History of Drug and Clinical Research Regulations

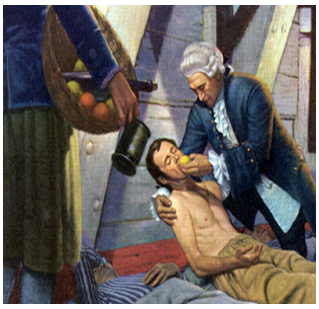
1. Key Dates in the Development of Drug and Clinical Study Regulation

Several events have prompted federal and international action to **protect** human subjects involved in all types of research. The **key dates and events** in drug regulation development are **highlighted** in a grey background as they are often part of exam questionnaires. Even if it is not mandatory to learn them by heart, it is good to know the key dates.

The concept behind **clinical trials** is quite ancient. The biblical **Book of Daniel**, for instance, describes a planned experiment with **baseline** and **follow-up** observations of 2 groups who either ate or did not eat the free "King's meat" over a **trial period** of 10 days. (Daniel, Hananiah, Mishael and Azariah considered the meat that had been **sacrificed** to pagan gods unholy by their faith and instead requested **vegetables**. Despite that, "at the end of 10 days their **appearance** looked fairer and fatter in flesh than all the children who did eat the king's meat")

Persian physician and philosopher, **Avicenna**, gave a more **formal structure** to such inquiries. In ***The Canon of Medicine*** in 1025 CE, he laid down **rules** for the **experimental use** and **testing** of drugs. He wrote a precise **guide** for practical **experimentation** in the process of **discovering** and proving the **effectiveness** of medical drugs and substances. He laid out the following **rules** and **principles** for testing the **effectiveness** of new drugs and medications:

1. The drug must be free from any **extraneous** accidental quality.
2. It must be used on a **simple disease**, not a composite one.
3. The drug must be tested with **two contrary types** of diseases, because sometimes a drug **cures** one disease by its **essential qualities** and another by its **accidental ones**.
4. The **quality** of the drug must correspond to the **strength** of the disease. For example, there are some drugs whose heat (*efficacy*) is less than the coldness (*severity*) of certain diseases, so that they would have **no effect** on them.
5. The **time of action** must be **observed**, so that essence and accident are not confused.
6. The **effect** of the drug must be seen to **occur constantly** or **in many cases**. If this did not happen, it was an **accidental** effect.
7. The **experimentation** must be done with the **human body**, because testing a drug on a lion or a horse might not prove anything about its effect on man.



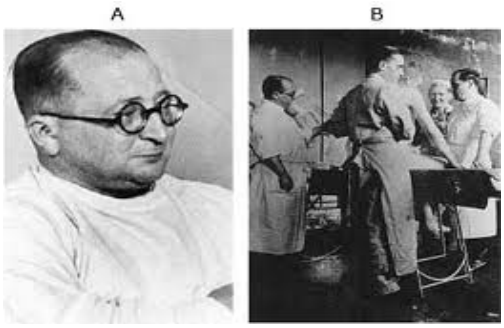
One of the most famous clinical trials was **James Lind**'s demonstration in 1747 that **citrus fruits** can cure **scurvy**. He was not the first to suggest **citrus fruits** as a cure for scurvy; he was the first to **study** and prove their effect by a **systematic experiment**. He **compared** the effects of 6 various **acidic substances**, ranging from vinegar to cider, on 6 groups of 2 **sailors** afflicted by **scurvy** and found that the group who were given **oranges** and **lemons** had largely **recovered** from scurvy after 6 days while the others didn't.

Frederick Akbar Mahomed (d. 1884), who worked at Guy's Hospital in London, made substantial contributions to the clinical trial process. During his detailed clinical studies, he separated **chronic nephritis** with **secondary hypertension** from what we now call **essential hypertension**. He also founded the **Collective Investigation Record** for the ***British Medical Association***. This organization collected data from physicians practicing **outside** the hospital setting and was the precursor of modern **collaborative clinical trials**"

2. Key Events in the Development of Drug and Clinical Research Regulations

- **1940s**

- Non-consenting war prisoners and Jewish detainees were **subject** to **coerced and cruel** "medical experiments" by Nazi doctors during the World War II. Twenty-six **Nazi physicians** were **tried** at **Nuremberg**, Germany in **1947** for such research activities. This lead to the **proclamation** of the **Nuremberg Code (1947)**.



The **Nuremberg Code** was written as part of the **concluding section** of the **judgment** at the ***Nuremberg Trials*** (1949). It is a **10-point code** on the **ethics** of **human experimentation**, which recognized the potential **value** of research to society, but emphasized the **absolute necessity** of **voluntary consent** from the subjects.

The Nuremberg Code established that **to be ethical**, the conduct of research must have as its **utmost priority** the **rights and welfare** of the research subject. Most of the subsequent laws and **guidelines** about **ethical conduct** of research **maintained** this emphasis and **incorporated** the necessity of **informed consent**. (See the annex)

- **1940s**

- Research abuses in Tuskegee, Alabama, where an **unethical study** on the **natural development** of *untreated syphilis* **enrolled poor rural African-American men,** who were left **uninformed** of their disease**, misinformed** about the **purposes** of the study and **denied treatment** even after a treatment was found in 1947**.** The 'study' continued till **1972**. It gave birth to the **Belmont Report** in **1979.**

- Secret radiation experiments and **plutonium injections** of **Indigent patients** and **mentally handicapped children** who were given **the wrong information** about the **nature** of their treatment**.** The experiments were revealed by **The Albuquerque *Tribune*** in **1993** and **declared unethical** by the **President's Advisory Committee on Human Radiation Experiments** in **1995.**

- **1962**

- *Thalidomide,* a sleeping pill popular in the 50s and taken by **pregnant women** caused thousands of **birth defects** in **babies** in Western Europe. This led to the **Kefauver-Harris Amendment**, which introduced a **requirement** in **1962** for drug manufacturers to provide **proof** of the drug **effectiveness** and **safety** before the marketing approval is granted.

Many informative videos covering these critical turning points in bioethics are available on YouTube.

3. Chronology of Drug and Research Regulations in USA

1848:

Drug Importation Act - required U.S. Customs Inspection Service to **stop entry** of adulterated drugs from overseas

1862:

Bureau of Chemistry, the predecessor of the Food and Drug Administration, was founded by President Lincoln

1906:

