Review Article

GLP (Good Laboratory Practice) Guidelines in Academic and Clinical Research: Ensuring Protection and Safety

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ABSTRACT

Laboratory testing is a science professionally conducted with rigorous statistical analysis, quality control, and extensive oversight. Despite of considerable advancements, error originates from the laboratory investigations continue to increase multi-fold annually. Continuous quality improvement strategy through regulatory guidelines like (GLP) could serve as a key for error reduction. GLP is a easily understandable, internationally accepted quality system, a crucial code essential academic research. GLP has become a mandatory in the laboratories involved in clinical research particularly it serves as a solid standard for registration and regulatory research settings. GLP consist of information, managerial suggestions, rules exclusively designed to reduce bias, discrepancy of results, promotes mutually accepted data which serve as a helpful tool in ensuring laboratory staff integrity, data reliability, sensitivity and test specificity and help the laboratory researchers to avoid unnecessary repeating of laboratory tests. GLP was initially adopted by USA as US-FDA-GLP and was accepted by OECD and without modifying the essence of US-FDA-GLP, GLP was practiced globally. In this review, we discuss the applications, objectives, training needs and focus on the amalgamation of different GLP guidelines and their advantageous in the field of clinical research and academic research.

Keywords: GLP, lab safety, regulatory guidelines, GLP in global situations, GLP in academic and clinical research

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INTRODUCTION

Human beings are prone to error. Many of us commit mistake because we are not aware and many of us are tightly bound within illusion. Everyone expect that they are allowed to do mistake to some extent. Occurrence of mistakes in our daily work is governed by many factors such as age, state of mind, physical health, attitude and emotions. As far as possible we try not to repeat the mistakes the reason being is that human errors can contribute to possible adverse consequences especially when we (human) expected to play a crucial part of large socio-technical system. The very first step to overcome human error is to discard unnecessary illusion and ignorance. Human error problem can be approached in two ways the person approach and system approach. The person approach focuses on the errors of individuals, blaming them for forgetfulness, inattention, or moral weakness (**Fig.1**). The system approach contributes to the conditions under which individuals work and tries to build defence to avert error or mitigate their effect (1).

Laboratory services are an essential part of all health systems. Health care laboratories are utilized more often now than in the past. Nearly 100,000 death of human life annually are attributed to medical error (2,3). Identification of errors and rectification strategies in laboratory medicine received a great deal of attention

in the field of laboratory medicine (4). Unreliable results might not only be contested in court, but could also lead to unjustified legal consequences for the defendant or to wrong treatment of the patient. Over the past decade bio-medical scientists probe into factors responsible for human error and trouble shootings from the laboratory instruments to ensure safety and efficacy in the laboratories to avoid unsafe acts because, error in laboratory testing have the potential to cause serious effect in the well-being of the subjects investigated (5).

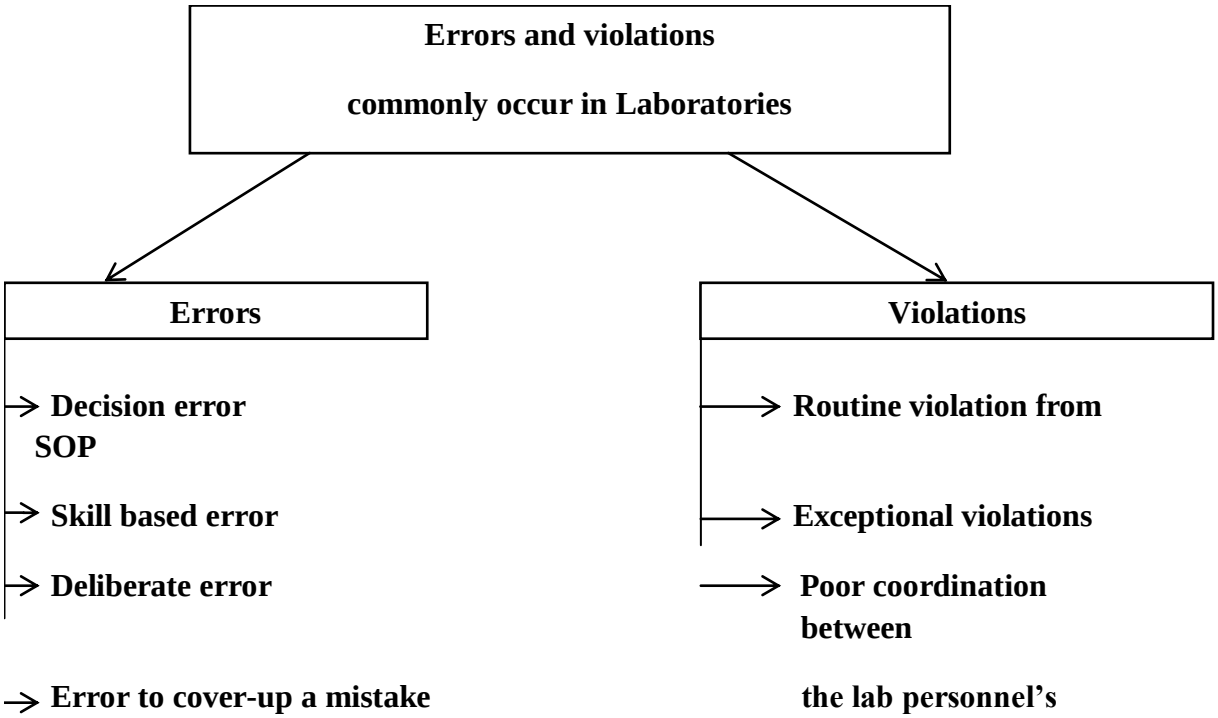


Fig 1: Possible Human errors/Violations in Laboratories

Of the very many factors that lead to indifferent work in laboratories especially to safety issues concern three factors are very important: Human operation methodology, Adverse internal standards and types of chemicals instruments used in test systems plays key role in ensuring quality of the work in the laboratories. The fourth factor is operators ability and the task demands; Poor operator practices are another type of precondition for unsafe acts. These include poor technical knowledge, lack of training, violating the requirements and poor hygiene practice (6). GLP covers the adherence of ethical aspects of methods used in laboratory animal experimentation including the experimental design, adherence to ethical guidelines issued by the animal ethical bodies, dosing strategies, number of animals used in each study group and meaningful statistical analysis of data obtained, measurement of data, quality assurance (7).

Objectives of GLP

The main objective and goal of GLP is to help the bio- medical laboratory scientists to obtain results of high quality. Especially, when a laboratory method used for investigation is repeated the data obtained from two different investigators should be comparable and acceptable.

Hence GLP suggest that whatever method used in laboratory investigation for diagnosis, treatment, research or bio-analysis should be validated (8). Incorporation of GLP in contract research organizations assures that the protocols and standard operating procedures for each study component are developed meticulously and carefully and followed completely by the laboratory personnel. GLP also covers the adherence of ethical

aspects of methods used in laboratory animal experimentation including the experimental design, adherence to ethical guidelines issued by the animal ethical bodies, dosing strategies, number of animals used in each study group and meaningful statistical analysis of data obtained, measurement of data, quality assurance. Overwhelming literature on the laboratory error together with the prevalence of evidence that most errors occur in the pre-analytical phase suggest that the implementation of more rigorous methodology for error detection and classification and the adoption of proper technologies for error reduction.

