The Evolution of the Clinical Trials Process – A Brief History Lesson

In this chapter, the history of clinical trials and the different regulatory agencies will be explored. Human curiosity has been the impetus for the advancement of science and medicine since these disciplines came into existence. In addition, human subjects have been used to substantiate the theories of those innovators involved in the pursuit of this knowledge. The first reference to a clinical trial can be found in the Bible. King Nebuchadnezzar II (605-562 BCE) ordered a group of children be fed a strict diet of meat and wine and then followed for 3 years. These children were compared to Daniel and 3 other children who refused the king’s decree and instead were allowed to eat pulses (e.g., beans, peas, lentils) and water. After 10 days, the king saw that those who ate the diet of pulses and water were fitter than those who ate the diet of meat and wine. He stopped the trial and switched those who had received the meat and wine over to pulses.

Around the 10th century, the Persian scientist Ibn Sina (Avicenna) wrote *Al-Quanun fi al-Tibb* or the *Canon of Medicine*, a book that represented a comprehensive collection of all existing medical knowledge, incorporating Arabic medical lore and personal experience into the writings of Hippocrates, Galen, Dioscorides, and others. Importantly, he recommended the testing of new drugs on animals and humans before general use and set down a series of 7 basic rules for clinical drug trials (reworded for brevity): 1) the drug must be pure; 2) the drug must be used on a “simple” disease; 3) the drug must be tested on at least 2 different types of disease; 4) the quality of the drug must correspond with the strength of the disease; 5) the timing of observations should be measured to rule out the effects of natural healing; 6) the drug must show consistency over several trials; and 7) a drug should be tested in animals first, thereafter in humans, as the effects in animals and humans may not be the same. The Canon was the medical authority for centuries and set the standards for the practice of medicine in Europe, as well as the Middle East.

James Lind, however, is generally considered the originator of the modern clinical trial because he was the first to introduce the use of a control group. In 1747, he found that the addition of citrus fruits could prevent scurvy. He administered the same general diet to scurvy patients on board a British naval vessel but supplemented the diet with various additional items, such as cider, elixir vitriol, vinegar, seawater, nutmeg, and citrus fruit (oranges and lemons). In 6 days, those who had received the citrus fruit were cured. Interestingly, although the results were indisputable, Lind hesitated to recommend the widespread use of citrus fruits because they were too expensive; it took 50 years before the British Navy made lemon juice a requisite part of the seaman’s diet, which was later switched to the less expensive lime juice.

The first direct comparison of an active treatment to placebo was performed by Austin Flint in 1863. Flint administered a placebo remedy to 13 hospital inmates with rheumatic fever and compared the results to the previously described effects of an active treatment. In 12 of 13 patients, no significant differences between the placebo and active therapy were observed; in the 13th case the possibility was raised that the active treatment might have been effective in preventing the complications that had emerged (pericarditis, endocarditis, pneumonia). Prior to this investigation, outcomes from a particular intervention had been weighed against the natural history of untreated disease.

There is some debate regarding when the concept of randomization was introduced. Some scholars propose that R. A. Fisher was the first to employ randomization in a study setting with his agricultural experiment (crop variation) in 1923. Others propose that the study by Charles Peirce and Joseph Jastrow in 1883 was the first example. They sought to determine if blindfolded people could detect the difference between a 1000 g weight from a 1001 g or 1002 g weight. The amount of weight that was placed on the scale was governed by the random drawing of a card from a specialized deck by the investigator, eliminating any bias that might have been introduced by the investigator.
The first (debatable) use of randomization in a medical trial was in 1926 (published in 1931) when J. Burns Amberson tested a drug for tuberculosis on patients of the Detroit Municipal Tuberculosis Sanatorium. In this study, 24 patients were divided into 2 approximately equivalent groups of 12 based on clinical, X-ray, and laboratory findings; a flip of the coin decided which group would receive the active treatment and which would be the control group. The first trial attributed to utilizing “proper” randomization was that performed by the British Medical Research Council in 1948 to evaluate the effects of streptomycin in tuberculosis. In this study, patients were assigned to groups (streptomycin and bed rest or best rest alone) using random sampling numbers and sealed envelopes. In addition, blinded assessment was employed, and neither the researchers nor the patients knew in which treatment group the patients were in at the time of the study.

Despite the evolution in clinical research procedures, only recently has the protection of human subjects has been of paramount concern. The ancient Hippocratic Oath that both contemporary medical professionals and laymen are familiar with was not widely subscribed to by the majority of physicians of the day. Early advances in the protection of human subjects usually were a reaction to a particular abuse or scandal.

