conducted only after the approval of health authority/ethics committee in the country of the therapy (Table 1). The authorities are responsible for vetting the risk/benefit ratio of the trial.[1-5] In the present scenario, pharmaceuticals are considered as the most highly regulated industries worldwide. The regulatory body ensures compliances in various legal and regulatory aspects of a drug. Every country has its own regulatory authority, which is responsible to enforce the rules and regulations and issue the guidelines to regulate drug development process, licensing, registration, manufacturing, marketing and labelling of pharmaceutical products.

World Health Organization (WHO), Pan American Health Organization (PAHO), World Trade Organization (WTO), International Conference on Harmonization (ICH), World Intellectual Property Organization (WIPO) are some of the international regulatory agencies and organizations which also play essential role in all aspects of pharmaceutical regulations related to drug product registration, manufacturing, distribution, price control, marketing, research and development, and intellectual property protection.[7] India had been a favourite destination for major pharmaceutical companies for conduct of clinical trials due to the advantage of large number of naive un-treated patients, which are difficult to find in developed countries. However, a common trend in the analytical and clinical trials sector is to compromise

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Table 1 — List of regulatory authorities[6]

S. No	Regulatory Authority
1	USFDA- United States Food And Drug Administration (USA)
2	MHRA- The Medicines and Health products Regulatory Agency (UK)
3	TGA- Therapeutic Goods Administration (Australia)
4	CDSCO- The Central Drugs Standard Control Organization (India)
5	HEALTH CANADA (Canada)
6	MCC-Medicines Control Council (South Africa)
7	ANVISA- National Health Surveillance Agency (Brazil)
8	EMA- European Medicines Agency (European Union)
9	SFDA- State Food and Drug Administration; replaced by the China Food and Drug Administration (China)
10	NAFDAC- The National Agency for Food and Drug Administration and Control (Nigeria)
11	MEDSAFE- Medicines and Medical Devices Safety Authority (New Zealand)
12	MHLW- The Ministry of Health, Labour and Welfare (Japan)
13	MCAZ- Medicines Control Authority of Zimbabwe
14	SWISSMEDIC- The Swiss Surveillance Authority for Medicines and Medical Devices (Switzerland)
15	KFDA- The Korea Food & Drug Administration, changed to The Ministry of Food and Drug Safety (Korea)
16	CDDA- Cosmetics, Devices and Drug Regulatory Authority (Sri Lanka)
17	GCCDR- Gulf Central Committee for Drug Registration (Gulf countries)
18	DGDA- Directorate General of Drug Administration (Bangladesh)
19	DDA- Department of Drug Administration (Nepal)
20	DRAP- Drug Regulatory Authority of Pakistan (Pakistan)
21	DMA- Danish Medicines Agency (Denmark)
22	AGES- Agency for Health and Food Safety (Austria)
23	NIP- National Institute of Pharmacy (Hungary)
24	Medicines Evaluation Board (Netherlands)
25	Federal Agency for Medicines and Health Products (Belgium)
26	National Institute of Health (Italy)
27	Ministry of Health (Egypt, Iran, Israel, UAE, Jamaica, Botswana, Malaysia, Rwanda, Morocco, Swaziland, Ukraine, Slovenia, Cyprus, Luxembourg)
28	TFDA- Tanzania Food and Drug Authority (Tanzania)
29	National Drug Authority (Uganda)
30	Health Sciences Authority (Singapore)
31	DOH- Department of Health (Philippines)
32	TFDA- Taiwan Food and Drug Administration (Taiwan)
33	Department of Drug Administration (Nepal)
34	POM- Pangawas Obut Dan Makanan (Indonesia)
35	DRA- Drug Regulatory Authority (Bhutan)
36	Ministry of Health and Population (Algeria)
37	Pharmacy and Poisons Board (Kenya)
38	Bulgarian Drug Agency (Bulgaria)
39	National Medicines Agency (Romania)
40	Norwegian Medicines Agency (Norway)
41	The Office for Registration of Medicinal products, Medical Devices and Biocidal products (Poland)
42	National Authority of Medicines and Health products (Portugal)

quality for cost cutting and to meet timelines. There is a requirement for developing strategies to increase quality of study conduct in order for to produce studies with acceptable compliance to the regulatory requirements.

