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History

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GCP Key Point
Good Clinical Practice might be termed a cultural approach to applying ethics and integrity to human biomedical clinical trials with investigational products.

1.1 Introduction

This chapter will briefly outline the history of biomedical clinical trials from the standpoints of regulatory oversight and ethical expectations and the emergence of good clinical practice (GCP).

1.2 Objectives

The objectives of this chapter are to:

- Provide an outline of legislation, events, and circumstances which provide the background and history for the development of the ICH GCP Guideline E6 R2.
- Offer thoughts and points of view on why the GCP mindset emerged among the global regions most involved in pharmaceutical drug development occurred.

1.3 Chronology

If you research the history of GCP, you will find that it is aligned with the events which form the stepping stones on the pathway of clinical trial regulation. The best known events involve abuses of humans during medical experimentation

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and the subsequent legislative and regulatory initiatives to prevent the recurrence of those abuses. The following events, policies, and legislation stand out.

- 1902 – The Biologics Control Act [1] is enacted by the US Congress requiring licensing of vaccines, serums, and similar products. The legislation was prompted by the distribution of a contaminated batch of diphtheria antitoxin contaminated with tetanus which killed 13 children. This legislation eventually became part of the Public Health Service Act and serves as the primary regulatory control for the same group of products which now includes cell therapies and many biotechnology-derived products.
- 1906 – The Food and Drugs Act [2] is passed by the US Congress and gives the Federal Government control over misbranded or adulterated drugs.
- 1938 – The US Congress enacts the Federal Food, Drug and Cosmetic Act (FFDCA) [3] in part due to the Elixir of Sulfanilamide [3] episode in which 107 deaths occurred. The new law required proof of safety prior to marketing and drew cosmetics and therapeutic devices into the regulatory scheme.
- 1949 – The Nuremburg Code [4] is born out of the criminal trials of Nazi researchers who conducted unethical experiments on humans during WWII. The Code is a set of 10 points that establishes a foundation for voluntary consent of research subjects as well as most of the key ethical principles which emerge in subsequent documents.
- 1962 – The Kefauver–Harris Drug Amendments to the FFDCA [5] required that drugs must demonstrate efficacy as well as safety and the investigational new drug (IND) application as we know it today is launched in the regulations. One of the driving forces behind these legislative amendments to the FFDCA was the thalidomide tragedy of 1961 when newborns suffered severe birth defects. The FDA's IND regulations followed circa 1963.
- 1964 – The Declaration of Helsinki [6] takes the ethical principles for conducting research on humans to a new level through the efforts of the World Medical Association.
- 1965 – The US National Institutes of Health proposed that their research involving humans be examined by an impartial panel of peers to ensure ethical integrity. By 1971 the Public health Services' policy of ethical review for human research was expanded to include Department of Health Education and Welfare research however the policy was not well enforced. In 1974. Regulations requiring group ethics review were published and the term institutional review board was born [7].
- 1972 – The US Public Health Service's Tuskegee Syphilis Study [8], which began circa 1932, is publically exposed for its deficiencies and ethical failures.
- 1974 – The US Congress reacts to the Tuskegee study episode by enacting the National Research Act [9] (National Research Act 1974) which establishes the

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (National Commission).

- 1976 – the US Congress is provided a report [10] from the General Accounting Office which reported that based on a special survey of sponsor and investigator inspections 74% failed to comply with legal requirements pertaining to informed consent, drug accountability, adherence to protocol, record accuracy, and availability as well as the appropriate supervision by the clinical investigator. This report prompts Congress to recommend that FDA undertake adequate monitoring / inspection programs of clinical trial sponsors, investigators, and institutional review boards.

> "the Food and Drug Administration (FDA) is not adequately regulating new drug testing to insure that human subjects are protected and the test data is accurate and reliable."

- In 1979 the Belmont Report [11] is published by the National Commission and joins the Nuremburg Code and Declaration of Helsinki as a fundamental policy document describing the application of ethical principles such as respect for persons, beneficence, and justice in the conduct of behavioral and biomedical research involving humans.

- 1980s – Global regions, countries with mature drug regulatory systems such as Japan, the European Union (EU), and the United States, as well as global health authorities, e.g. World Health Association, independently establish or enhance regulations and guidelines governing the conduct of human clinical trials. Harmonization of requirements for drug approval is championed by many.
- 1990 – The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) [12] is founded by the regulatory authorities and pharmaceutical associations of Japan, the United States and the European Union.
- 1996 – The ICH guidance GUIDELINE FOR GOOD CLINICAL PRACTICE E6 (R1) [13] (ICH E6(R2) is finalized. It remains the gold standard for the design, conduct, recording, and reporting of clinical trials involving human subjects. Note – It was revised in 2016 to (R2).
- 2004 – The EU Clinical Trial Directive 2001/20/EC [14] becomes effective and EU member states must move to adopt it into their legal requirements. The Directive sets universal requirements for clinical trials including approval by an

ethics committee, harmonization of technical requirements through participation in the ICH, and application of GCPs in the conduct of human trials.

> The verification of compliance with the standards of GCP and the need to subject data, information, and documents to inspection in order to confirm that they have been properly generated, recorded, and reported are essential in order to justify the involvement of human subjects in clinical trials.

- 2011 – The International Standards Organization (ISO) in conjunction with its standard setting partners publishes the medical device version of the GCP requirements in the form of the standard ANSI/AAMI/ISO 14155 Clinical investigation of medical devices for human subjects – GCP [15] (ISO 14155-2011). 14155 Represents the medical device version of the ICH GCP standard for pharmaceuticals. This publication solidified the application of GCP expectations for human clinical trials in essentially all investigative (unapproved) articles intended for the cure, mitigation, or treatment of disease and injury in man.