The greatest modern representation of such abuses occurred during World War II, with the horrific experiments carried out on humans in the name of science. The creation of the Nuremberg Code, a set of principles for ethical human experimentation, was the global response to those atrocities. The judges of the “Doctors’ Trial” against Karl Brandt and others led to the creation of the Nuremberg Code in 1947. Earlier that same year, Dr. Leo Alexander had submitted to the Counsel for War Crimes 6 points to define legitimate medical research, which were incorporated into the trial verdict. The final decree consisted of 10 points that included such principles as informed consent, properly formulated experiments, and benevolence toward study subjects.

The Declaration of Helsinki was developed by the World Medical Association and is also a set of ethical principles for the proper conduct of human experimentation. Originally adopted in 1964, it has undergone a total of 8 revisions, the most recent in 2000. The Declaration expands on the Nuremberg Code by applying the doctrines specifically to clinical research. Included is the foundation for the creation of institutional review boards (IRBs). The latest revision put forth the principle that the standards of care upheld in the developed world should be administered to developing countries when conducting research in those countries. The Declaration is significant in that it is the first effort of the medical community to regulate itself.

Aside from the global efforts to establish ethical clinical trial procedures, individual countries have developed their own systems for regulating the conduct of clinical trials. Perhaps the 3 most influential institutions include the Food and Drug Administration (FDA) of the United States, the European Medicines Agency (EMEA), and Japan’s Pharmaceuticals and Medical Devices Agency (PMDA). The following provides some historical perspective as to the origins and subsequent maturation of these organizations.

*History in the United States and the Food and Drug Administration (FDA)*

In the 19th century, what little control over food and medications existed was the responsibility of the individual states and was inconsistent from state to state. The adulteration and misbranding of foods and drugs was commonplace, with snake oil salesmen increasing as the century progressed. Furthermore, many medicinal products were compounded in individual pharmacies, making oversight difficult.
The medicine men competed with the circuses, the minstrel shows, and “Wild West” performers to entertain the public – and sell their products. Hamlin’s Wizard Oil had one of the most popular and spectacular of the big touring medicine shows. For minor aches and pains, this liniment continued to be sold for many years after the shows had ceased.

The first federal law that addressed consumer protection with regard to therapeutic substances was the Vaccine Act of 1813, which established a national source for uncontaminated smallpox vaccine. However, the Vaccine Act was repealed after only 9 years because of a fatal accident and public scandal involving contaminated vaccine.

In 1862, President Lincoln created the Division of Chemistry, the predecessor of the FDA, as part of the new Department of Agriculture. Starting in 1867, the Division of Chemistry began investigating the corruption of agricultural commodities. Harvey Washington Wiley in his role as chief chemist expanded the investigative role of the Division of Chemistry in 1883. He was instrumental in the enactment of the Biologics Act of 1902 in response to the deaths of several children caused by contaminated smallpox vaccines and diphtheria antitoxins. This Act granted the federal government premarket approval for every biological drug and approval over the process and facility producing such drugs. He also compiled *Foods and Food Adulterants*, a 10-part study published from 1887 to 1902. In this study he administered varying amounts of the questionable food additives that had been in use to healthy volunteers to determine their affects on health. Based on these results and the filthy conditions described in Upton Sinclair’s book, *The Jungle*, he unified a diverse group that included state chemists, food and drug inspectors, the General Federation of Women’s Clubs, and national associations of physicians and pharmacists behind the Pure Food and Drugs Act (also known as the Wiley Act), which was signed into law by President Theodore Roosevelt on June 30, 1906. The 1906 law recognized the privately produced US Pharmacopoeia (USP, originated in 1820) and the National Formulary as the official standards for the strength, quality, and purity of drugs, and defined adulterated drugs as those that were listed in the USP but failed USP specifications. The law included provisions against misbranding, but they pertained only to the drug’s label and not to any related advertising. The law was tested in 1910 when Dr. Johnson fought prosecution against his “Dr. Johnson’s Mild Combination Treatment for Cancer” all the way to the Supreme Court. The Court agreed with Johnson, ruling that therapeutic claim is a matter of opinion. The Sherley Amendment was passed in 1912 to attempt to overcome the limitations imparted by the Supreme Court ruling, but this amendment banned only “false and fraudulent” claims, which necessitated proof of intent to deceive. Wiley resigned in 1912 amid conflict within the incumbent Taft administration.
In 1927, the Bureau of Chemistry was reorganized into the Food, Drug, and Insecticide Administration to oversee regulatory functions, and the Bureau of Chemistry and Soils to conduct nonregulatory research. In 1930, under an agricultural appropriation act, the name of the Food, Drug, and Insecticide Administration was shortened to the familiar “Food and Drug Administration” (FDA).