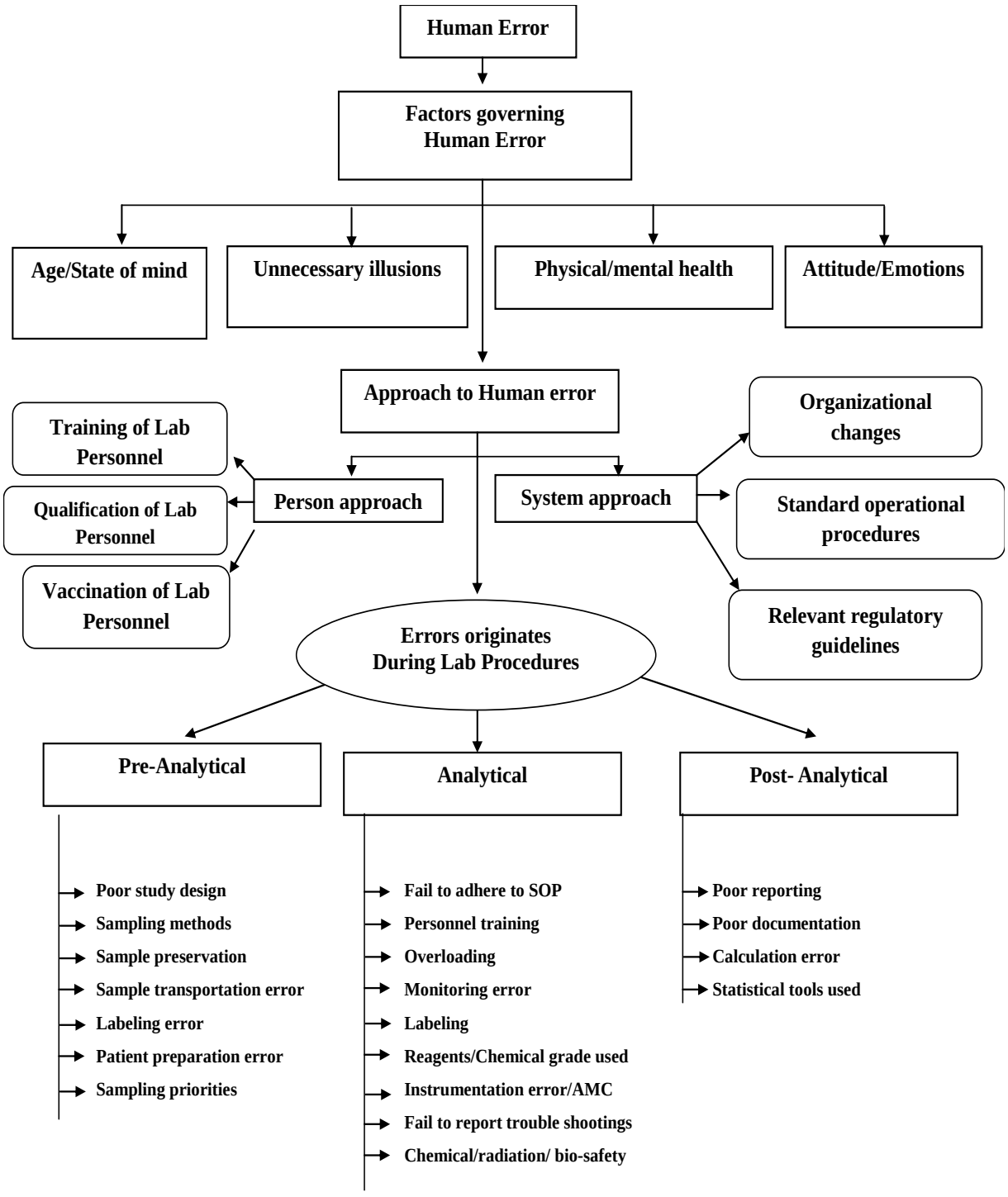


Figure 2: Factors Governing Errors and Violations during Lab Investigation

Table 1: Year wise Development of GLP in USA, Europe and Asian Countries

Year	Developmental Process with Updated Regulatory Guidelines
1972	New Zealand formally introduced GLP as the Testing Laboratory guideline and a Act was developed
1973	Denmark implemented GLPs
1976	Series of audits by the FDA reveal serious discrepancies in toxicological tests at several CRO and pharmaceutical companies in the USA
1978	FDA GLP regulations finalized as 21 CFR Part 58
1978	OECD established expert group on GLP
1979	FDA GLP regulations are implemented
1981	OECD Council decision on OECD Test Guidelines and Principles of GLP concerning mutual acceptance of data
1982	United Kingdom implemented Principles of GLP0 (Final draft)
1984	Japan introduced GLP Guidelines
1989	OECD Council decision on compliance with Principles of GLP and national procedures [C(89) 87 (Final draft)
1997	OECD Council decision on adherence of non-member countries to the Council Acts related to the mutual acceptance of data [C(97) 114 (Final draft) & C(97) 186 (Final)