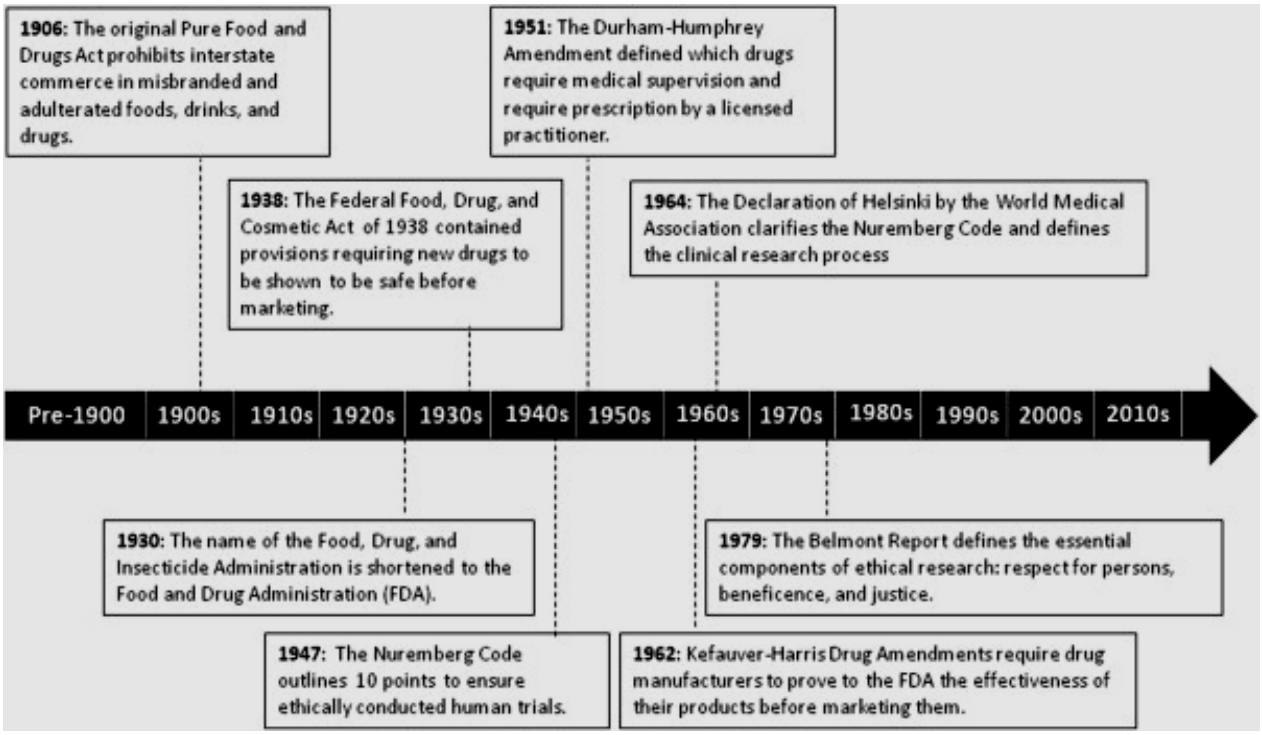
Food and Drug Act - prohibited **interstate commerce** of misbranded and adulterated food, drinks and drugs

1912:

Shirley Amendment - prohibited labelling medicines with **false therapeutic claims** intended to defraud the purchaser

1927:

Food, Drug & Insecticide Administration (regulatory functions) and the **Bureau of Chemistry and Soils** (non-regulatory) replaced the Bureau of Chemistry



1930:

Food and Drug Administration became the **new name** of the Food, Drug and Insecticide Administration

1938:

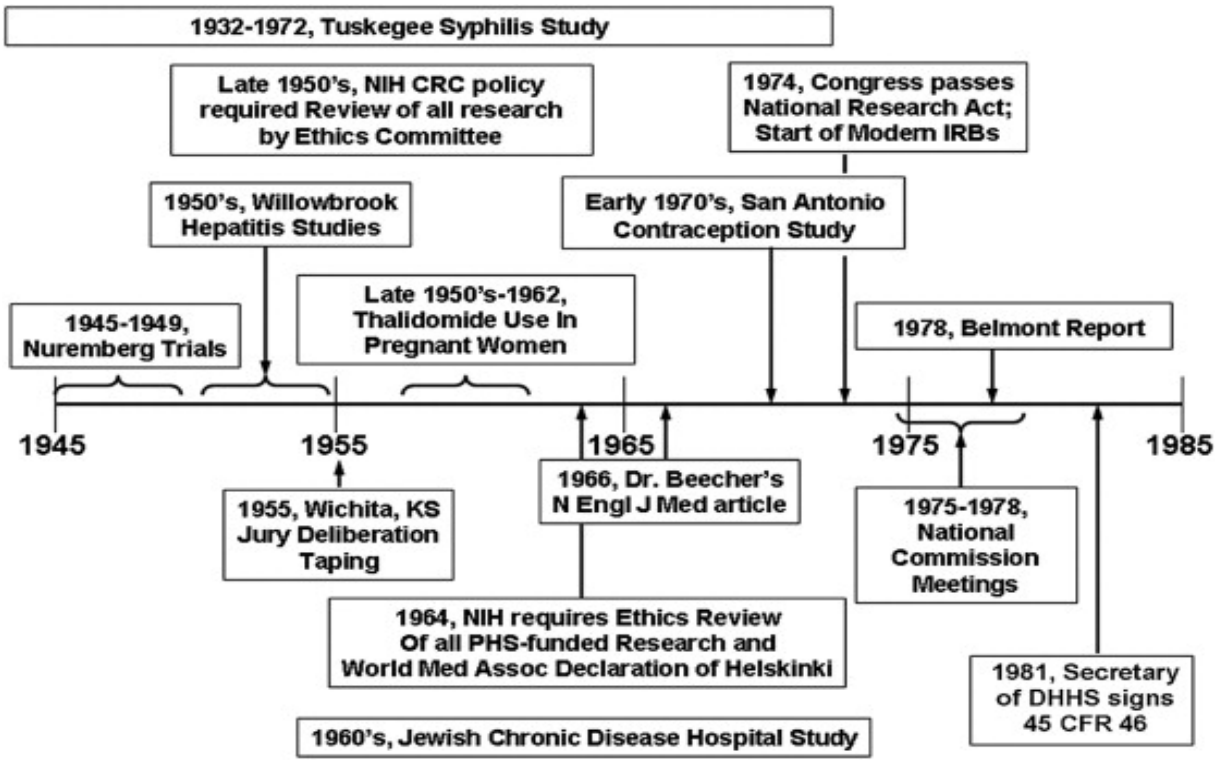
The Federal Food, Drug & Cosmetic Act (FDC) authorized **FDA** to oversee the **safety** of food, drugs, and cosmetics (Sometimes the abbreviations FDCA or FFDC are also used)

1940:

The first **Guidance for the pharmaceutical industry** was published by FDA. The agency was transferred to the *Federal Security Agency*

1947:

The **Nuremberg Code**, the first internationally recognized code of research ethics, became a prototype for the **Declaration of Helsinki** and later ethics codes



1962:

The **Kefauver-Harris Amendment** required that the new drugs have *proven efficacy and safety*.