Although several other laws and litigation continued to shape the food and drugs landscape, the next significant milestone occurred on June 25, 1938, when President Franklin D. Roosevelt signed the Food, Drugs, and Cosmetic Act. A well-established pharmaceutical company released a new sulfa drug (Elixir Sulfanilamide) without testing the solvent (diethylene glycol) used in making the product. As a result, 107 people, mostly children, died before the product could be recalled. This episode was branded as an example of ineffective federal control, and within months the Food, Drugs, and Cosmetic Act of 1938 was passed by Congress. This piece of legislation brought cosmetics and medical devices under the control of the FDA, mandating premarket approval of all new drugs, prohibiting false therapeutic claims, overseeing food packaging and quality, mandating legally enforceable food standards, authorizing factory inspections, and adding injunctions to the agency’s enforcement tools.

A number of amendments to the Food, Drugs, and Cosmetics Act were enacted during the latter part of the 20th century. The Durham-Humphrey Amendment of 1951 resolved the debate about what constituted a prescription medication and what could be considered over-the-counter. This amendment stated that any drug that is habit-forming or potentially harmful is to be dispensed under the supervision of a health practitioner as a prescription drug. The James Delaney hearings lead to the Miller Pesticide Amendments of 1954, which required premarket approval of pesticide residues in or on food; the Food Additives Amendment of 1958, which required premarket approval of food additives;
and the Color Additive Amendments of 1960, which required premarket approval of color additives.

Originally proposed in 1960 by Senator Estes Kefauver, the Kefauver-Harris Amendments of 1962 was passed in direct response to the thalidomide disaster in Europe. These Amendments mandated that efficacy, in addition to safety, be established for a new drug, and that the FDA review the efficacy of all drugs introduced since 1938. These amendments also instituted stricter control over drug trials and transferred the regulation of prescription drug advertising and manufacturing from the Federal Trade Commission to the FDA.

The Food Additives Amendment of 1958 allowed the FDA to regulate dietary supplements, but in 1976 Congress prohibited the FDA from controlling these products in response to pressure from supplement manufacturers. Also in 1976, the Medical Device Amendments were passed, which divided devices into 3 categories: Class I (eg, tongue depressors, gauze) are subject to reporting requirements and Good Manufacturing Practices; Class II (eg, blood pressure cuffs, sutures) are subject to the same controls as Class I plus product-specific performance standards developed by the FDA; and Class III (eg, angioplasty catheters, artificial hearts) must pass an FDA approval process similar to new drugs. All new devices are categorized as Class III unless it can be shown to be “substantially equivalent to a previously approved device.” The role of Class II devices has been largely obsolete because FDA performance standards were not developed until 1997.

In 1983, the Orphan Drug Act was passed to reduce the barriers for producing drugs used to treat “rare” diseases affecting less than 200,000 cases in the United States. The Act gave tax breaks, subsidies, and special exclusivity privileges to sponsors of these drugs with the purpose of reversing the negative impact of previous FDA regulations on the development of drugs that would not become blockbusters.

The aforementioned are just some of the amendments that affected drug development, manufacturing, and marketing. What started as an organization of only 1 chemist in 1862 is now an organization of more than 9,000 employees that monitors and processes more than $1.5 trillion worth of products each year. Today, the FDA consists of 9 centers/offices, including the Office of Regulatory Affairs, the National Center for Toxicological Research, the Center for Drug Evaluation and Research, the Center for Devices and Radiological Health, the Center for Food Safety and Applied Nutrition, and the Center for Veterinary Medicine.

Creation of the European Medicines Agency (EMEA)

Although the EMEA was not established until 1995, numerous events paved the way for its creation. The European Union (EU) was first conceptualized in 1951 when 6 countries (Belgium, France, West Germany, Italy, Luxembourg, and the Netherlands) created the European Coal and Steel Community by pooling their resources into a common market. In 1957, the European Economic Community, the predecessor to the EU, expanded the common market beyond just coal and steel to all economic sectors of the member countries through the Rome Treaties. In 1973, the United Kingdom, Ireland, and Denmark joined the EU; Greece joined in 1981, Portugal and Spain in 1986, and Austria, Finland, and Sweden joined in 1995. In 2004, the Czech Republic, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, the Republic of Cyprus, the Slovak Republic, and Slovenia joined the EU, and, in 2007, Bulgaria and Romania joined for a total of 27 countries or member states.