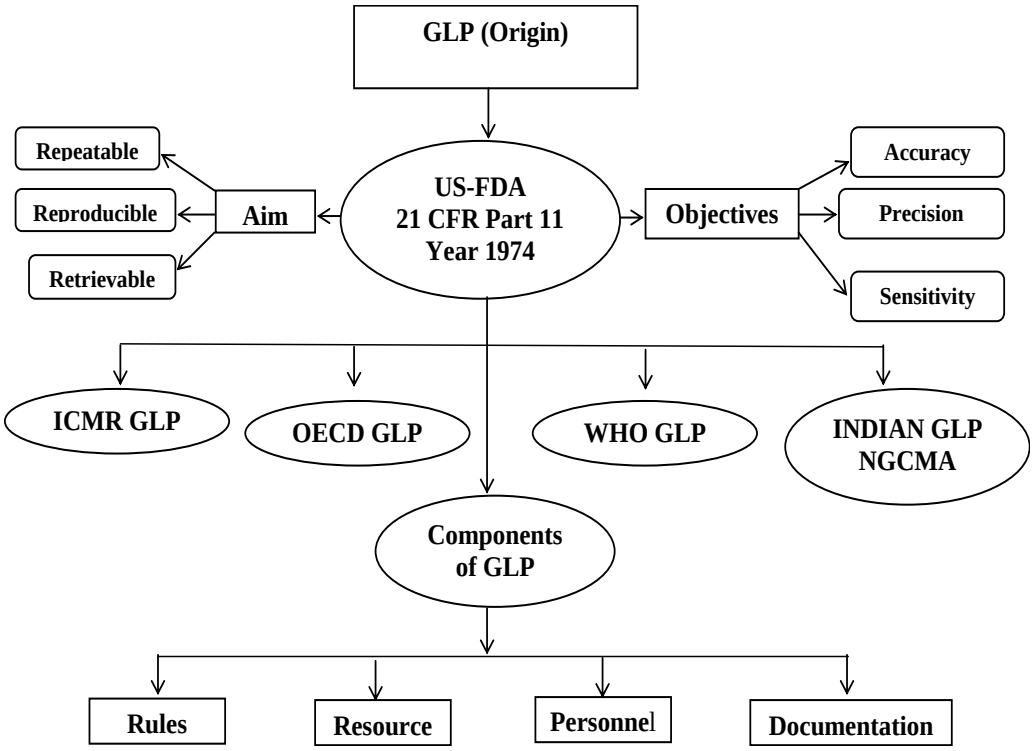
Origin of GLP

GLP was instituted following the discrepancies and cases of animal test fraud by pharmaceutical and industrial chemical manufacturers (particularly pesticide manufacturer). Industrial Bio-test was the most notable case, where thousands of safety tests for chemical manufacturers were falsely claimed to have been performed. The Original GLP regulatory mandate was promulgated in 1978 by US-FDA (though they may have got it from the New Zealand medicines agency) and published in the federal register 43 FR 59985-60020. GLP was originally originated in USA when US FDA made inspection and noticed discrepancies in several labs and thus recommended the importance of GLP. The Draft of GLP regulation was designed in the year 1976 and it has become enforceable USA regulation from 1979 onwards (9). It was followed a few years later by US-EPA, and OECD. Since the objectives of US-FDA–GLP guidelines are found to be sound many European countries showed their interest in adopting US-FDA-GLP through OECD (Organization of Economic Cooperation and Development) this gave rise to the birth of OECD-GLP guidelines and the signatory of OECD also accepted the OECD-GLP and without modifying the objectives and aims of GLP many revision has been made. India is a signatory of OECD and Government of India has adopted Indian GLP through the department of Science and Technology and ICMR (Indian Council for Medical Research). The Original GLP regulatory mandate was promulgated in 1978 by US-FDA (though they may have got it from the New Zealand medicines agency) and published in the Federal register 43 FR 59985-60020. It was followed a few years later by US-EPA, and OECD.

OECD-GLP

The organization of economic development and cooperation is one of the organizations of the United Nations is based in Paris, France is a organizational and functional unit of the united nations. Since the scope and objective of the US-FDA-GLP is novel and found to be certainly sound and widely applicable many EU countries involved in the manufacture of bio-pharmaceutical products and research labs engaged in infectious and metabolic research focused their attention towards adopting GLP in their countries. Since GLP is originally originated in USA by US-FDA the OECD adopted GLP guidelines without altering the aim, scope and objectives (6). Number of EU countries and Asian countries (who are signatories of OECD) adopted OECD-GLP guidelines (10). In 1981, the Organization for Economic Co-operation and Development (OECD) principles of Good

Laboratory Practice (GLP) were finalized and led to the OECD Council Decision on the Mutual Acceptance of Data (MAD) which states that "Data generated in the testing of chemicals in an OECD member country in accordance with OECD Test Guidelines and OECD principles of Good Laboratory Practice shall be accepted in other member countries for purposes of assessment and other uses relating to the protection of man and the environment". At a meeting in 1983, concerning the mutual recognition of compliance with GLP, the OECD recommended that implementation of GLP compliance should be verified by laboratory inspections and study audits.



The European Commission (EC) later ratified the OECD principles and a number of directives stipulate that tests must be carried out to the principles of GLP and also that EC Member States must incorporate into their laws the requirement for all non-clinical safety studies to be conducted in compliance with GLP, and that premises conducting such studies must be inspected by a national authority. Consequently, on 1 April 1997 there came into force in the UK a Statutory Instrument (SI) entitled 'The Good Laboratory Practice Regulations 1997' which superseded the existing voluntary United Kingdom Good Laboratory Practice Compliance program. In 1998, the OECD issued the revised Principles of GLP and Compliance Monitoring. These were adopted by the EC in October 1998 and issued as Directives 1999/11/EC and 1999/12/EC which amended the existing directives which were 87/18/EEC and 88/320/EEC. Consequently, in 1999, the UK Regulations were also updated by SI 3106, as amended by SI 994, 2004, and are accompanied by a guide that interprets them and explains how compliance will be verified.Since publication of the UK regulations the original EU Directives have been replaced by the codified directives 2004/9/EC which relates to inspection of facilities and verification of GLP compliance, and 2004/10/EC which describes the principles themselves. The OECD Council Decision on the mutual acceptance of data (MAD) relies upon the fact that OECD member countries follow OECD guidance and recommendations and have implemented an effective GLP compliance monitoring system that serves to verify the GLP compliance status of test facilities within their territory (11).

GLP current situation in EU countries

The Federal ministry of agriculture, forestry, environmental and water management department is the GLP monitoring authority for all chemicals except medicinal products and veterinary drugs in Austria. The Austrian federal office for safety in health care is the competent authority for substances related to medicinal products. GLP inspections are performed on its behalf by the Austrian agency for health and food safety. Routine inspections take place every 2 to 3 years. GLP monitoring program started in 1989 for industrial chemicals and 1991 for pesticides in Austria. In Belgium laboratories are inspected every 2 to 3 years, GLP monitoring was started in the 1988 itself. The test facilities in the national monitoring program work on a wide range of chemical products like industrial chemicals, medicinal products, veterinary products, phyto-pharmaceuticals, food additives and cosmetic products. The federal department of public health, the food chain safety and environment is in charge of the GLP monitoring authority in Belgium.

In Cyprus the competent authority of GLP is the ministry of commerce, industry and tourism and in particular the Cyprus organization for promoting quality. A memorandum of cooperation between the Cyprus Organization for promoting quality and general state laboratory of Greece has been signed on 18th July 2007. It includes the possibility to carryout joint GLP inspections on Cyprus. In Czech republic the ministry of environment is responsible for ASLAB, the national GLP monitoring authority dealing with all sectors except pharmaceuticals. The state institute for drug control (SUKL), under the responsibility of the ministry of health, is responsible for both human and veterinary pharmaceutical products. Routine inspections are carried out every 2 to 3 years. GLP monitoring programs started in the year 1997. Denmark Ministry of Health and Ministry of trade and industry are in charge of the designation of the GLP monitoring authorities. Danish medicines agency covers medicinal products and veterinary medicinal products. The Danish Accreditation and Metrology Fund (DANAK) covers plant protection products, biocides and food additives. Inspections are carried out by the Danish medicine agency and the Danish Accreditation and metrology fund. Routine inspections are carried out every 2 to 3 years. The GLP monitoring programs were launched on 1st March 1989, but there has been a GLP inspection program for the Chemicals since the year 1981 onwards.