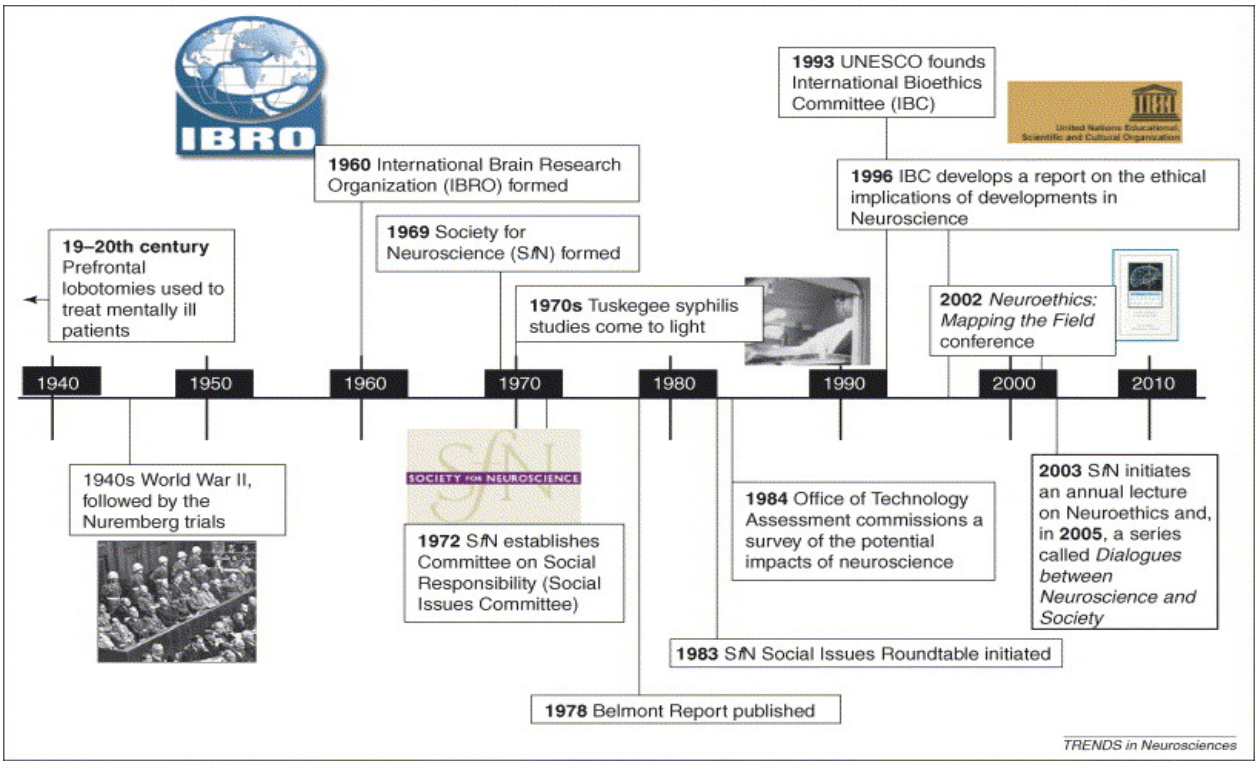
1964:

The 18th **World Medical Association** met in **Helsinki**, Finland, and issued **recommendations** to guide physicians in **biomedical research** involving human subjects, known as the **Declaration of Helsinki**.

The **Declaration of Helsinki** was developed by the ***World Medical Association*** (WMA) in **1964** as a guide for the world's physicians involved in human subjects research.

The **Declaration of Helsinki** recognized that **some, but not all** medical research is **combined with clinical care** and emphasized that **patients' participation** in research **should not** put them at a **disadvantage** with respect to **medical care**.

The **Declaration of Helsinki** also **legitimatized** research with **incapacitated** people, who **cannot give** their own **informed consent**, but for whom an **informed permission** can be obtained from a **legal guardian**.



The **Declaration of Helsinki** has been **revised** several times (**1975, 1983, 1989, 1996**), and has grown in length from 11 to 32 paragraphs (35 paragraphs in the **2008** version). Some additions to the 2000 version, especially those related to the use of **placebo controls** and obligations to assure **post-trial access** to tested interventions, have been the subject of **continued debate** among international researchers. (View Declaration of Helsinki in the Annex)

1968:

Beginning of the **Drug Efficacy Study Implementation** (DESI) program; **Electronic Product Radiation Control** provisions were added to the **FDC Act.**

1971:

The U.S. *Department of Health, Education and Welfare*, began to **require** the creation of **Institutional Review Boards** (IRBs) to evaluate **risk/benefits** ratio and study **ethics**.

1972:

The **abuses** in the **Tuskegee syphilis study** in Alabama were **revealed** and led to the **discussion** of research ethical principles.

1974:

The *National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research* was established, and the **National Research Act** was passed by Congress. This Act *required* establishment of **IRB**s at the local level and **IRB review** and **approval** of all *federally* funded research involving human participants.

1979:

The *National Commission for the Protection of Human Subjects of Biomedical & Behavioral Research* published **The Belmont Report**: Ethical Principles and Guidelines for Protection of Human Subjects of Research - a **guide** for U.S. research with human subjects.

The **Belmont Report** described ***three broad ethical principles*** that guide the conduct of research and form "the **basis** on which specific rules could be formulated, criticized, and interpreted." The **3 principles** are **respect** for persons, **beneficence**, and **justice**.

Respect for persons requires respect for the **autonomous decision making** of capable individuals and **protection** of those with **diminished autonomy**. The ***Informed consent*** is the **application** of this **principle in clinical research**.

Beneficence requires **not *deliberately* harming** others, as well as **maximizing benefits** and **minimizing harms**. This principle is applied to clinical research through **careful *risk–benefit evaluation*.**

Justice requires a **fair distribution** of the benefits and burdens of research and **equitable** selection of **research subjects**.

1981:

The **Common Rule:** Based on the recommendations of the *National Commission*, federal regulations for **research, funded** by the *Department of Health and Human Services* (DHHS) through governmental **grants**, were first promulgated in **1981.** They are found in **Title 45** of the U.S. *Code of Federal Regulations*, **Part 46** (**45 CFR 46**)

They stipulate the **membership** and **function of IRBs** and specify the **criteria** IRBs should **employ** when **reviewing** a research protocol and determining whether to **approve it**.

They also delineate the types of **information** that should be **included** in an **Informed Consent Document** (ICD) and **how** consent should be **documented**.

Subparts B, C and **D** of 45 CFR 46 describe **additional protections** for **foetuses**, **pregnant women**, **prisoners** and **children**.

These **regulations** were **extended** in **1991** as the ***Federal Common Rule***, applicable to research **funded** by any of the **17 U.S. federal agencies**.

1982:

The CIOMS Guidelines: The ***Council of International Organizations of Medical Sciences*** (CIOMS) in conjunction with the ***World Health Organization*** (WHO) issued **International Ethical Guidelines for Biomedical Research Involving Human Subjects**, first in **1982** and revised in **1993** and **2002**, that explored the application of the Helsinki principles to the "**special circumstances** of many **technologically developing countries."**

CIOMS **adopts** the **three ethical principles** spelled out in the **Belmont Report** and maintains most of the tenets of **Nuremberg** and **Helsinki**, but **provides** additional and valuable guidance and commentary on **externally sponsored research** and research with **vulnerable populations**.

The **CIOMS Guidelines** note an increase in **international research** and acknowledge different circumstances in non-Western **developing countries**, where there is generally **less focus** on the **individual** and **his rights**.

1988:

Expedited NDA approval - allowed requests for **expedited review** of ***generic drugs*** through Abbreviated New Drug Applications (ANDA)

1990:

***ICH GCP (International Conference for Harmonization of the Good Clinical Practices)* – Founded** in Brussels by the **EU**, the **US** & **Japan**. Its Headquarter is based in London, UK. **Canada**, **WHO** and countries of the **European Free Trade Association** are only o**bservers**.