As in the United States, disasters often prompted change in the EU. Thalidomide was introduced in Europe in 1957 to alleviate morning sickness in pregnant women. By 1960, thalidomide was available in more than 20 countries in Europe and Africa (it was never granted approval in the United States).
Despite growing evidence to the contrary, and the lack of a formal approval process of the drug across Europe, thalidomide was widely distributed based on safety profiles derived from animal experiments. By the end of 1961, thalidomide was removed from the market because it was associated with severe teratogenic effects. Unfortunately, the damage was catastrophic, with thousands of thalidomide-exposed babies born before access to the drug was denied. In 1965, the First European Directive, known as 65/65/EEC, was enacted by the Council of the European Economic Community and stated that no medicinal product could be placed on the market in a member state unless authorization had been issued by the competent authority in that member state. Thus, pharmaceutical manufacturers had to seek approval from each individual country before marketing could commence in that country.

The Second European Directive (75/319/EEC) in 1975, hoped to alleviate some of the multiplicity involved in seeking approval across Europe by introducing mutual recognition, so that authorization in one member country would allow marketing in other member countries without having to repeat the entire approval process. 75/319/EEC also established the Committee for Proprietary Medicinal Products (CPMP), which consisted of representatives of the member states to provide an opinion if there was a dispute about any particular product in the various member states. The procedure as practiced was that a company that had obtained product license in one particular member state would submit an application to the licensing authorities in the other states. The other authorities had 120 days in which to either grant the license or raise scientific concerns, which were discussed in the member state where the original license was granted. Any unresolved objections would be addressed by the CPMP. However, the process resulted in only 1 product being approved without objection out of more than 300 products that had entered the system.

In 1987, the Concertation Procedure was established and provided a simple community-wide licensing option for new biotechnology, such as recombinant DNA products or monoclonal antibodies. This schema provided for product assessment by the CPMP, before the normal national regulatory review, and was the precursor to the centralized process in use today.

In 1992, the Single Market Project was launched with the goal of united all of the EU states under one currency and establishing a unified economy. In 1993, the European System for Marketing Authorization of Medicinal Products, referred to as the EMEA, was established through the incorporation of the CPMP and the Committee for Veterinary Medicinal Products. In 1995, the EMEA was inaugurated, and the current system of either centralized or decentralized licensing procedures went into full effect. The centralized procedure eliminated the need for individual member state review. The decentralized procedure is reserved for those drug classes not mandated by the centralized system and is similar to the former procedure where an applicant goes directly to a single member state and, once the drug is approved by that authority, seeks to have other member states recognize the approval and grant their own marketing authorizations.

In 2001, the Committee for Orphan Medicinal Products (COMP) was established to review the applications of medicines for rare diseases. The Committee on Herbal Medicinal Products (HMPC) was established in 2004 to provide scientific opinions on traditional herbal medicines. In 2004, the full name of the organization was shortened to the European Medicines Agency but the acronym EMEA remained, and the CPMP was renamed the Committee for Medicinal Products for Human Use (CHMP).

The EMEA system has been refined with the introduction of a number of regulations. For example, in 2005, the Sunset Clause was introduced, which states that any drug granted approval but not placed on the market within 3 years will have its authorization revoked; this also applies to products that have previously been placed on the market but were taken off the market for a period of 3 consecutive
years. In 2006, provisions for conditional marketing authorization similar to the Orphan Drug Act were enacted.

The EMEA is headed by an Executive Director and currently has a secretariat of approximately 440 staff members. A network of 4,000 European experts from the various member states underpins the scientific work of the EMEA and its committees.

*The Emergence of the Japanese Pharmaceuticals and Medical Devices Agency (PMDA)*

Pharmaceuticals, in one form or another, have been important throughout Japanese history and culture. In 593 CE a Buddhist temple in Osaka organized the first national social institution for the benefit and welfare of mankind, which relied on folk medicines of herbs and indigenous lay healers. Christianity and Western medicine were introduced into Japan in the 16th century, with the first European hospital erected in Japan in 1557 by the Portuguese monk, Luis de Almeidia. Although initially embraced, Western medicine was rejected after European colonization of the South Pacific, allowing for traditional practices to become dominant again. The 19th century witnessed a reemergence of Western medicine with the reconstruction of the healthcare system by the Meiji government of Japan.