Indian pharmaceutical industry is under increased scrutiny from the regulatory bodies especially FDA and WHO and the regulatory inspections had been intensified in recent times. The frequency of surprise audits had been increased marginally over the last few

years. There were many instances of issuance of form 483 and warning letters from FDA for serious violations of regulatory norms. A number of Indian CROs had been closed and some are on the verge of closing. Despite the challenges faced, international clinical trials remain critically important for global diseases that require international cooperation. International researchers and sponsors have to be aware of the regulatory requirements and expectations in the various countries in which they operate. Hence it is very important that the research centres and organizations conducting trials shall ensure that studies are conducted with high level quality which meets all the requirements of GCP and GLP.

Basic Understanding of Regulations and Regulatory Bodies

The Food and Drug Administration (FDA or USFDA)

It is a federal agency of the United States Department of Health and Human Services, one of the United States Federal Executive Departments. The FDA is responsible for protecting and promoting public health through the regulations and supervision of food safety, tobacco products, dietary supplements, prescription and over-the-counter pharmaceutical drugs and vaccines, biopharmaceuticals, blood transfusion products, medical and electromagnetic devices, cosmetics, animal foods and feed and veterinary products. FDA periodically audits the laboratories which conduct studies in support of the marketing authorization requests. FDA identifies the lapses during the conduct of study and issues observations, listed in the form 483 in order of significance. The format for any single observation begins with a statement based in a citation of law, regulation or Act and is followed by a statement of specific conditions observed during the inspection. FDA's Bio-research monitoring program is a comprehensive program of on-site inspections and data audits designed to monitor all aspects of the conduct and reporting of FDA-regulated research.[2]

The European Medicines Agency (EMA)

It is a decentralized agency of the European Union (EU), located in London. It began operating in 1995. The Agency is responsible for the scientific evaluation, supervision and safety monitoring of medicines developed by pharmaceutical companies for use in the EU. It protects public and animal health in 28 EU Member States, as well as the countries of the European Economic Area, by ensuring that all medicines available on the EU market are safe, effective and of high quality.[1,6]

Good Clinical Practice (GCP)

It is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected; consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.[1, 3]

Good Laboratory Practices

GLP is an FDA regulation which includes a set of principles which regulates planning, performance, monitoring, reporting and archival of the laboratory studies. The GLP includes use of calibrated instruments which is proven to be producing accurate, repeatable and reliable results, documentation practices which accurately reflects the original flow of events and results. Every activity shall be documented and the documentation practice as per GLP shall allow the exact reconstruction of events as it happened. The documents are required to be archived for a stipulated period of time and shall be made available for regulatory audits when requested. All the procedures in the laboratory shall be defined in standard operating procedures and shall be followed. A proper quality assurance unit should be functional in the laboratory independent of the analytical department.[1]

The International Council on Harmonization (ICH)

Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of pharmaceutical product registration.

The purpose of ICH is to reduce or eliminate the need to duplicate the testing carried out during the research and development of new medicines by recommending ways to achieve greater harmonization in the interpretation and application of technical guidelines and requirements for product registration. Harmonization would lead to a more economical use of human, non-human animal and material resources, and the elimination of unnecessary delay in the global

development and availability of new medicines while maintaining safeguards on quality, safety, and efficacy, and regulatory obligations to protect public health.[1]

Classification of Regulatory Observations

World Health Organization (WHO) and ICH declared in the prequalification Inspection processes that non-compliance of Good Clinical Practices (GCP) as deficiencies might be due to the result of a defective procedures or failure to comply with the systems and procedures, problems due to lack of integrity, archiving and retrieval of documents, manual representation of peaks, data manipulation etc are few deficiencies. Thus, such deficiencies are classified as: critical observations, major observations and minor observations.

Critical

Conditions, practices or processes that adversely affect the rights, safety or wellbeing of the subjects and/or the quality and integrity of data which might cause potential risk to the user are considered as- Critical observations that are totally unacceptable. Observations classified as critical may include a pattern of deviations classified as major, bad quality of the data and/or absence of source documents. Manipulation and intentional misrepresentation of data belong to this group. Possible consequences include rejection of data and/or initiation of legal action.