In Estonia the Ministry of Social affairs is in charge of the GLP monitoring authority, the Estonian accreditation centre (EAK) is cooperating with the Swedish Board of accreditation and conformity assessment, SWEDAC will take part in joint inspections with EAK in Estonia and will also train Estonian personal in the field of GLP. The GLP monitoring authority in Finland is the National Product Control Agency for welfare and Health (STTV) which is responsible for GLP program and also monitors directly test facilities carrying out safety studies on chemicals. The agency has delegated GLP inspections of test facilities carrying out safety studies on medicinal products to the national agency for medicines. The GLP inspection program started in 1990 itself. In France, Groupe Interministeriael des products chimiques (GIPC) is in charge of GLP monitoring for chemicals, medicinal products, cosmetics and veterinary drugs. The ministry of Labour and Social affairs is in charge of the GLP monitoring authority. The AgenceFrancaise de securiteSantaire des produits de santé (AFSSAPS) is particularly responsible for medicinal and cosmetic products in France. The Ministry of Labor and Social affairs together with the ministry of agriculture and fisheries are responsible for the (AFSSAPS) comprising the Agency nationale du medicament veterinaire, the GLP authority for veterinary drugs. The test facilities in the three monitoring programs work on a wide range of chemical products, new and existing chemicals and medicinal products, veterinary drugs, cosmentics, food additives, animal feed additives and pesticides. Routine inspections are carried out in interval of between 15 months (GIPC) and to two Years (AFSSAPS). The GLP monitoring program was started in 1984 for medicinal products in 1999 for

veterinary products and in 1985 for chemicals.

In Germany, the federal ministry for environment, nature conservation and nuclear safety is in charge of the designation of the GLP monitoring authorities. There is one GLP monitoring authority in each land. Their work is coordinated by the Bundes institute fur Risikobewertung (Federal Institute for Risk Assessment- BFR). Routine inspections of the test facilities are conducted on a regular basis. The test facilities have to apply for a renewed routine inspection at the latest four years after the last inspection. Additional inspections and study audits may be carried out on request. The GLP monitoring authority was launched in August 1990. In Hungary, the ministry of health is in charge of GLP monitoring for medicinal products for human use. Routine inspections are carried out every two years. GLP monitoring program was launched by a Joint Decree of the ministers of health and of agriculture and rural development in the year 1999.

In Ireland, the department of enterprise, trade and employment is in charge of the designation of the GLP monitoring authority. The INAB (Irish National Accreditation Board) is responsible for GLP monitoring. Products involved are chemical substances as defined in the directive 67/548/ EEC. Routine inspections are performed every second year. Legislation was approved in the year 1991 and the irish authorities implemented the GLP monitoring program in 1992. In Italy, the ministry of Health is in charge of GLP monitoring authority.

Dipartimentoprevenzione (Department of prevention) which operates through an ad-hoc committee comprising those department of the ministry of health involved in GLP (Department of prevention, Department of Pharmaceuticals and Pharmcaco-surveliance), department of veterinary drugs and department of food and nutrition and the Instituto Superiore di santa (National Institute of health). Test facilities in the national monitoring program mainly work on the medicinal products, veterinary medicinal products, pesticides, food additives, cosmetics and industrial chemicals. Routine inspections are carried out every two years. GLP monitoring program was started in 1986.

The Lithuanian National Accreditation Board (LA) is cooperating with the Irish GLP monitoring authority INAB (Irish National Accreditation Board) to ensure GLP. Routine inspection were carried out every second year. Luxembourg has transported directives 2004/9/EC and 2004/10/EC, but has no functioning GLP compliance program. The GLP monitoring authority in Malta is National Accreditation Body (NAB-MSA). This is a technically independent directorate of the MSA (Malta Standard Authority) which is a public authority established by an act of parliament in Malta. MSA has agreement with INAB (Irish National Accreditation Board to carry out joint GLP inspection on Malta on 15th Dec 2005. The agreement has been concluded for an initial duration of three years and may be prolonged by the two parties. There are no GLP compliant test facilities in Malta yet.

In the Netherlands, the ministry of health, welfare and sport is in charge of GLP monitoring authority, Inspectorate of health protection, commodities and veterinary public health is responsible for ensuring GLP. The test facilities in the national monitoring program work on a wide range of chemical products, industrial chemicals, medicinal products, veterinary drugs and pesticides. The GLP monitoring program was started in 1987 itself. Poland Ministry of Health is in charge to indicate Poland's GLP monitoring authority. The Bureau for Chemical substances and preparations is Poland GLP monitoring authority. The GLP monitoring authority in Poland was started in the year 2002. The Ministry of Health is in charge of GLP monitoring in Portugal. Instituto da Farmacia e do Medicamento (Institute for Pharmacy and Medicaments) for medical products, veterinary products and cosmetics and the ministry of Economy is in charge of GLP monitoring authority. The IPQ (Instituto Protugues da Qualidade: Portunguese Institute for quality) is responsible for other chemical products in Portugal. Routine Inspections are carried out every two years. The GLP monitoring program started in 1993 for industrial

chemicals and in 1994 for medicines. The Ministry of Economy is the governmental body in charge of the GLP monitoring authority. The Slovak National Accreditation Service (SNAS) is responsible for GLP in Slovakia. Routine inspections are carried out every 16 months. At present medicinal products, veterinary products , industrial chemicals, plant protection products, cosmetics, biocides, food and feed additives are covered by GLP monitoring in Slovakia. The GLP monitoring program in Slovakia was launched under SNAS in 1996.

In Slovania the ministry of health is in charge of GLP monitoring. The National Chemicals Bureau covers all chemical. The facilities in slovania work on medicinal products, veterinary products, feed additives, biocides and industrial chemicals. Routine inspections are carried out every two years. The GLP monitoring program was launched in the year 2000. In Spain the Ministry of Health and consumption, Directorate General of Pharmacy and Hygine is in charge of the GLP monitoring authority. Agency Espanola del Medicamento (Spanish Agency for Medicinal Products) is responsible for ensuring GLP in Spain. The Entidad Nacional de Acreditacion (ENAC: National Entity for Accreditation) is dealing with all other products. At present only medicinal products and plant protection products are covered by GLP monitoring. GLP monitoring was initiated in 1995 for medicinal products and GLP monitoring for plant protection products was initiated in the year 1998.

In Sweden, the Ministry of Social affairs is in charge of the GLP monitoring for chemicals, cosmetics and hygienic products and the ministry of foreign affairs is in charge of the GLP monitoring authority. The SWEDAC (Swedish Board of Accreditation and Conformity Assessment) is responsible for other chemicals. Since 1998, there exists an agreement between the MPA and SWEDAC concerning GLP monitoring. Routine inspections are carried out by every year SWEDAC and every two years by Medicinal products Agency. The GLP monitoring was started in the year 1979 and 1991 (SWEDAC).

In the United Kingdom, the department of Health is in charge of the GLP monitoring authority. United Kingdom GLP compliance monitoring authority, which is a part of the Medicine Control Agency and is responsible for all Chemicals. The test facilities in the national monitoring program work on a wide range of chemical products, new and existing chemicals, medicinal products, veterinary drugs, cosmetics, food additives, animal feed additives and pesticides. The GLP monitoring program was started in the year Jan1983. Among the countries in the Asian continent India and Singapore are candidates in MAD (Mutual Acceptance of Data) in terms of their compliance with GLP. This news is indeed beneficial to contract research organizations and pharmaceutical companies intended to carryout drug discovery related research using Bio-analytical methods.