Regulation of medicine began in 1874, when the Meiji government enacted and promulgated a law providing the right of dispensing drugs to drugstore owners (later pharmacists). In 1889, the government established rules for handling drugs and regulated the name and function of pharmacists, who could both prescribe and dispense drugs.


The Fund for Adverse Drug Reactions Suffering Relief was established in 1979, partly in response to the thalidomide disaster, and was reorganized in 1987 into the Fund for Adverse Drug Reaction Relief and R&D Promotion. The original purpose of this fund was to reimburse citizens for damages as a result of drug-related adverse events; the revision added research and development operations. In 1994, the Fund was reorganized again into the Organization for Pharmaceutical Safety and Research (OPSR/Kiko) and began to review medical products. The year 1997 marked the point of modern reform with the establishment of the Pharmaceuticals and Medical Devices Evaluation Center (PMDEC) at the National Institute of Health Sciences and the development of a systematic approval review system. However, prior to 2002, Japan was not a significant member of the global medical market as any drugs to be licensed in Japan had to have phase 1 through 3 clinical trials specifically performed on Japanese subjects (in Japan), even if the drug had been previously approved elsewhere. In 2002, the Minister of Health issued a “pharmaceutical vision statement” that acknowledged the need to become more internationally competitive. As a direct result, in 2004 the Pharmaceuticals and Medical Devices Agency (PMDA) was established as an independent, nongovernmental agency separate from the Ministry of Health, Labor, and Welfare. The PMDA replaced the responsibilities of the OPSR/Kiko, the Japan Association of Advanced Medical Equipments (JAAME), and the PMDEC to better guarantee safety and improve efficiency. To further streamline the process, the R&D Promotion Services of the PMDA was transferred to the National Institute of Biomedical Innovation (NiBio) in 2005, so that the PMDA could concentrate on review, safety, and relief operations.

*Conclusions*

The history of medicine has paralleled the history of society, with tragedy often leading to great
innovations. Changes in the conduct of clinical trials and the evolution of the regulatory process have allowed for a significant improvement in patient care, safety, and clinical outcomes. Undoubtedly, medicine will continue to mature and adapt to new advances and ever-changing world politics to the overall betterment of clinical research and, ultimately, the well-being of the world population.

Timeline

Key: Global, Japan, Europe, United States

600 BCE: First mention of clinical trial in the bible: King Nebuchadnezzar II and Daniel compared diet of pulses and water to diet of meat and wine

593: Buddhist temple in Osaka, Japan organized

10th century: Ibn Sina wrote the Canon of Medicine

1557: First European Hospital erected in Japan

1747: James Lind conducted the first modern clinical trial on scurvy in British sailors

1813: US Vaccine Act

1820: US Pharmacopoeia originated

1862: Creation of the US Division of Chemistry (predecessor of the FDA)

1863: Austin Flint compared active treatment to placebo

1874: Meiji Government of Japan initiates drug regulation

1883: Harvey Washington Wiley joined the US Division of Chemistry

1883: Randomization used by Charles Peirce and Joseph Jastrow in an experiment testing whether subjects could differentiate among weights

1902: US Act of 1902 granting the government premarket approval over drugs

1906: US Pure Food and Drugs Act was signed into law

1923: RA Fisher’s agricultural experiment utilizing randomization

1926: J Burn Amberson’s tuberculosis experiment using a flip of the coin to determine group assignments

1938: US Food, Drugs, and Cosmetic Act signed into law

1943: Japan passes the first Pharmaceutical Affairs Law

1947: Nuremberg Code created

1948: British Medical Research Council experiment on streptomycin using “proper” randomization techniques
1951: US Durham-Humprey Amendment

1951: European Coal and Steel Community created

1954: US Miller Pesticide Amendments

1957-61: Thalidomide disaster

1962: US Kefauver-Harris Amendments

1964: Declaration of Helsinki developed

1965: First European Directive (creation of the CHMP)

1976: US Medical Device Amendment

1979: Japan’s Fund for Adverse Drug Reactions Suffering Relief established

1983: US Orphan Drug Act

1987: EMEA Concertation Procedure established

1992: European Single Market Project launched

1995: EMEA established

1997: Japan established the PMDEC

2002: EMEA COMP established

2004: Japan established the PMDA

Resources


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