Major

A non-critical observation that does not comply with specified guidelines having major deviation from GCP guidelines. Observations classified as major, may include a pattern of deviations and/or numerous minor observations. Possible consequences include rejection of data and/or initiation of legal action.

Minor

Conditions, practices or processes that would not be expected to adversely affect the right, safety or well-being of the subjects and/or the quality and integrity of data. Possible consequences include the need for improvement of conditions, practices and processes. Many minor observations might indicate a bad quality and the sum might be equal to a major finding with its consequences.

Methodology

This Study was conducted to analyse various kinds of noncompliance as pointed out by two major regulatory bodies- FDA and EMA. Conclusions were drawn based on the commonly observed noncompliance across the laboratories and sites. Strategies to overcome the commonly observed deficiencies were prepared by keeping the guidelines provided by the regulatory authorities as the reference. The study includes- defining the objectives; data collection and analysis; identification of critical area and specific recommendations; summary and discussion; and conclusion. Major areas of critical findings were study monitoring, data management and clinical study reports.

The study aimed to identify the lapses in systems followed by the sites and laboratories conducting clinical trials which result in regulatory queries regarding compliance to Good Laboratory Practices and Good Clinical Practices. It was also aimed to identify the possible reasons behind the noncompliance to the regulatory requirements and to suggest certain strategies to conduct clinical trials in effective compliance towards the GLP/GCP requirements. Basic concepts of regulations in clinical research are:

a) Study various regulatory observations given to different companies

b) Identify the lapses in systems followed by the laboratories and Contract Research Organizations

c) Identification of reasons behind non-compliance to regulatory requirements

d) Conclude strategies to conduct clinical trials with effective compliance to regulatory requirements.

Data was collected from warning letters and inspectional observations issued by FDA and EMA to various Clinical Research Organizations. The data was analysed thoroughly and the basic trends were identified and categorized into critical, major or minor observations according to the criticality and repetitive nature of the observations.

FDA Findings from Bio - Research Monitoring Program

Categories coming under FDA-BIMO Program are clinical investigators, Sponsor/monitor/CRO, bioequivalence/good laboratory practice, IRB (Institutional Review Board). BIMO inspections cover FDA-regulated products and conducted based on the FDA Compliance program guidance manual. Generally, inspections are carried out after the study is completed; however, FDA is contemplating to shift the inspection to 'Real time'. The findings of FDA-BIMO are classified as - No Action Indicated (NAI) - no objectionable conditions or practices were found

during the inspection and Voluntary Action Indicated (VAI) - objectionable conditions or practices were found during the inspection that represented departures from the regulations. VAI observations include- meeting minutes without sufficient details (attendance, actions); failure to maintain copies of all research proposals reviewed; failure to maintain list of IRB members; failure to follow written procedures; quorum related issues; subpart D related issues (usually not categorized); inappropriate use of expedited review; and failure to inform IRB of research approved by expedited review. Further, Official Action Indicated (OAI) – the objectionable conditions or practices found during the inspection represented significant departures from the regulations and may require the imposition of administrative/regulatory sanctions. OAI observations include- no written procedures; ICF consistently lacks required elements; continuing review dates consistently and substantially not met; consistently lack quorum; repeatedly allow conflicted IRB member to vote; repeatedly failed to maintain adequate records; substantially failed to minimize risk; failed to implement promised corrective actions; and behavior that results in referral to Office of Criminal Investigation (e.g. falsification of records). Statistical data of observations found as part of FDA-BIMO program in 2015 is given in Table 2. The observations of FDA-BIMO during inspection in 2015 are given in Fig. 1. Similarly, by analysing the data of regulatory audits conducted by EMA with respect to clinical trials from 2002-2012 (10 - year duration) the basic trends and common observations were identified (Fig. 2).