This chronology does not however speak directly to the driving forces that were in play as the events unfolded and the progress towards an international acceptance of GCP as a standard was underway.

1.4 The Emergence of the ICH and Its Guidelines

GCP as we know it today was born not just out of tragic episodes in human experimentation such as the Tuskegee Syphilis Study and the abuses of Nazi researchers in the WWII concentration camps. It was very much a work-product of the for-profit drug industry which needed harmonized standards to facilitate the marketing application process among the world's primary producers and consumers of pharmaceuticals. An additional motivation for the ICH concept was to remove duplicative testing which would reduce the exposure of humans to investigational medicinal products, unnecessarily. Viola!, the emergence of the ICH. The ICH was born out of collaboration between the regulatory authorities and industry trade associations. It therefore had the best of both regulatory thinking and for-profit science. The newly born organization moved quickly to develop and propose a number of key guidelines which would benefit the entire pharmaceutical industry. GCP was one of the efficacy guidelines defining approaches to clinical trial activities. Others included clinical safety for Drugs Used in Long Term Treatment (E1) and general considerations in clinical trials (E8).

It is important to note that in establishing the ICH approach the industry and regulators did not attempt to cut corners or somehow create a shortcut bypassing

a structured process. Instead the ICH framework has become a model for sound business accomplishment while operating in a transparent and efficient manner. Inclusion of interested parties was encouraged and while the founding members remain in place as the governing entity, participation by other global regions and countries has been fostered and encouraged as observers and as part of global cooperation. Canada, Brazil, China and Australia to name a few participate in ICH meetings and workgroups.

In 2015 the ICH took several steps to solidify its organizational presence and expand its influence. It established itself as an association under Swiss law and it invited regulators and industry counterparts from Switzerland, and Canada to join as full members. It also adopted a name change – The International Council for Harmonization – and continues to grow and prosper today.

Notwithstanding the harmonization mission of the ICH, implementation of guidelines such as GCP even among the founding members of the ICH has not been identical. The European Union and Japan have adopted the GCP guideline into their legal requirements for the conduct of clinical trials. The United States has not, however, done so. The reasons for this difference in adoption of the GCP, as well as other ICH guidelines, lie primarily in the legal system supporting the regulatory framework. For example the United States has had in place regulations governing new drug studies since the early 1960s including requirements associated with informed consent. Modifying those regulations to integrate or adopt the GCP guideline would have been a monumental task. In addition, the system in place to modify/change regulations is a cumbersome one which would encounter difficulties and complexities in keeping up with the technology changes that can more efficiently be processed by a nongovernmental entity such as the ICH.

Without doubt, the US FDA agrees with the ICH GCP guidance, they helped write it! The manner in which the FDA has integrated GCP into its regulatory scheme provides a good example of harmonization with its ICH counterparts as well as demonstrating its support and approval for the application of GCP for human clinical trials.

FDA in a 2004 Federal Register Notice of Proposed Rulemaking (NOPR) [16] to adopt GCP in 21 Code of Federal Regulations (CFR) 312.120 as a reference point for the acceptance of foreign clinical studies not conducted under an IND. At the time, the criteria in 21 CFR 312.120 called for foreign clinical studies to be conducted in accordance with the ethical principles in the Declaration of Helsinki. In reviewing the Preambles to both the NOPR and the 2008 Final Rule [17] it is apparent that the FDA wanted to demonstrate its support and agreement with GCP but was grappling with adopting GCP as a document into law because it would pose administrative difficulties from a procedural and regulatory standpoint. The end product is that FDA removed the reference to the Declaration of Helsinki, which itself had become problematic from several policy standpoints

and substituted GCP as the criteria for acceptance of data generated in studies not conducted under an IND. They even devised a set of 11 specific pieces of information that should be described as evidence that GCP was followed during the course of the human clinical trial. It was a win for the FDA and a win for GCP.

Contemporaneous with the development of the ICH GCP was the development of a set of GCP expectations by the World Health Organization [18]. Subsequent to the publication of the ICH GCP, a number of countries has published its own version by modifying the standard to include requirements that fit their regulatory model.

In the next Chapters we will outline the regulatory environment within which GCP is enabled.

1.5 Summary

The advent of the GCP Guideline and its adoption as a global reference for the conduct of human biomedical clinical trials is a story that emerges from a number of business and regulatory objectives that came together in the early 1990s. The chronology of regulatory legislation, historical incidents, and ethical policy development listed earlier formed the backdrop for the success of the ICH organization. It is noteworthy that GCP stood out as a key early guideline development project. Protection of trial subjects and the assurance that data can be trusted were central themes for regulators and the pharmaceutical drug manufacturers were keen to find the protocols which would have a universal appeal. The story of the ICH in general and the development of GCP in particular is one where everyone was a winner.

Knowledge Check Questions

1) The emergence of legislative regulatory controls over pharmaceutical drug development and clinical trials was often prompted by:
   a) Protests from university medical students _____
   b) Tragic outcomes from administration of unsafe and/or ineffective drug products_____
   c) Promises made to voters by candidates for political office_____
2) Failure of medical researchers to apply ethical principles has never been a problem that needed solving? True ____ False _____
3) The Belmont Report was authorized by the National Research Act of 1974. True ____ False _____
4) The ICH Efficacy Guideline – GCP – is considered the industry standard for the conduct of human biomedical clinical trials with drug products. It was developed because:

a) Of continuing abuses against study subjects by drug researchers _____
b) The United States, Japan, and the European Union wanted manufacturers in their countries to have a monopoly on drug marketing _____
c) Manufactures and regulatory authorities wanted to establish harmonized standards to facilitate the mutual acceptance of clinical data supporting drug approval_____

5) The ICH headquarters are located in the United States and the organization is under the US FDA. True _____ False _____

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