The **ICH** developed mutually acceptable and scientifically sound **international quality standards** that governments *can* **transpose** in their clinical trial **regulations** involving **human subjects** in order to **harmonize** the regulations Worldwide and make the results of clinical tria**ls comparable** regardless of the country where they have been conducted

The **ICH guidelines** reduce or eliminate **duplicate tests** during research and development of new medicines in member countries. They **recommend** ways to achieve greater **harmonisation** in the **interpretation** and **application** of technical **guidelines** and requirements for **product registration**

1992:

Prescription Drugs User Fees Act – law, allowing FDA to *collect fees* from the pharmaceutical companies to fund the new drug approval process.

1993:

The *Albuquerque Tribune* made public the information about the 1940s secret radiation experiments with plutonium injections on human. **Indigent patients** and **children** with intellectual disabilities used as research subjects were given the **wrong information** about the nature of their treatment.

1995:

The President's Advisory Committee on Human Radiation Experiments concluded that some of the **radiation experiments** from the 1940s were **unethical**.

1997:

President Clinton issued a **formal apology** to the subjects of the Tuskegee syphilis experiments.

1997:

The **FDA Modernization Act** (FDAMA) – increased the ***access*** *to experimental therapies*, simplified and accelerated the **review process** of important new medications for **unmet** medical needs of serious diseases (HIV), expanded consumer **access to information** on unapproved or "*off-label*" drugs*****, strengthening **risk-based regulation** of medical devices, ensured *accurate* ***food labelling*** in case of health and nutrient content claims

1998:

ICH GCP Guidelines were **adopted** in several countries such as the EU, but **FDA** still uses them *only* as **guidance,** as they didn't yet become a part of the law.

***** **Off-label use** is the practice of prescribing drugs **for an unapproved indication**, not mentioned on the drug's label**.** Contrary to the popular notion, in the United States and in many other countries it is legal to use off-label drugs, including even controlled substances such as opiates. The FDA does not have the legal authority to regulate the practice of the medicine, and the physician may prescribe an off-label drug.

Under the *Food, Drug, and Cosmetic Act* (**FDAC**), manufacturers are prohibited from directly marketing drugs, other than those approved by FDA. In 1997 the *Food and Drug Administration Modernization Act* created an exception to the prohibition of off-label marketing and now manufacturers are able to provide medical practitioners with off-label information in response to an unsolicited request.

4. Canadian Drug Regulations History

- 1909 – ***The Proprietary or Patent Medicine Act*** –the first legislation to register medicines, which it limited to secret-formula, non-pharmacopoeia packaged 1919 medicines
- 1911– Establishment of ***Federal Department of Health***

- 1920 – ***Food and Drug Act*** – established specific requirements for licensing drugs
- 1947 –***Food and Drug Regulations*** were reworked, which led to today's regulations
- 1951 - manufacturers were required to file a **New Drug Submission** (NDS) prior to marketing their drugs

II. Important to remember (summary)

1. ***Nuremberg Code (1947)***: Developed after discovering that **non-consenting** war prisoners were subject to **coerced** medical **experiments** by **Nazi doctors**.

- **Principles**
    - **Informed consent** should be obtained **without coercion**
    - The **experiment** should be **useful and necessary**
    - Human studies should be based on **previous animal studies**
    - Physical and mental **suffering** should be **avoided**
    - **Death and disability** should ***not*** be expected **outcomes**
    - The **risk** should *not* exceed the **humanitarian importance** of the **solution**
    - Only **qualified scientists** should conduct medical research
    - Human subjects should be **free to end** an experiment **at any time**
    - The **scientist** in charge must be **prepared to end** an experiment **at any stage**.

2. ***Declaration of Helsinki (1964)***: A statement of **ethical principles** set forth by the **World Medical Association** (WMA) after 10 years of reflection and approved in Helsinki in 1964

- **Principles**
  - Defined **rules** for "**therapeutic**" and "**non-therapeutic**" research (*these two notions were abolished in October 2000*)
  - Allowed for **enrolling** certain patients in **emergency life-threatening** conditions **without consent**
  - In 1975 required **previous review and approval** of the study Protocol by an IRB
  - Concepts of **safeguarding animals** and **publication ethics** were also introduced
  - In 1983 allowed **legal guardians** to grant permission to enrol minors in trials
  - In 1996 Fourth revision **concerning placebos** added the phrase "*This does not exclude the use of inert placebo in studies of where no proven diagnostic or therapeutic method exists*"
  - After 6 revisions, in **April 2008** it was finally **replaced** by the **GCP Guidelines** (*Good Clinical Practices*), that **incorporate** the internationally accepted final version

3. ***The Belmont Report (1979)***: "**Ethical Principles and Guidelines for the Protection of Human Subjects of Research**'' prepared by the US *National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research,* after an **unethical study** on syphilis which enrolled **poor rural African-American men**, who were both **misinformed** about the purposes of the study and were ***not*** **treated** for the disease.

- **Principles**:
  - **Respect for persons**
    - use of the **Informed consent** process,
    - **safeguards** for **vulnerable populations** like children, pregnant women, and prisoners,
    - respect for persons **privacy and confidentiality**
  - **Beneficence**
    - **do not harm**, and
    - **maximise benefit** while minimising risk
  - **Justice**
    - **fairness**, and
    - **equitable selection** of the subjects for research, i.e. appropriate **inclusion/exclusion criteria** and a **fair** system of recruitment

4. ***ICH GCP - International Conference for Harmonization of the Good Clinical Practices* (1990): Founded** at a meeting in Brussels by the European Union, the United States & Japan, Headquarters are based in London. Canada, the World Health Organization and countries of the European Free Trade Association serve as **observers**.

- **Principles:**
  - **Develops mutually acceptable** and **scientifically sound international quality standards** that governments *can* adopt into regulation for clinical trials involving human subjects in order to **harmonize the regulations worldwide** and **make clinical trial results comparable** regardless of the country where they have been conducted
  - **Reduces** or **eliminates duplicate tests** during research and development of new medicines in member countries
  - **Recommends** ways to achieve greater **harmonisation** in the **interpretation** and **application** of **technical guidelines** and **requirements** for **product registration**

- **Approval steps of the ICH guidelines**:
  1) Discussion by **Expert Working Groups** (EWG) and consensus building
  2) The **Steering Committee** confirms the EWG consensus
  3) **Consultations and discussions** between regulatory authorities
  4) Adoption of an ICH **Harmonised Tripartite Guideline**
  5) **Implementation** in the legislation of the participating countries

III. New Products Regulatory Process: Short Overview

New therapeutic products can be **sold** only after they have successfully passed a **review process** to assess their **safety**, **efficacy** and **quality**.

The **Food and Drugs Administration** (FDA) in USA and the **Health Products and Food Branch** (HPFB) in Canada respectively **evaluate** and **monitor** the **safety, efficacy and quality** of thousands of products:

- human and veterinary **drugs**,
- medical **devices**,
- **natural health** products,
- **biologics** (vaccines, blood components, allergenics, etc),
- **food** and nutritional **supplements.**

The best **balance** between **benefits and risks** is sought when **approving** therapeutic products. **Public safety** is always the **priority number one**.

1. Clinical Trial Regulations

The FDA clinical trial regulations: US Code of Federal Regulations (CFR) Title 21, Part 50 & Part 56 (21 CFR 50 & 21 CFR 56)

The **regulations** for conducting trials on humans cover the requirements of **FDA** and **NIH,** which are part of the *Code of Federal Regulations* (**CFR**) including **21 CFR** and **45 CFR**, as well as **ICH-GCP** guidelines.