Table 2 — Statistical data of observations found as part of FDA-BIMO Program in 2015

Category	CI	IRB	Sponsor/monitor/CRO	BEQ	GLP	Total
NAI	64%	59%	61%	67%	36%	63%
VAI	33%	37%	31%	24%	56%	32%
OAI	3%	4%	8%	9%	8%	5%

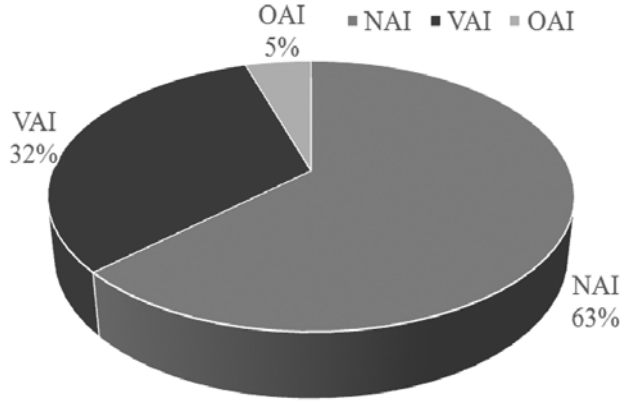

Fig. 1 — The observations of FDA-BIMO during inspection in 2015.

Identification of Critical Area

Observations related to IRB include-inadequate initial and /or continuing review; inadequate SOPs; inadequate membership rosters; inadequate meeting minutes; quorum issues; and inadequate communications with CI/institution. Observations related to CI include- clinical investigation is well organized and performed with a detailed study protocol where in many observations are considered as follows:

Failure to Follow Investigational Plan

a) Subjects enrollment without following inclusion/exclusion criteria like age, concomitant meds, history of systemic disorders and testing.

b) Improper protocol design, employee training and supervision of employees

c) Change of protocol during the study. The Principal Investigator (PI) can never change the protocol unless it is revised by the sponsor and approved by IRB.

d) Failure to report serious adverse events (SAE) or Serious Adverse Device Effects (SADE) in accordance with the protocol. As per 21CFR 812.150 Unanticipated ADE must be reported to sponsor and IRB within 10 working days. 21CFR 312.64(b) says, promptly report AE reasonably or probably caused by drug. If AE is alarming, report immediately.

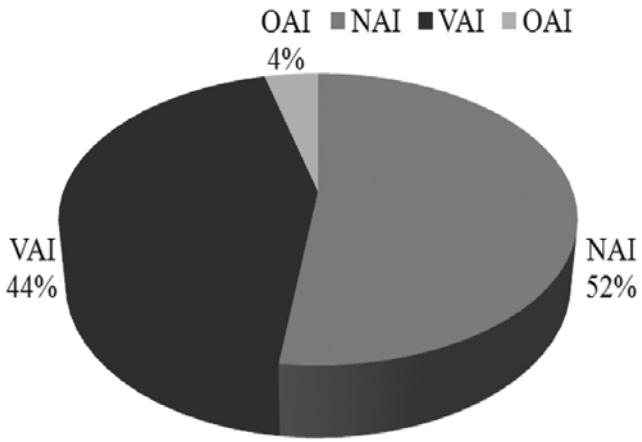

Fig. 2 — The observations of EMA during inspection in 2015

Protocol Deviations

a) Improper, un-calibrated testing procedures during analysis of the samples.

b) Follow up visits outside protocol window or incomplete (6 months contact by phone or visit).

c) Improper documentation related to adverse events, blood data and other relevant data.

d) Signed investigator statement without the list of co-investigators with significant responsibilities.

e) Co-investigator enrolled subjects with exclusion criteria.

f) No information of co-investigator's training on research study.

Inadequate Record Keeping

a) No Source documentation to verify eligibility for a specific enrollment criterion.

b) Study records show discrepancies between CRFs and source documents.

c) CRFs can't be verified by source documents and are not completed as source documents.

Inadequate Accountability for Investigational Product

a) Incomplete pharmacy records.

b) Sponsor's form is inadequate/ confusing details.

Inadequate Communications with IRB

a) Report not made to IRB for continuing review and approval lapsed. Subjects enrolled, devices implanted or study agents issued.

Failure to Personally Conduct/ Adequately Supervise Trial

a) Employee training and documentation.

b) Screening and enrolling subjects.

c) Informed consent issues.

d) Lab results documentation.

e) Follow-up evaluations done by staff members.

Inadequate Subject Protection

a) Inclusion criteria include– safety issues for subjects- enrollment of subject with exclusion criteria resulted in GI bleed requiring hospitalization.

b) Protocol excludes device implant in subjects with arthritis in area. MRI showed exclusion criteria. Subject required revision surgery and device removal.

c) Protocol deviations for safety testing in hematology/urinalysis pre/post treatment; lab work performed outside protocol window; and lab work missed.