Indian GLP

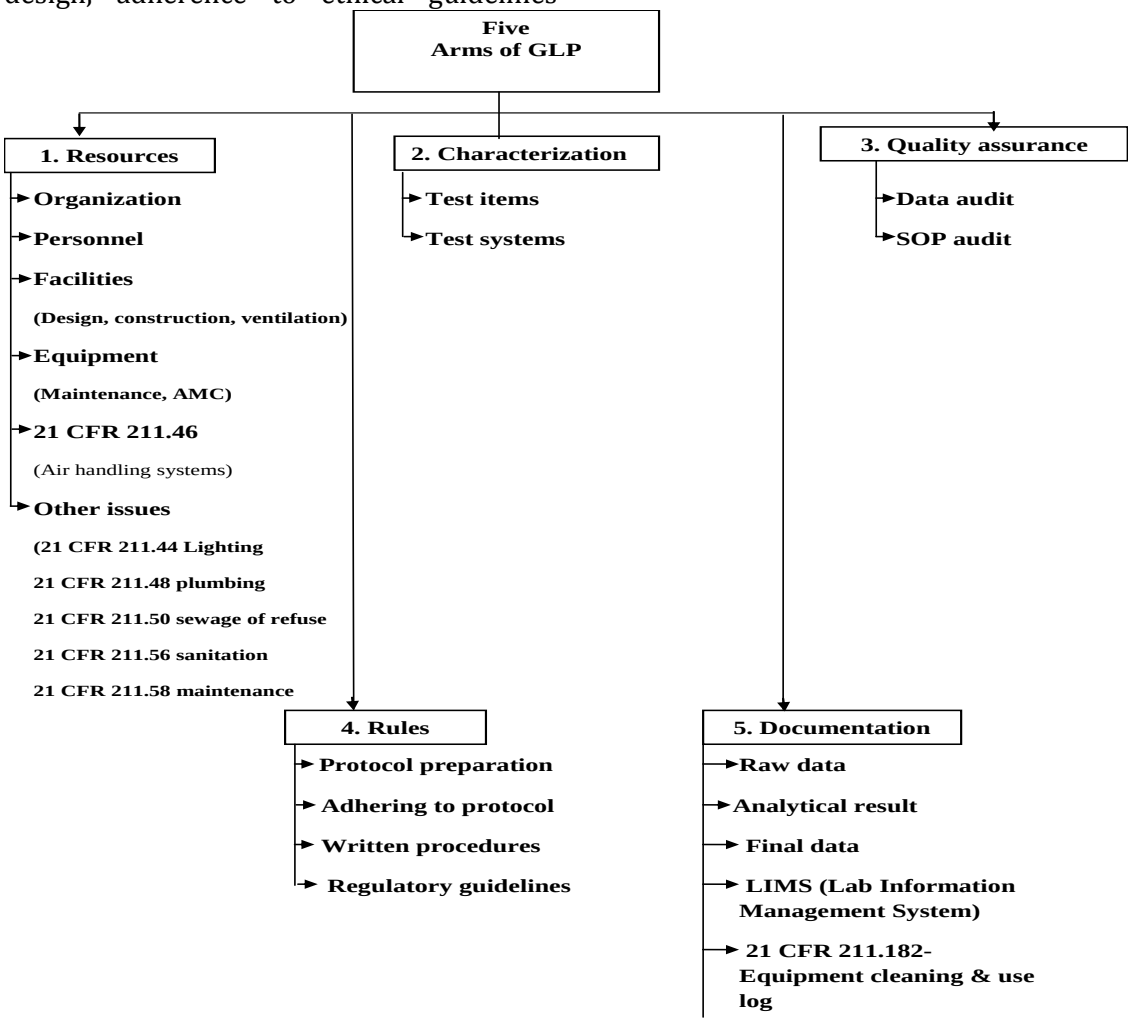
The globalization of Indian economy and the liberalization policies initiated by the government of India to reduce the trade barriers made the necessity in providing greater trust to quality of international standard in almost all areas of commercial importance (12).

In the field of clinical research great necessity arises to ensure quality and international standard in the methods employed and the procedures used. The Indian GLP program has empanelled experts as its GLP inspectors, with prescribed qualification, experience and training (as approved by the Technical Committee), for assessment of test facility/laboratory. The inspectors evaluate the technical competence of the applicant test facility/laboratory in all respects for its compliance to GLP. GLP Certification is voluntary. The test facilities/laboratories have to apply in the prescribed application form. After the application for GLP certification is received, a pre-inspection of the laboratory is carried out by the GLP inspectors, followed by a final inspection. The report, prepared by the inspection team, is put to the Technical Committee for recommendation to Chairman, National GLP Compliance Monitoring Authority, ex-officio, Secretary-DST, for issue of GLP Certificate, if recommended. GLP

Certification is valid for a period of three years and the Secretariat organizes annual surveillance and a re-assessment during third year for maintaining the certification. The NGCMP (National GLP Compliance Monitoring Program) provides recognition to the test facilities, which are involved in conducting safety studies on chemicals (viz. industrial chemicals, pharmaceuticals, veterinary drugs, pesticides, cosmetic products, food products, feed additives, etc). in accordance with Organization for Economic co-operation and Development Council Norms. It aims to assure the regulatory authorities that the safety data they receive from GLP-certified laboratories can be relied upon when making assessments of hazards or risk to man, animal and/or the environment.

Components of GLP

GLP covers the adherence of ethical aspects of methods used in laboratory animal experimentation including the experimental design, adherence to ethical guidelines issued by the animal ethical bodies, dosing strategies, number of animals used in each study group and meaningful statistical analysis of data obtained, measurement of data, quality assurance. This high level of scientific rigor, in conjunction with the detailed processes of GLP using its components like *Rules, Characterization, Quality assurance, Resources, Personnel and Documentation*provides regulatory agencies increased confidence in both the relevance and quality of GLP scientific studies for safety decisions, and it is the reason it is wholly appropriate in regulatory decision making for greater weight and confidence to be afforded to studies conducted in accordance with GLP. Incorporation of GLP in contract research organizations assures that the protocols and standard operating procedures for each study component are developed meticulously and carefully and followed completely by the laboratory personnel (**Fig.3**).



GLP in academic research

Research is a continuously evolving process aimed at discovering new facts and concepts. Academic basic research is very different from regulatory research. Academic research focuses on developing and evaluating new hypotheses, on creating novel methods, and on discovering new findings. By its own nature, the nature of work of a research scholar or research scientist is always subjected to changes in direction in response to new and often unexpected results. In fact the end result of research may be unrelated to the initial aims of the research work. Academic research is open to wide interpretation and may require significant additional studies to clarify and determine whether and how broadly the results apply. Although novel techniques and discoveries of academic investigations stimulate further research, they must also stand up to the scientific method: hypothesis formulation, hypothesis testing, and validation by independent replication. Independent replication provides critical information on the strength of the hypothesis and reliability of test methods. Inconsistent results can arise from use of novel techniques, different test systems, uncertainty and differences in test chemical composition and purity, and a myriad of other factors. These facts, in conjunction with the more limited availability of actual data in most journal publications, means regulatory agencies can face significant challenges in confirming the quality, performance, or data integrity of results obtained solely from information available from a typical article in peer-reviewed journals. Whereas all study records and data from GLP investigations are available to agencies, rarely, if ever, are such details made available as part of the peer-review process for publishing a manuscript in a scientific journal. This can limit the ability of an agency to independently evaluate conclusions or to conduct alternative analyses of the data (13).