The U.S. *Food and Drug Administration* (**FDA**) regulations are found in **Title 21, CFR, Part 50**, **"*Protection of Human Subjects*,"** and **Part 56**, **"*Institutional Review Boards*,", and** contain regulations that are **similar**, but ***not identical***, to those found in the ***Common Rule*** **45 CFR 46**.

- **45 CFR** relates to **NIH** (National Institutes of Health) regulations for **federally-funded** studies. These regulations on research, financed by the *US Department of Health and Human Services* (**DHHS**), are also referred to as the **Common Rule.**
- The **FFDCA** (*Federal Food, Drug, and Cosmetic Act*) and the **PHSA** (*Public Health Service Act*) require that every new drug or biological product be **approved** before it can enter **interstate commerce** (i.e. to be exported to another province or country - *sold* and even *shipped* out of the state where it was manufactured).
- The sponsor is **required by law** to conduct clinical trials on human subjects in order to assess the *efficacy* and *safety* of the new product and to regularly **monitor** the compliance of trial **conduct** with the protocol and regulations during the trial. The FDA verifies only about **2%** of the trials **on a regular basis** and performs **for-cause inspections** if there are indications of **non-compliance** at certain sites.
- **Compliance** with **FDA regulations** is required for research that is testing a **drug, biologic,** or **medical device**, for which **FDA approval** will ultimately be **sought**.
- To make the **conduct of clinical trials possible** not only in one, but **in different states**, the FDA allows **an exemption** from this approval requirement through the 21 CFR **Part 312** (IND application). This part applies to **IND**s (investigational new drugs) and **biologics**, for which an **IND application** is in effect (has been deposited and granted).

  This exemption allows investigational products to be **legally shipped** *out of the state* of manufacture in order **to conduct** clinical *investigations* (for this purpose only, not for marketing).

- The **Part 312** regulations (IND application) address 2 aims:
  - the **protection** of human subjects from unreasonable research risks, and
  - the **reliability of the data** used to support the approval of the product.
- The **duration** of the **approval phase** of product development (clinical trials) is generally **from 2-3 to 10-12 years**, depending on nature of the product and intended clinical use.
- The Sponsor is **required by law** to monitor regularly the clinical trials on human subjects from the first enrolment in the trial, in order to proactively assure that the approved protocol is followed and the safety and the rights of the subjects are protected by the clinical investigators. The sponsor's **monitors** (**CRAs**) also verify if the site staff correctly understand the protocol, in order to assure valid usable data.
- **Everything** done during the trial has to be **documented,** in order to be reproducible if needed.
- **Legal requirements** on clinical trials are described in the **Food, Drug and Cosmetics Act** (FDCA) and can be found on FDA's web site www.fda.gov

- The equivalent institutions in Canada are the **Health Products and Food Branch** (HPFB) and its **Therapeutic Products Directorate** (TPD). Applicable law is the **Food & Drug Act** (FDA) which is based on the Section **E6** of ICH GCP and the US FDA regulations with some minor differences.
- **21 CFR** regulations relate to FDA requirements for Sponsors, Investigators and IRBs of clinical **trials financed by the industry**. They form the basis of the regulations, pertinent to conducting clinical trials in the United States. They include the six following parts that encompass the FDA **Good Clinical Practice** (GCP) sections of the CFR:

  21 CFR Part **11** - Electronic Records and Electronic Signatures
  21 CFR Part **50** - Protection of Human Subjects (Appendix G)
  21 CFR Part **54** - Financial Disclosure by Clinical Investigators
  21 CFR Part **56** - Institutional Review Boards (Appendix G)
  21 CFR Part **312** - Investigational New Drug Application (Appendix G)
  21 CFR Part **314** - Applications for FDA Approval to Market a New Drug

  These six parts also apply to **Canada**, where the regulations are based both on the **FDA** regulations, with some minor differences, and on the **ICH GCP** Guidelines.

- *The International Conference for Harmonization of the Good Clinical Practices* (**ICH GCP**): provides a **unified standard** for designing, conducting, recording and reporting on clinical trials involving human subjects. **Compliance** with the *Good Clinical Practices* ensures that the rights, well-being and confidentiality of human subjects are **protected** and that trial **data** are **credible**. The **ICH guidelines** can be found in the **Efficacy section** of the ICH official web site at:

http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html

1.1. Pre-marketing review process

Before a therapeutic product is **authorized for sale**, the manufacturer must get an authorization to perform a **clinical trial** on humans (clinical trial application; CTA). This allows the accumulation of sufficient **statistical data** about its **safety, efficacy** and **quality** based on a **pre-approved** scientifically sound and ethically acceptable **protocol**.

The authorized national **regulatory agency** performs a thorough **review** of the accumulated **scientific evidence** on the **safety, efficacy** and **quality** of pharmaceutical products by the ***Food and Drugs Administration*** (FDA) and ***National Institutes of Health*** (NIH) in the USA, and the ***Health Products and Food Branch*** (HPFB) in Canada respectively, in order t**o determine** whether the **risks** from **using the product** are **acceptable** in light of its **potential benefits.**

- **Approval** of the new products – If the product is found to be ***safe*** and ***effective*,** it can be **approved for sale**
- **Priority** is given to **public safety,** seeking the **best balance** between **risks and benefits**. If the **risks** from using the product are found to be **acceptable** in light of its **potential benefits,** then it can be **approved** for sale.