ICF Issues

ICF issues include any of the 8 basic elements missing, i.e., statement of research: purpose, duration, procedures; foreseeable risks or discomforts; benefits that may reasonably be expected; alternative procedures; confidentiality and record review by FDA; compensation and injury treatment; contact for questions and injury report; and voluntary participation. Other ICF issues like, consent obtained prior to IRB approval; consent for wrong study was used to enrol; current IRB approved version not used; and consent form is dated by coordinator for the subject.

Sponsor/Monitor/CRO Issues

Inadequate monitoring; failure to bring investigators into compliance; inadequate accountability for the investigational product; and failure to obtain FDA and/or IRB approval prior to study initiation are few monitoring issues. Record keeping; inclusion/exclusion criteria issues; informed consent issues; dosage issues; analytical concerns-validation, stability; and inadequate SOPs are the issues related to bioequivalence. Issues related to good laboratory practices, to name a few are-organizational and/or personnel inadequacies incomplete/inadequate/no study records; inadequate archiving; inadequate/no standard operating procedures (SOPs); and protocol deviations.

Recommendations for Critical Areas

Based on the study of various regulatory observations, critical areas were identified and specific recommendations are framed as follows:

Quality Control Unit

Failure of the quality control unit in ensuring quality outcome was found to be the major area of concern, as most of the regulatory observations were of simple nature, and could have been identified internally if a proper quality assurance system was in place. It was recommended that the internal quality assurance unit shall function independently and focus on regular monitoring. All the observations to be reported, corrective and preventive actions shall be ensured. Critical observations shall be made to the notice of the management also.

Establish Written Procedures

The insufficiency in written procedures such as, protocol, reports etc., is due to unawareness or negligence about the regulatory requirements. Most of the laboratories have written procedures and standard operating procedures in place for various activities. Laboratories need to ensure that all the activities are carried out based on written and approved procedures. This ensures that uniformity is maintained in various

lab activities irrespective of the personnel involved. It is also important to have proper training on standard operating procedures and continuous monitoring to ensure the compliance to the SOPs.

Stability

It is important to use any compound, stock solutions or dilutions within the established stability period. It is a common practice to use the compound beyond expiry and then prove stability later to cover the usage duration. However, this practice is not in compliance with the GLP requirements. Compounds for which the stability is proved and documented shall only be used for analytical research, as the results are greatly impacted due to the stability of stock and stock dilutions. Stability needs to be checked and documented under all conditions which the compound is expected to be associated with.

Falsifying Test Data or Reporting Failed Results

There were instances where the regulatory authorities were able to clearly establish that the data has been falsified. Most often, the discussions with the analysts in the laboratories reveal that the falsification of data is even with consent from the seniors at managerial level. This indicates serious noncompliance from the laboratory. Most often this is done to save time and management may not be aware of this practice. An independent Quality assurance system becomes most important here. The laboratory management shall ensure that trained personnel independent of the analytical department are monitoring the activities online. The QA shall directly report to the management and shall have the authority to stop activities if any falsification of data is found. Frequent review of audit trail entries is very important. Regulatory authorities expect the audit trails to be activated every time and available for reference at the time of inspection. All the data generated electronically need to meet the requirements as per the 21 CFR Part 11, which includes the requirement of audit trails. The analytical instrument needs to be configured in such a way that the audit trail is always enabled and cannot be disabled by the user. Quality Assurance unit shall ensure frequent review of audit trail and a proper back procedure for audit trail needs to be established.

Adequate Controls to Prevent Manipulation and Omission of Data

Data integrity and data safety are the most heard words recently associated with regulatory inspections. It is very clear from the recent increase in regulatory observations related to data safety and data integrity is the result of increase in focus of the regulatory bodies towards this. Many of the laboratories were lacking a proper system to ensure data integrity and data safety until recently. Observations made it clear that some of the laboratories still do not have proper system for controlled access to data. In some instances, analysts used administrator privileges even to the extent that analysts were able to change the date and time in the computer used with analytical instruments. Inspectors were able to provide proof for misuse of the administration rights. This shows complete failure of internal quality control systems. It needs to be ensured that every staff member has unique user name and password. Levels of access permissions need to be decided on the job functions of each staff and to be defined in a standard operating procedure. It is also important to conduct periodic checking on use of administrator rights.