GLP insist Laboratory accreditation

The concept of laboratory accreditation was developed to provide a means for third-party certification of the competence of laboratories to perform specific type(s) of testing and calibration. Laboratory accreditation provides formal recognition of competent laboratories, thus providing a ready means for customer to find reliable testing and calibration services in order to meet their demands. Laboratory accreditation enhances patient or investigator confidence in accepting testing/calibration reports issued by accredited laboratories. Laboratory accreditation increase confidence between the principle investigator and the laboratory staff by saving time and money due to reduction or elimination of the need for re-testing of the investigations or products (produced in lab). Accreditation of labs brings about better control of laboratory operations and feedback to laboratories as to whether they have sound quality assurance system and are technically competent. Users of accredited laboratories will enjoy greater access for their products, in both domestic and international markets, when tested by accredited laboratories. Accreditation to a laboratory is given on the basis of its capability to perform test(s)/ calibration(s) and provide accurate and reliable results. A laboratory may apply for accreditation from as little as one to as many tests/ calibrations provided it is performing these according the accreditation authority like NABL in India. The accreditation granted to a laboratory shall remain valid for a period of 2 years subject to satisfactory periodical (annual) surveillance. Laboratory also has an option to widen the scope of accreditation in terms of specific tests and calibrations. NABL has established policies and procedures for granting, suspending and withdrawal of accreditation of accreditation in accordance with ISO/IEC 17011:2004. The accreditation granted to a laboratory shall remain valid for a period of 2 years subject to satisfactory periodical (annual) surveillance. Laboratory also has an option to widen the scope of accreditation in terms of specific tests and calibrations. NABL has established policies and procedures for granting, suspending and withdrawal of accreditation of accreditation in accordance with ISO/IEC 17011:2004. Directory of NABL Accredited Laboratories is published at regular

interval, which contains laboratories' contact details and information on their Scope of Accreditation. Laboratories seeking accreditation are assessed in accordance with ISO/IEC 17025:2005 for testing and calibration laboratories and ISO 15189:2007 for medical laboratories. The laboratory management team shall demonstrate to the NABL assessment team that all requirements are laid down in the ISO/IEC 17025/ISO 15189 standard, specific criteria and other guidelines/requirements of NABL are being followed. NABL accreditation process is done by five different stage viz preparation of labs for accreditation of laboratories are required to submit three sets of duly filled in application forms for each field of testing / calibration along with two sets of Quality Manual and Application Fees. Laboratory has to take special care in filling the scope of accreditation for which the laboratory wishes to apply. In case, the laboratory finds any clause (in part or full) not applicable to the laboratory, it shall furnish the reasons. NABL Secretariat on receipt of application will issue acknowledgement to the laboratory. After scrutiny of application for it being complete in all respects, a unique Customer Registration Number will be allocated to laboratory for further processing of application. After safety and correct action done by the labs, a pre-assessment audit of laboratory will be organized by NABL and during this audit they ensure their preparedness by carrying out its internal audit before pre-assessment (14).

Method development and method validation

In contract research organizations, most cases the testing facility does not develop a method for analytical work since the method is already specified in the protocol and be available for the PI (Principle Investigator). This method may be modified according to the test facility conditions. Study director approves the modification to the method . MV (Method Validation) is required even valid methods are used for compliance with analytical work. Fortified samples are prepared by spiking untreated control samples with known amount of chemicals (15, 16). After going through sample preparation process, fortified samples are analyzed. Recovery rates are calculated using amount obtained being divided by spiked amount.

Reference intervals

Laboratory reports must include a framework for interpreting the results, which is referred to as the "reference interval." Each laboratory must establish a reference interval for every test they offer or provide a written interpretation of the test results (17). Variations in these intervals may be observed from laboratory to laboratory due to differences in instrumentation or testing methods. They also may be adjusted for biological factors such as gender, age, or other clinical situations. When a specific test is used to monitor a patient over a period of time, using the same laboratory to obtain those results provides a level of consistency to the treatment plan.

Critical limits

Each laboratory has in place a system for immediate reporting to the ordering physician any finding that reflects a critical or life-threatening condition. When a test value falls within the critical limits, immediate action is required. Failure to report critical values may result in a patient's death or a medical condition that cannot be reversed. Most laboratory results are collated and managed by a sophisticated computer system (Laboratory Information System or LIS) capable of sending electronic reports to the health care provider by directly printing the report in a physician's office, by email, or by automated faxing. These computers can track test orders, provide pre-analytical information, assist in quality control and quality assurance procedures, alert laboratory staff of an unusual finding such as a critical value, and report and store all laboratory results. Laboratory reports generated by the system can also highlight values that fall outside the expected or reference interval to help the physician focus on the tests that are of most concern. LIS is a powerful tool to manage complex process , ensure GLP regulatory compliance and promote collaboration between multiple laboratories by its ability in data sharing within laboratories and across laboratories. LIS

function in such a way that it interact with other devices or programs in effective documentation which include data entry, data transmission, calculations, data storage and data retrieval. Laboratories must ensure that LIS access is limited to authorized individuals for data handling in order to protect the data (18). All laboratory test methods must meet scientifically rigorous criteria before they can be used in clinical practice. A laboratory must demonstrate that it is able to perform that test in a clinically acceptable way irrespective of the study location in response to a particular test article tested in a uniform conditions. The term "normal range" is not used very much today because it is considered to be misleading. If a patient's results are outside the range for that test, it does not automatically mean that the result is abnormal. Therefore, today *"reference range"* or *"reference values"* are considered the more appropriate terms, for reasons explained on the next page. The term reference value is increasing in use and is often used interchangeably with reference range. For simplicity, we use the term reference range in this article. The interpretation of any clinical laboratory test must consider this important concept when comparing the patient's results to the test's *"reference range."*

EQAS (External Quality Assurance System)

Laboratories must perform routine quality control tests, usually every day. Quality control tests usually include normal and abnormal samples to ensure the equipment, the technologist, and the reagents used in the test are performing to established standards. Laboratories must participate in proficiency testing programs in addition to quality control testing (19). For proficiency testing, an external agency sends "challenge" samples to be tested. The laboratory must report results back to the agency. The agency has already evaluated each of the challenge samples and knows the expected results. The laboratory must get the right result in order to be allowed to continue to test patient samples. If the lab repeatedly fails to get the right result, it is prohibited from continuing the performance of that test until it can demonstrate that it has corrected the problems that led to the unacceptable results. Laboratories must demonstrate that they have written policies and procedures in place to specifically document how the sample is collected, transported, evaluated, and reported in an appropriate manner. These requirements ensure that the tests performed by clinical laboratories for patient care will generate results that are reproducible and can be trusted.