1.2. Clinical trial application (CTA)

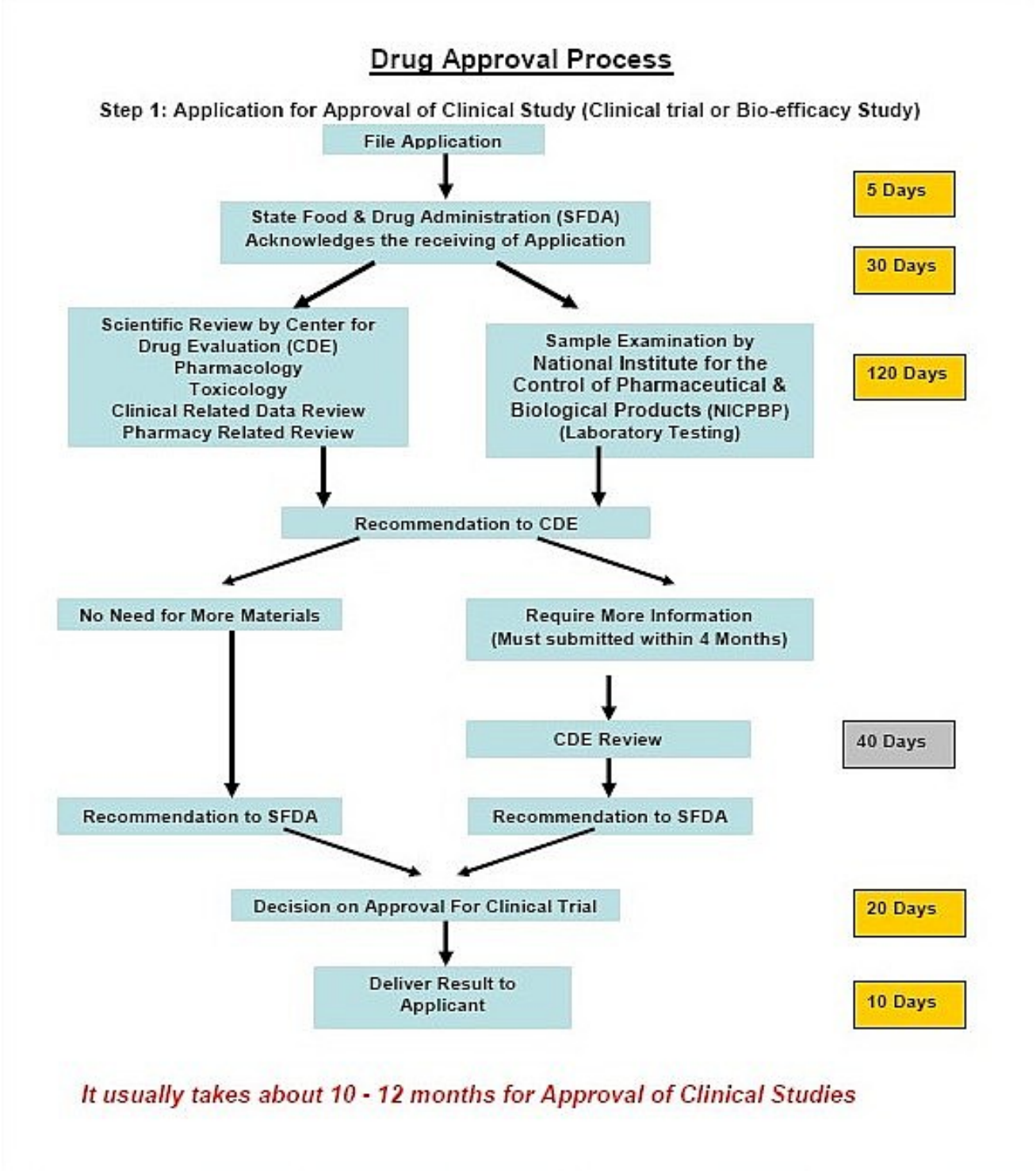
Before a clinical trial is **authorised to start**, all available **scientific information** is submitted in the **CTA** and **reviewed** by the regulatory agency to ensure that the trial is **properly designed** and that participants are **not exposed** to undue risk. In the USA this is called an ***Investigational New Drug Application*** (INDA or IND) and in Canada it is called a ***Clinical Trial Application*** (CTA)

In the case of **natural health products**, clinical trials are required only when certain new and untested **therapeutic claims** are made.

Clinical trials for **drugs** and **natural health products** must be conducted in accordance with the internationally accepted *quality standard* – the principles of the **Good Clinical Practices** (GCP) defined by the **International Conference of Harmonization** (ICH) and of the national **laws** and clinical trials **regulations.**

Clinical trials for **medical devices** must be conducted according to the **Medical devices guidelines**.

The regulations require the *Sponsor* to periodically **inspect (monitor)**the conduct of the trials and **assure** that everything is done according to the **regulations** and the pre-approved study **protocol**.



1.3. Expedited review for *minimal risk* procedures

The **Expedited Review** procedure, authorized in 21 CFR 56.110, allows research on human subjects, involving only ***minimal risk procedures***, to be **reviewed** by:

a. **the IRB chairperson** only**,** or

b. one **experienced reviewer** (or more)**,** designated by the chairperson from among members of the IRB.

The following **categories** of research activities on human subjects, carried out through **standard methods** and involving **only minimal risk**, may be reviewed by an IRB through the **Expedited Review procedure**:

- collection of **samples** of:

  - **blood** (by venipuncture, in pre-defined limited quantity for minors),
  - **deciduous teeth** or **extracted** permanent teeth,
  - supra- and sub-gingival **dental plaque** and **calculus**,
  - **external secretions** including **sweat** and **saliva**,
  - **placenta** at delivery, or
  - **amniotic fluid** at the time of membrane rupture,
  - **hair** and **nail clippings**, etc.

- collection of **data** through **non-invasive procedures** (not involving general anaesthesia or sedation), routinely employed in clinical practice, excluding procedures involving x-rays or microwaves.

1.4. New Drug Application/Submission

If the results of the clinical trials indicate that a new drug has a **potential therapeutic value**, which **outweighs** the risks (the **adverse effects** or **toxicity**), the manufacturer may seek **authorization to sell** the product by filing an application for marketing, called:

- **New Drug Application** (NDA) in USA, or
- **New Drug Submission** (NDS) in Canada

The **NDA**/**NDS** includes:

- the results of both the **pre-clinical and clinical studies**,
- details on the **production, packaging and labelling** of the drug,
- information about its **claimed therapeutic value,** conditions for use and **side effects**.

The New Drug Application/Submission (**NDA** or **NDS**) contains **all the scientific data,** gathered about the product's **safety, efficacy and quality** and typically involves between 100 and 800 binders of data (a semi-trailer of documents, delivered to the FDA).

This is what a **New Drug Application** (e.g., marketing application) looks like – and this is a small one:

1.4.1 Abbreviated NDA/NDS (ANDA or ANDS) for **generic products**

Generic products are manufactured by different companies after expiration of the original drug patent and contain **the same active substance** as the approved product. For **generic products** an **abbreviated New Drug Application/New Drug Submission** (ANDA or ANDS) is used, which typically involves only between 10 and 20 binders of data.

This application includes scientific information, which **compares** the generic product **with the brand-name product***, as well as providing details on the:

- *production*,
- *packaging*, and
- labelling of the generic drug.

The generic drug must deliver the **same amount** of medicinal ingredient and **at the same rate** as the brand-name product.

This comparison is usually done through comparative **Bioavailability studies** and takes a substantially **shorter time** than full scale trials.

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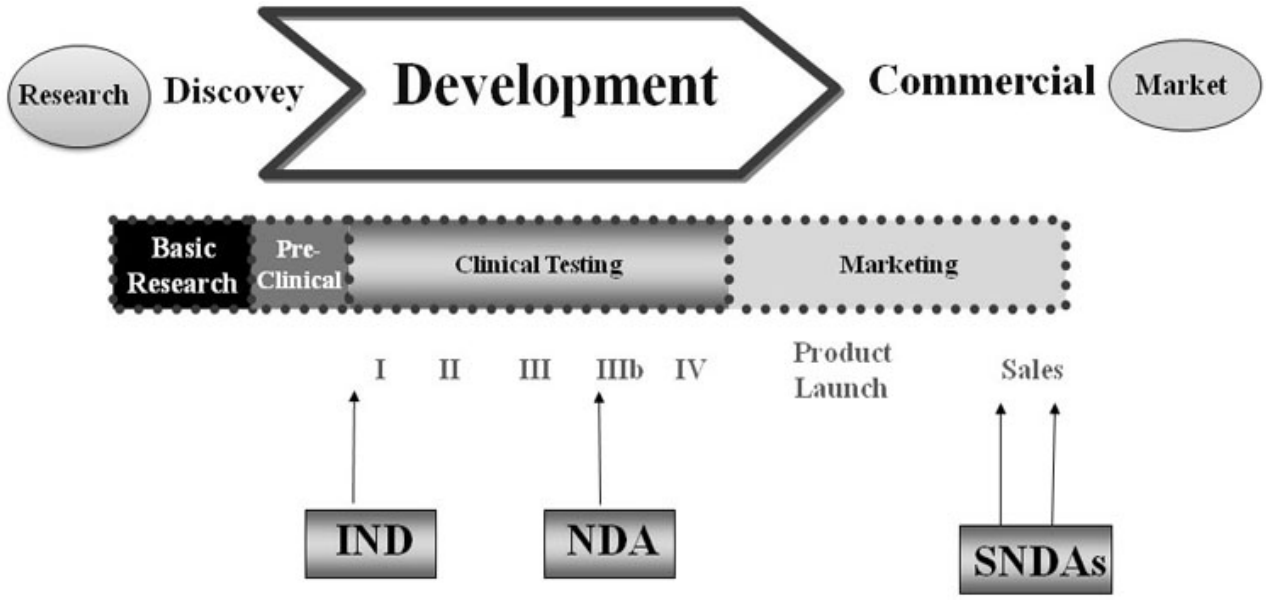
* New developed drugs are commonly called **brand-name products** because they have been **created** and **patented** by a company rather than reproduced by a competitor.