Investigation of Critical Deviations

In most cases, the organizations try to hide the exact cause of failure or deviation fearing that revealing the exact reason will have a negative impact on the firm. But most often, it is easy for the auditors to find that actual reasons are not investigated perfectly. The organizations should take adequate care in investigating the failures and deviations completely to find out the root cause. Adequate measures shall be taken to establish corrective and preventive actions and recurrence shall be strictly avoided. If the auditor finds that proper investigation is being carried out for failures, which gives the confidence to auditor that the internal systems are working well and compliance is assured.

Record Activities at the Time of Performance

Online documentation is the most important compliance factor for a laboratory. As per the good laboratory practices, an activity should be logged/documented at the time of carrying out the activity. Even most sophisticated laboratories fail to comply 100% online documentation. There are several reasons for this including the negligence from the analysts. Another possibility is that some firms perform trial tests without documenting the procedure and if the test passes then they complete the documentation, which is not an acceptable practice as per the GLP standards. This practice is evident from other inspectional observations from FDA. Most of the miss matches in documentation happen due to the

practice of offline documentation. A proper quality assurance system is the only solution for this issue. QA should independently carry out in process audits for all the tests performed

Governing the Functions and Operations of IRB

Institutional review board or Internal Ethics committee plays a major role in assessing the study protocols and proposals. The ethics committee comprises people from various disciplines including a lay person. Responsibility and morale are expected from the ethics committee normally and it is the first independent check point for a study initiation. The regulatory expects all the meetings and discussions with IRB to be properly documented and the records are retained for inspection procedures.

Backup system for Data

In one of the audit observations, a computer system used for data collection in the organization, was crashed and there was no data available for inspection. Complete data was stored in the system and no back up was taken. This is a serious data safety issue and the regulatory bodies are more stringent about data integrity and data safety. Backup facility and other measure to store the data safely is mandatory.

Audit Trail System for Electronically Generated Data

Unauthorized analysis in the analytical system shall be prevented by enabling audit trail entry for electronically generated data. The audit trail shall be compared with the instrument log book in regular basis, and the backup of audit trail shall be taken. There were instances where auditors compared the instrument log with the electronic audit trail and found that there were unauthorized analyses conducted without recording in the log book. An SOP for audit trail management shall be in place and strict adherence to this SOP shall be ensured by the quality control unit.

Administrative Privileges in Computers

One of the observations read that 'your quality control analysts used administrator privileges to change the controls for the time and date settings and manipulate file names to overwrite injections and delete original HPLC test data'. Analysts also routinely turned HPLC audit trails on and off. User levels the system shall be defined and different users shall log in with different user name and password. Only an IT administrator, who is independent of the laboratory activities, shall have administrative privileges for the computer systems. Frequent challenge tests shall be conducted to check if the user has options to change time or delete/modify the data.

The study highlighted the importance of a proper Quality Management System in the laboratories/ organizations conducting clinical trials. The characteristics of a good Quality Management system include- standard operating procedures (SOPs) and continuous monitoring. SOPs are the most important part of any quality management system. SOP ensures that the procedure is done uniformly irrespective of the performer. It ensures quality and it reduces errors. As the SOPs are prepared after adequate review and discussions, it ensures quality in various angles. In addition to SOPs, specific protocols shall be prepared in a case to case basis. Procedure for review, approval, distribution and revision of SOPs shall be pre-defined. Continuous monitoring of all the activities is the key for success of any Quality Management System. Online and retrospective audits shall be conducted for every project. Audit observations shall be communicated and the compliance to be ensured. Review meetings shall be conducted frequently, which shall include user departments, Quality Assurance Team and management representative.

Conclusion

The study concluded that simple and strict steps taken to strengthen the internal quality management system can effectively contribute for the successful conductance of clinical trials in compliance to all the regulatory requirements. The challenges are complicated but can be met with simple improvement steps suggested by the regulatory bodies. The significant parameter in conducting the study is the time line along with the Quality. It is not required to follow different strategies for different regulatory bodies. A common strategy which focuses on internal Quality management system will help the organization to conduct studies with better compliance to the regulatory requirements. This will ensure faster growth of the clinical research industry, by gaining confidence from regulatory bodies.

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