Protocol

Each research study protocol should clearly indicate the objective and conduct of the study. In case if the protocol does not reflect the technical aspect in the conduction of a study or a particular test procedure it should be mentioned in the SOP (Standard Operation Procedure) is a document that describes the step-wise procedure of a laboratory test. Strict adherence to SOP ensures the quality and integrity of data generated and allows comparison of results from different experiments (20). When a SOP is developed it is given a version number and SOP's are reviewed once in a year by the ethical board members, quality assurance managers and principle investigators and when a new methodology is approved SOP undergo change in the version and accordingly a new SOP version number is given. When a SOP is generated it is circulated for approval. QA personnel coordinate for all the revisions of SOP and the distribution of SOP to the concerned departments and retain all the original SOP (21). Any deviation from the SOP is documented in each study related books and acknowledged by the study director who evaluates the necessity and impact of these deviations in relation to the whole study. SOP in the laboratories usually cover the following areas. All test facilities must have SOP for all the important aspects of laboratory operation considering that SOP is one of the most important documents for controlling facility operations. These relate directly to the routine elements of tests conducted in a test facility. If the SOP is written for a particular drug and the laboratory assay employed is LC-MS/MS the following points has to be kept in mind. Receipt of the

sample, determination of identity, purity and composition and stability; labeling, handling, sampling, usage, storage and reference substances. Considering the use of the test method the following points has to be considered in the SOP maintenance of equipments, cleaning and calibration and validation of the measuring apparatus, When computerized systems used check the system and environmental control needed for the equipment.

Role of GLP in Evidence based medicine education

The systematic review of instruments for evaluating education in evidence-based practice (EBP) by Dr. Shaneyfelt and colleagues 1 is an essential first step for teachers of evidence-based medicine seeking valid instruments for assessing the effect of their teaching. However, I believe that their approach to evaluation of primary studies was too simplistic. While basic classification of instruments into knowledge, attitudes, or behaviors is appealing, detailed analyses might have been achieved through use of a more comprehensive classification system, such as Bloom's taxonomy of educational objectives. 2 This would allow curriculum developers to identify instruments that test 1 of 20 specific subdomains within the broad cognitive, affective, or psychomotor domains. In addition, conformity of their classification with existing recommend-dations for outcome assessment by educational networks such as Best Evidence Medical Education (BEME) 3 would have aided better application within educational reviews. An example would be use of an (22).

DISCUSSION

Good Laboratory Practice (GLP) requirements, based on these fundamental scientific principles and practices, are indispensable for providing scientific confidence in studies conducted for chemical safety determinations (23). The biggest difference between GLP and Non-GLP work is the type and amount of documentation. Principle investigators with the cooperation of co-investigators should establish quality programs for continuing education pertaining to GLP compliance and personnel competence assessment. PI should establish a continuous quality assurance program that consistently focus on the improvement of processes in laboratory. Current climates are supportive of identifying errors in laboratories (24). They should also make elaborate arrangement for good hygiene practice and good documentation practice which include labeling of specimens by means of manual and automated methods. The objective of GLP is not only quality of data but also concerned with the traceability and integrity of data. SOP provided in support of the various proceedings in the laboratory will certainly bring about staff integrity and will reduce the stress level to a greater extent and GLP regulations can be easily be met with (25). Several validation and laboratory standardization procedures also support this concept. GLP audit provides details of the following 1. Who has done the study, 2. How the experiment was carried out, 3. Which procedures have been used and 4. Whether there has been any problem and if so how it has been solved. GLP strongly support the documentation including raw data, preliminary data and final data acquired, processed and archived to ensure integrity of data. In recent years evidenced based medicine has been focused on the applications of systematic reviews and meta-analysis principle which are used for obtaining highest level of evidence. So far these efforts have been largely confined to the evaluation of the efficacy and effectiveness of therapeutic and preventive interventions. Systematic reviews in laboratories are scarce and many of them do not meet essential quality criteria (26). Most of these problems are related to poor design and heterogeneity of primary research and that there are no agreed methods or quality standards for making systematic reviews in laboratory medicine. For better evidence in laboratory medicine, not only higher quality primary studies but also standardized methodologies for designing, conducting and reporting systematic reviews in diagnostics are needed. The process of systematic reviewing consists of six key steps: (1) preparation for the review, (2) systematic search of the primary literature,

(3) selection of papers for review, (4) critical appraisal of the selected literature, (5) analysis and synthesis of data, and (6) interpretation of data. The most important technical and methodological aspects of each step and the essential elements of a good systematic review in laboratory medicine are presented. When human genome project was implemented nearly 3 to 5 % of its whole project budget was spent on the ethical issues pertaining to the project. We agree that GLP can be one of the criteria in ensuring safety of the laboratory and the participants but we strongly recommend training in GLP as a essential criteria for all those involved in academic and clinical research. The laboratory director or principle investigator must designate one of the staff member or hire a GLP trainer on contract basis who has the overall responsibility for the GLP related document control, continuing education in GLP so that they can understand and carryout the necessary lab investigation as per the GLP guideline in the country of origin and country of performance of a particular lab investigation (27,28). When the laboratory methodology involves high performance and complex test procedure training in GLP is absolutely essential and the suitability of the person who needs training and relevant qualification of the person who needs training certainly matters (29,30). In recent years GLP compliance for non-toxicology studies were also established and updated (31). Part 493 and Sub Part K (493.1291) provides relevant information pertaining to laboratory report formatting this part of CFR certainly serve as a guiding tool for preparation of lab report format specific for the study (32). Regulatory agencies should try to create awareness about GLP at graduate and undergraduate level as it is not easy for a person to abruptly adopt to GLP environ (33). Hence those who serve in GLP environment should come forward to become a tutor and mentor for teaching GLP guidelines at graduate and undergraduate level (34). For ready reference on GLP in Indian and global situations downloadable information are available online which can give a quick orientation on GLP in Clinical and non-clinical and research environment (35, 36). For Good Laboratory Practice related aspects pertaining to non-clinical safety studies particularly in Pharmaceutical and drug development process suitable information are available (37). In recent years Lean and Six Sigma business management strategies are employed in Bio-medical field to ensure quality, avoiding delay and error and in recent years the NIH (National Institutes of Health) formed a road map for application of Lean and Six Sigma in addition to GLP guidelines and such a new avenue will provide new insights and development of new guidelines in Bio-medical research (38-40). Globally there is a great need arises for archival of laboratory data and elaborate measures should be taken by the national governmental administration and the health ministries in formation of a archive for laboratory data this will help the researchers to trace all laboratory related data in short period of time (41). When a protocol pertaining to laboratory research is submitted necessary mention about the personnel protection , documentation plan, fire protection plan, waste management (Bio-waste disposal) plan, space available for lab should be clearly be mentioned (42,43).

CONCLUSION

Implementation of GLP should start from top level management and investigators. Management must be willing to consider GLP although some amount of funding is necessary but considering the long term benefit and safety and protection of lab personnel. If one of the top management is GLP trained or educated or aware of GLP it is rather easy for the implementation of GLP at all levels in a research organization. Principle investigators should keep watching the recent updates in the regulatory guidelines pertaining to GLP issue by the national health administration. GLP training is not a "*one time event*" it is a periodical process and all necessary arrangements should be made for periodical training in GLP in order to update the laboratory

investigators and researchers because Human Being by their very nature are mistake prone.