1.4.2. Supplemental NDA/NDS for changes in marketed products

If certain ***changes*** are made to *already-authorized* products, a **Supplemental NDA/NDS** (SNDA or SNDS) must be filed by the manufacturer.



Such **changes** might include:

- **dosage form** or **strength** of the drug,
- change in the **formulation**,
- method of **manufacturing,**
- change in the **labelling**
- **route of administration,** or
- **new indications** for use

Additional therapeutic applications are often discovered during the post-marketing *surveillance activities* and a new SNDA/SNDS must also be submitted if the manufacturer wants to **expand the indications** (therapeutic claims or conditions of use) for the drug product.

New **therapeutic indications** or possibilities of use in another **patient population** (women, children) are a good way to **extend the validity** of expiring **patents**, so companies are interested in proving such claims.

1.5. Medical devices

Based on the **level of risk** associated with their use, **Medical devices** are divided into 3 classes in the USA and 4 classes in Canada.

Class I devices present the lowest potential risk and do not require a medical device licence for their sale. Typical examples here are thermometers. However, the manufacturers of **Class I** devices must ensure they are **designed** and manufactured **to be safe** as defined under the *Medical Devices Regulations*.

Manufacturers of **Class II, III** (and **IV** in Canada) devices, which have more contact with body liquids and present higher risk of adverse effects, must obtain a **Medical Device Licence** before their products can be legally sold.

1.6. Errors and omissions

Errors and omissions are extremely **costly** for the Sponsor. If they are discovered during an FDA audit, they may lead to **discarding** a part of the collected information and even of the whole study.

Therefore the **Sponsor is very interested** in carefully verifying the conduct of the study to assure its **compliance**. This is also a regulatory requirement of FDA and it is the **main task** of the CRA.

If errors or omissions are **not discovered** in time and the investigational product is approved with unrevealed **serious adverse effects**, this may have disastrous consequences for the manufacturing company and may **cost** human lives and billions of dollars in **legal pursuits**. Recent examples are the case of VIOXX of Merck Frosst, Baycol of Bayer, Mediator in France etc.

2. Post-Market Surveillance, Inspection and Investigation

- Once the therapeutic products reach the market, they are **monitored** for **long-term** ***safety, efficacy*** and ***quality***. This process is called **Pharmacovigilance** and is needed to discover the rare and **extremely rare** adverse effects that appear only when millions of people use the drug and **cannot** be seen with the few thousand subjects in a clinical trial.
- The regulatory authorities **collect reports** of **suspected problems** from manufacturers, health care professionals or consumers, and they are evaluated to take appropriate **actions** if a serious health risk is identified.

- Such **actions** can range from **issuing warnings** to the public and the health care community, **reducing dosage,** excluding some **vulnerable sub-populations**, and up to **removing a product** from the market.

Rem: Annexes are for information only. Detailed discussion is in the next module

ANNEX I

The **10 principles** of the **Nuremberg code**

1. The **voluntary consent** of the human subject is absolutely essential. This means that the person involved should have **legal capacity** to give consent;
   - should be **able** to exercise **free power of choice,** without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other form of constraint or coercion;
   - should have **sufficient knowledge** and **comprehension** of the elements of the subject matter involved as to enable him/her to make an enlightened decision.
   - **before accepting,** the experimental subject should be **informed** about
     = the **nature**, **duration**, and **purpose** of the experiment;
     = the **method** and **means** by which it is to be conducted;
     = all **inconveniences** and **hazards** reasonable to be expected; and
     = the **effects** on his **health** or person, which may **possibly** result from his participation in the experiment.

   The **duty** and **responsibility** for ascertaining the **quality of the consent** rests upon each individual, **who initiates**, **directs** or **engages** in the experiment. It is a **personal duty** and responsibility, which **may not** be delegated to another person with impunity.
2. The experiment should be such as to provide **fruitful results** for the good of society, **unprocurable** by other methods or means of study, and **not** random and unnecessary in nature.
3. The **design** of the experiment should be based on results of **animal experimentation** and knowledge of the **natural history** of the disease (or other problem under study) and the anticipated results should **justify** the performance of the experiment.
4. The experiment should be conducted so as to **avoid** all unnecessary physical and mental **suffering** and **injury**.
5. **No experiment** should be conducted if there is a **reason** to believe that **death** or some **disabling injury** will occur; **except**, perhaps, in those experiments, where the experimental **physicians** also serve as subjects.
6. The **degree of risk** to be taken should **never exceed** that determined by the **humanitarian importance** of the problem to be solved by the experiment.
7. Proper **preparations** should be made and **adequate facilities** provided to **protect** the experimental subject against **even remote** possibilities of injury, disability, or death.
8. The experiment should be conducted only by **scientifically qualified** persons. The **highest degree** of skills and care should be required through **all stages** of the experiment of those **who conduct** or engage in the experiment.
9. The human subject should be **at liberty** to bring the experiment to **an end** if he has reached the physical or mental state where **continuation** of the experiment seems to him to be impossible.
10. During the course of the experiment **the scientist in charge** must be prepared to **terminate** the experiment **at any stage**, if he has reason to **believe**, based on his good faith, skills and judgment, that continuation of the experiment is **likely to result** in injury, disability, or death to the experimental subject.

ANNEX II

Declaration of Helsinki

The **Declaration of Helsinki** states the following **ethical principles** for medical research involving **human subjects,** including research on **identifiable human material** and **data:**

1. It is the **duty of the physician** to promote and **safeguard the health** of the patients, who are involved in medical research. The Declaration of Geneva of the WMA binds the physician with the words, "*The health of my patient will be my first consideration*," and the International Code of Medical Ethics declares that, "*A physician shall act in the patient's best interests when providing medical care*."
2. **Medical progress** is based on research that ultimately **must include** studies involving human subjects. Populations that are **underrepresented** in medical research should be provided **appropriate access** to participation in research.
3. In medical research involving human subjects, the **well-being** of the research subject must take **precedence** over all other interests.
4. The primary **purpose** of medical research involving human subjects is to **understand** the causes, development and effects of diseases and **improve** preventative, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best **current interventions** must be **evaluated continually** through research for their safety, effectiveness, efficiency, accessibility and quality.
5. In **medical practice** and in **medical research**, most interventions **involve risks** and **burdens**.
6. Medical research is subject to **ethical standards** that promote **respect** for all human subjects and protect their **health and rights**. Some research populations are particularly **vulnerable** and need **special protection**. These include those who **cannot give or refuse consent** for themselves and those who may be **vulnerable to coercion** or **undue influence**.
7. Physicians should consider the **ethical, legal and regulatory norms** and **standards** for research involving human subjects **in their own countries** as well as applicable **international norms and standards**.
8. **No national or international** ethical, legal or regulatory requirement **should reduce or eliminate** any of the **protections** for research subjects set forth in this Declaration.
9. It is the **duty of physicians** who participate in medical research to **protect** the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.
10. **Medical research** involving human subjects must **conform** to generally accepted **scientific principles**, be based on a **thorough knowledge** of the **scientific literatur**e, other relevant sources of

information, and adequate **laboratory** and, as appropriate, **animal experimentation**. The welfare of animals used for research must be respected.

