

Milestones In Development Of Good Clinical Practice

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Abstract

Good Clinical Practice (GCP) is a standard for design, conduct, performance, monitoring, auditing, recording, analysis and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity and confidentiality of trial subjects are protected. The present day guidelines on GCP have evolved through a series of regulations and policy formulations. This is increasingly considered as an essential part of drug regulation. These guidelines have been evolved with consideration of WHO, ICH, USFDA and European GCP guidelines as well as the Ethical guidelines for Biomedical Research on Human Subjects issued by the Indian Council of Medical Research. They should be followed for carrying out all biomedical research in India at all stages of drug development, whether prior or subsequent to product registration in India. This article describes the major milestones in the evolution of Good Clinical Practices.

Good clinical practice (GCP) is an international ethical scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. It also ensures that the rights, welfare and safety of subjects involved in trials are maintained and are consistent with the principles stated in the World Medical Association Declaration of Helsinki, entitled 'ethical principles for medical research involving human subjects',

'Guideline CPMP/ICH/135/95 entitled good clinical practice' was developed under the subject of International Conference on the Harmonisation of the technical requirements for the registration of human pharmaceuticals (ICH process) and is applicable in the European union of the United States and Japan. Clinical trial data that have developed according to the guideline should therefore be acceptable by regulatory authorities in each of the three regions, together with Australia, Canada, Nordic countries and the World Health Organisation which was also involved

in its development.

The definition of GCP given in the guideline is 'a standard for the design, conduct, performance monitoring, auditing, recording, analysing and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity and confidentiality of trial subjects are protected.'

The present day guideline on GCP has evolved through a series of regulation and policy formulations. The major milestones in the evolution of GCP are as follows.

1. FEDERAL FOOD AND DRUGS ACT OF 1906

The purpose of the FDA is to prohibit adulterated/ misbranded food or drugs from interstate commerce. The act is originally enacted in 1906 brought "truth in labelling". This act was emerged in consequences of a most dramatic report of Sinclair's book, the Jungle, which graphically illustrated problems in the nation's meat processing industry. Samuel Haukin's, Adams magazine article concerning what he called the great American fraud sparked similar concerns about fraudulent patent medicines containing dangerous ingredients such as alcohol, cocaine, morphine and opium advertised by the amendments of 1906₃. However the 1906 act was considered inactivated because

False statements made about a drug by a manufacturer were held by the courts not to be misbranding

The act did not extend to cosmetics.

The act did not grant the authority to ban unsafe drugs.

2. SULPHANILAMIDE DISASTER, 1937

Sulfanilamide, a drug used to treat streptococcal infections, had been shown to have dramatic curative effects and had been used safely for some time in tablet and powder form. Experiments showed that sulfanilamide would dissolve in

diethylene glycol. The company control lab tested the mixture for flavor, appearance, and fragrance and found it satisfactory, and the product was marketed as “Elixir of Sulfanilamide”. No pharmacological studies had been done on the new sulfanilamide preparation and so there was a failure to note one characteristic of the solution. Diethylene glycol, a chemical normally used as antifreeze, is a deadly poison. This preparation took lives of more than 100 people in 15 states₄.

The drug and the deaths led to the passage of the 1938 Food, Drug, and Cosmetic Act, which increased FDA's authority to regulate drugs.

Among other things, this law required new drugs to be tested for safety before marketing, the results of which would be submitted to FDA in a new drug application (NDA). The law also required that drugs have adequate labeling for safe use. All drug advertising was assigned to the Federal Trade Commission.

3. FOOD, DRUG AND COSMETIC ACT, 1938.

The public furore over the sulphanilamide disaster finally resulted in a legislative demand for safety because all drugs are to some degree harmful if used contrary to common sense or the manufacturer's interest, safe meant not toxic when used in accordance with the conditions set forth on the label.

The term label is a term of art. It means “a display of written, printed or graphic matter upon the immediate container of any article”. The law requires that if certain information is required to be on the label of a drug, the information must also be on the outer or the inner label clearly visible through such outer wrapper. The law can, for instance, require that certain information accompany a drug as part of its labelling (package insert) while not requiring information to appear on drug's label.

This new label, in addition to require proof of safety, expanded the meaning of adulteration and misbranding that previously had been strictly enforced by the law. Labels were now required to provide adequate directions for use to the consumer₅.

4. DURHAM – HUMPHREY AMENDMENT OF 1951

Durham – Humphrey Amendment of 1951 exempted certain drugs from the requirement that their labelling contains adequate direction for use. The act was amended to formally

distinguish between prescription and over the counter drugs. Until that time all drugs could be purchased over the counter by the consumers. Prescription drugs were required to contain the warning that the drugs could be dispensed legally only with the authorisation of a health professional₆.

5. NUREMBERG CODE OF 1946

Nuremberg code includes ten principles to guide physician investigators in experiments involving human subjects. These principles, particularly the first principles on voluntary consent, primarily were based on legal concepts because medical codes of ethics existence at the time of the Nazi atrocities did not address consent and other safeguards for human subjects. ‘Societal necessity’ to protect soldiers and civilians from the ravages of war time conditions invoked also in the United States during World War II and later during the cold war was advanced by the Nazi physician as a justification for conducting experiments to find immediate answers to press problems, but they did not offer any justification for the brutal ways in which the research have been conducted₇.

The need to define the basic principles for the conduct of human research was focused on the patient protection and made no distinction between research with patient subjects and healthy persons, be there prisoners or volunteers. In Germany Nuremberg code is regarded as a guideline for medical research. Many of the principles are still valid today. That is the necessity of informed consent, the rule that the patient can withdraw from the experiment at any time and the ban against experimentation that in any way could result in major injury or death of the experimental subject. The ten principles of Nuremberg are rarely applied now-a-days. Its due mostly to the fact that they do not distinguish between therapeutic and purely scientific experiments and that there have been super seated by the revised declaration of Helsinki of the World Medical Association.