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REFERENCES

1. James Anderson (2000) Human error: models and management. BMJ, 320, 768.
2. Kohn L.T., Corrigan, J.M., and Donaldson M.S., (2000) To Err is Human: Building Safer and Health System. Institute of Medicine, Washington D.C., National Academy Press.
3. Crossing the Quality Chasm: A New Health system for the 21st Century (2001 a), Institute of Medicine, Washing. D.C., National Academy Press.
4. Khoury M, Burnett L, Mackay M.A (1996) Error rate in Australian Chemical Pathology laboratories, Med J Aust, 165, 128-130.
5. PierangeloBonini, Mario Plebani, FerruccioCeriotti, Francesca Rubboli (2002) Errors in Laboratory Medicine, Clinical Chemistry, 48 (5), 691-698.
6. Fernandes MF and Donna MR (1992) The nature of social desirability: Effect in ethics research, Bioethics Quarterly, 2, 183-205.
7. Vijayaraghavan, R (2009)Animal models in pre-clinical research and Bio-medical research: SOP and GLP compliance, Book: Emerging trends in modern biology, pg 93-111.
8. US FDA, Centre for drug evaluation and Research (CDER) Center for Veterinary Medicine (CVM), Bio-analytical method validation: Guidelines for Industries, Biotherapeutics, Revision # 1, Sept 2013.
9. Wayne Jiang (2005) Good Laboratory Practice in Analytical Laboratory. TheJ of American Science. 1(2), 93-94.
10. Bawa RS (2002) Challenges and opportunities of globalization- Implication for India, Indian Economic Journal, 49 (3), 5-6.
11. OECD (2002) OECD series on principles of GLP and compliance monitoring. Number 13, ENV/JM/MONO, 9.
12. OECD Principles of Good Laboratory Practice, OECD Environmental Health and safety publications. Series on Principles of GLP and compliance Monitorig number 1, OECD, Paris, 1988.
13. Adamo JE, Bauer G, Berro M, Burnett BK, Hartman KA, Masiello LM, Moorman-White D, Rubinstein EP and Schuff KG (2012) A road map for academic health centers to establish Good Laboratory Practice-compliant infrastructure. Acad Med, 87 (3), 279-284.
14. Chakrabarthy A.K. (2004) Relevance of NABL accreditation towards the quality scenario in India. MAPN, J of Metrology Society of India, 19 (1-2), 23-32.
15. Lauwaars M, Ankam E (2004) Method validation and reference materials. Accreditation QA, 9,4-5, 253-258.
16. Huang SB, Stanton JS, Lin Y (2003) Analytical method for determination of atrazine and its dealkylatedchloro-triatrazine metabolites in water using SPE sample preparation and GC-MSD analysis. J of Agri Food Chem, 51, 7252-7258.
17. Alexander Kratz, Maryjane Ferraro, Patrick M Sluss and Kent B Lewandrowski (2004) Laboratory Reference values, New Engl J Med, 351, 1548 -1563.
18. Robin Gall (2012). Use of LIMS to improve evidence management in the crime laboratory, American Laboratory, pg 1-2. http://www.starlims.com/getattachment/24cc4c72-0b31-4c60-8b52-0ecd225cc1db/Use-of-LIMS-to-Improve-Trace-Evidence-Management-i.aspx.
19. Geilo F (2000) Quality management in analytical R&D in the pharmaceutical industry: Building quality from GLP. Accred Qual Assur, 5, 16-20.
20. WHO/ TDR (2001) Good laboratory Practice, WHO/ TDR Generva, Switzerland.
21. Weinberg S (2005) Applying 21 CFR part II to laboratory environment (Weinberg S ed), pp 115-116, Marcel Dekker, New York.
22. Robert H Christianson (2011) Laboratory medicine best practices: Developing and Applying Systematic Evidence Review and Evaluation Methods for Quality Improvement 211, Annual meeting, Los Vegas, Abstract. American Society for clinical Pathology.
23. Myers JP, vomSaal FS, Akingbemi BT, Arizono K, Belcher S, Colborn T, et al. (2009) Why public health agencies cannot depend on Good Laboratory Practices as a criterion

for selecting data: the case of bisphenol A Environ Health Perspect 117: 309–315.
24. Berwick, D. M. (2003). Disseminating innovations in health care.The Journal of the American Medical Association, 289 (15), 1969–1975.
25. Witte DL, VanNess SA, Angstadt DS, Pennell BJ (1997). Errors, mistakes, blunders, outliers, or unacceptable results: how many?. Clin Chem , 43, 1952-1956.
26. Horvath AR and Pewsner D (2004) Systematic reviews in laboratory medicine: Principles, Process and practical considerations. Clinical ChimActa, April, 342 (1-2) pg 23-39.
27. 42 CFR, Part 493, Sub Part M (493.1407) Standard; Laboratory director responsibilities, Oct 2005.
28. 42 CFR, Part 493, Sub Part M (493.1445) Standard; Laboratory director responsibilities. Oct 2005.
29. 42 CFR, Part 493, Subpart M (493.1423) Standard; Testing personnel qualification, Oct 2005.
30. 42 CFR, Part 493, Sub part M (493.1487), Condition: Laboratories performing high complexity testing, testing personnel. Oct 2005.
31. Li H, Hawik S, Renfrow H, Hartwell R, Chao SF, Sharp G , Pilkington C, PettewayJr S, Remington K and Pifat D (2004) Establishing a GLP compliance program for non-toxicology safety studies. Qual Assur J , 8, 94-101.
32. 42 CFR, Part 493, Sub Part K (493.1291), Standard: Test report. Oct 2005.
33. Dent NJ (1998) Forget compliance, concentrate on science, Qual Assu J, 3, 103-108.
34. Hancock S (2002) Meeting the challengers of implementing good laboratory Practice compliances in a University Setting, Qual Assur J, 6, 16-21.
35. ICMR (2008), Guidelines for good clinical laboratory Practice, http://icmr.nic.in/ guidelines/GCLP.pdf
36. WHO: World Health Organization (2001) Handbook, Good Laboratory (GLP) quality practices for regulated and non-clinical research and development http;//WWW.who.int/entity/tdr/publications/documents/glp-handbook.pdf.
37. Sasaki M, Hinotsu S, Kawakami K (2009) Good Laboratory Practice (GLP) status of Asian countries and its implementation in non-clinical safety studies in pharmaceutical drug development. J Toxicology,Oct 34(5),493-500.
38. Riebling N, Tria L (2005) Six Sigma project reduces analytical errors in an automated lab. Med Lab Observer.37(6), 20, 22–23.
39. Elder BL(2008). Six Sigma in the microbiology laboratory. Clin Microbiol Newsletter.30(19):143–147.
40. Hurley B, Taylor T, Levett J (2008). Implementation of Six Sigma and Lean methodology into the anticoagulation management process. J Thromb Thrombolysis, 25:106.
41. Weinberg S (2005) Applying 21 CFR part II to laboratory environment (Weinberg S ed), pp 115-116, Marcel Dekker, New York.
42. CFR. Part 493, Subpart K (493.1252), Standard: Test systems, equipment, instruments, reagents, materials, and supplies. Oct, 2005.