6. THALIDOMIDE DISASTER OF 1962

In 1962, thalidomide, a sleeping pill developed and widely used abroad, was being studied for use in the United States. William S Merrell Company of Cincinnati was using the drug investigationally when it was discovered that the drug could harm the foetus when taken by a pregnant women during the first trimester of pregnancy. Children born to such mothers often were born without arms or other severe deformities. It was clear that people were taking drugs and neither the prescriber nor the manufacturer had a clear knowledge of the effects₈₉.

Under these circumstances the Durham Humfrey 1951 amendment was simply inadequate to protect the public. The series of law suits demonstrated that large prescribers are relying on manufactures for the information about the drugs and that information in some instances had been based on inadequate testing. This resulted in Kefauver – Harris Amendments of 1962 which addressed the issue of effectiveness and safety¹⁰.

7. KEFAUVER – HARRIS AMENDMENTS OF 1962

These amendments generally referred to as the drug efficacy amendments. They provided for registration of manufacturers and inspection of manufacturing sites and they required an unprecedented program of accountability from manufacturers¹¹.

Before marketing any new drug manufacturers were required to supply proof of effectiveness and proof of safety. Good manufacturing practices the so called GMP were established, and if a manufacturer produces a drug without adhering to such practices the drug was considered as adulterated. Prescription drug advertising was placed under the supervision of FDA while FTC continues to supervise the advertising of over the counter items. The Amendments established the procedures for new drug application and for investigational drug procedures which required assurance of informed consent of the research subjects and required reporting of adverse drug reaction. Qualification of drug investigators was subjected to review.

8. DECLARATION OF HELSINKI, 1964

Declaration of Helsinki was developed by the World Medical Association (WMA), as a set of ethical principles for the medical community regarding human experimentation. It is widely regarded as a cornerstone documentation of human research ethics, although it is not legally binding instrument in international law. It draws its authority from its degree to which it has been qualified in all influenced national or regional legislation and regulation¹². However courts and guidelines impact on practice in both symbolic and instrumental roles. Its role was described by a Brazilian forum in 2000 in these words. ‘Even though the declaration of Helsinki is the responsibility of World Medical Association the documents should be considered as all humanity’¹³.

Declaration of Helsinki laid down the ethical principles of medical research involving human subjects and as a major

landmark in the revolution of good clinical practices.

The first revision was made in 1975 which was almost twice the length of original and introduce the concept of oversight by an independent committee which became a system of institution review board in the US and research committees in other countries¹⁴. The duty to the individual was given primacy over that to the society, and concept of publication ethics was introduced. Any experimental manoeuvre was to be compared to the best available care as a comparator. And access to such care was assured. The document was also made gender neutral and provisions were made for safeguarding animals. Subsequent revisions were made between 1975 and 2000 were relatively minor, so the 1975 version was effectively that which govern research over a quarter of a century of relative stability¹⁵¹⁶. Fifth revision came up with a test that was endorsed by WMA’s council and passed by the general assembly on October 7, 2000¹⁷¹⁸¹⁹. This involved reconstruction of the documents including renumbering and reordering all the articles. The introduction establishes the rights of subjects and describes the inherent tension between the need for research to improve the common good and the rights of the individual. The basic principles establish a guide for judging to what extent proposed research meets the expected ethical standards²⁰²¹.

9. MEDICAL DEVICE AMENDMENT, 1976

In 1976 Medical Devices that previously had been subject to control only under the general adulteration and misbranded sections on the food drug and cosmetic act of 1938 (FDCA) where subjected to extensive new requirements. In order to keep pace with the rapidly expanding medical and scientific technology or devices were classified and subjected to varying degrees of control depending upon and evaluation of their function. For the first time, the safety and effectiveness of life sustaining and the life supporting devices are now required to have premarket approval of the FDA.

These all led to the evolution of Good Clinical Practice (GCP). This is a set of guidelines for biomedical studies which encompasses the design, conduct, termination, audit, analysis, reporting and documentation of the study involving human subjects. The fundamental tenet of GCP is that in research on man, the interest of science and society should never take precedence over considerations related to the well being of the study subjects. It aims to ensure that the studies are scientifically and ethically sound and that the clinical properties of the pharmaceutical substances under investigation are properly documented. The guidelines seek

to establish to cardinal principles protection of the rights to the human subjects and authenticity of biomedical data generated²².

The Food and Drug Administration has published the guidelines entitled "Good Clinical Practice; Consolidated Guideline". The guideline was prepared under the auspices of the International Conference on Harmonisation of Technical requirements for registration of pharmaceuticals for human use (ICH). The guideline is intended to define good clinical practice and to provide a unified ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with the standard provides public assurance that the rights, safety and well being of trial subjects are protected, consistent with the principles that the origin in the declaration of Helsinki and that the clinical trial data are credible. The objective of ICH-GCP guidelines is to provide a unified standard for the European Union (EU), Japan and United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions. The guidelines were developed with consideration of the current good clinical practices of the European Union, Japan and the United States as well as those of Australia, Canada, the Northern Countries and the World Health Organisation (WHO). These guidelines should be followed when generating clinical trial data that are intended to be submitted to regulatory authorities. The principle established in this guideline may also be applied to other clinical investigations that may have an impact on the safety and well being of human subject.

CONCLUSION

These regulations and policies played a vital role in the evolution of GCP and they considered as the major milestones. This helped the regulatory authorities to frame guidelines for conducting clinical trials with less harmful effects and to ensure the safety of the participants.

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