11. Appropriate **caution** must be exercised in the conduct of medical research that may **harm** the **environment**.

12. The **design** and **performance** of each research study involving human subjects must be **clearly described** in a research **protocol**. The protocol should contain a statement of the **ethical considerations** involved and should indicate **how** the principles in this Declaration have been addressed. The protocol should include information regarding **funding**, **sponsors**, institutional **affiliations**, other **potential conflicts of interest**, **incentives for subjects** and provisions for **treating and/or compensating** subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for **post-study access** by study subjects to **interventions** identified as **beneficial** in the study or access to other **appropriate care or benefits.**

13. The research **protocol** must be submitted for **consideration, comment, guidance** and **approval** to a **Research Ethics Committee** *before* the study begins. This committee must be **independent** of the researcher, the sponsor and any other **undue influence**. It must take into consideration the **laws** and **regulations** of the country or countries, in which the research is to be performed as well as applicable international norms and standards but these must **not** be allowed **to reduce or eliminate** any of the **protections** for research subjects. The committee must have the **right to monitor** ongoing studies. The **researcher** must provide **monitoring information** to the committee, especially information about any **Serious Adverse Events**. No change to the protocol may be made **without consideration** and **approval** by the committee.

14. Medical research involving human subjects must be **conducted** only by individuals with the appropriate **scientific training** and **qualifications**. Research on patients or healthy volunteers requires the **supervision** of a competent and **appropriately qualified** physician or other health care professional. The **responsibility** for the protection of research subjects must always rest with the **physician** or other health care professional and **never** the research subjects, even though they have given consent.

15. Medical research involving a **disadvantaged** or **vulnerable** population or community is only justified if the research is responsive to the **health needs** and **priorities** of this population or community and if there is a **reasonable likelihood** that this population or community will **benefit** from the results of the research.

16. Every medical research study involving human subjects must be **preceded** by careful **assessment** of **predictable risks** and burdens to the individuals and communities involved in the research **in comparison** with **foreseeable benefits** to them and to other individuals or communities, affected by the condition under investigation.

17. Every **clinical trial** must be **registered** in a publicly accessible **database** *before* **recruitment** of the first subject.

18. Physicians may not participate in a research study involving human subjects unless they are confident that the **risks** involved have been **adequately assessed** and can be satisfactorily **managed**. Medical research involving human subjects may only be **conducted** if the i**mportance** of the **objective** outweighs the **inherent risks** and burdens to the research subjects.

19. Physicians must **immediately stop** a study when the **risks** are found to **outweigh** the **potential benefits** or when there is **conclusive proof** of positive and beneficial results.

20. Participation of mentally **competent individuals** as subjects in medical research must be **voluntary**. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

21. Every **precaution** must be taken to protect **the privacy** of research subjects and the **confidentiality** of their **personal information** and to **minimize the impact** of the study on their physical, mental and social **integrity**.

22. In medical research involving competent human subjects, each potential subject must be **adequately informed** of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the **anticipated benefits** and **potential risks** of the study and the **discomfort** it may entail, and **any other** relevant aspects of the study.

23. The potential subject must be informed of the **right to refuse** to participate in the study or **to withdraw consent** to participate **at any time** without reprisal.

24. Special attention should be given to the **specific information needs** of potential subjects as well as to the **methods to deliver** the information. After ensuring that the potential subject has **understood** the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given **informed consent**, preferably in writing. If the consent **cannot be expressed** in writing, the **non-written consent** must be formally **documented** and **witnessed**.

25. For medical research using identifiable **human material or data**, physicians must normally seek **consent for the collection**, analysis, **storage** and/or reuse. There may be situations where consent would be **impossible** or **impractical** to obtain for such research or would **pose a threat** to the **validity** of the research. In such situations the research **may be done only** after consideration and **approval** of a **Research Ethics Committee**.

26. When seeking informed consent, the physician should be particularly cautious if the potential subject is **in a dependent relationship** with the physician or may consent **under pressure**. In such situations the informed consent should be sought by **another** appropriately qualified individual, who is completely **independent** of this relationship.

27. For a potential research subject who is **incompetent**, the physician must seek informed consent from the **Legally Authorized Representative** (LAR). These individuals should **not be included** in a research study that has **no likelihood of benefit** for them unless it is intended to promote the health of the population, represented by the potential subject, the research **cannot** be performed with competent persons, and the research entails **only minimal risk** and minimal burden.

28. When a potential research subject, who is **deemed incompetent**, is able to give **assent** to participation in research, the physician **must seek** that assent **in addition** to the consent of the **Legally Authorized Representative** (LAR). The potential subject's **dissent** should be **respected**.

29. Research involving subjects who are **physically or mentally incapable** of giving consent, for example, **unconscious** patients, may be done **only** if the physical or mental condition that prevents giving informed consent is a **necessary characteristic** of the research population. In such circumstances the physician should seek informed consent from the **Legally Authorized Representative**.

If such representative is **not available** and if the research **cannot be delayed**, the study **may proceed** without informed consent if the **specific reasons** for involving subjects unable to give informed consent have been **stated** in the research **protocol** and the study has been **approved** by a Research Ethics Committee. However, **consent** from the subject or a Legally Authorized Representative **to remain** in the research should be obtained **as soon as possible**

30. **Authors, editors and publishers** all have **ethical obligations** with regard to the **publication** of the results of research. Authors have a duty to **make publicly available** the results of their research on human subjects and are accountable for the **completeness** and **accuracy** of their reports. They should adhere to accepted guidelines for **ethical reporting**. Also, **negative** and **inconclusive** as well as **positive** results should be published or otherwise made **publicly available**. Sources of funding, institutional affiliations and conflicts of interest should be **declared** in the publication. Reports of research **not in accordance** with the principles of this Declaration should **not be accepted** for publication.

31. The physician may **combine** medical **research** with medical **care** only to the extent that the research is **justified** by its potential **preventive, diagnostic or therapeutic value** and if the physician has **good reason** to believe that participation in the research study will not **adversely affect** the health of the patients, who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be **tested** against those of the **best current proven intervention**, *except* in the following circumstances:

- The use of **placebo**, or **no treatment**, is acceptable in studies where **no current proven intervention** exists; or
- Where for convincing and **scientifically sound** methodological reasons, the use of placebo is **necessary** to determine the **efficacy** or **safety** of an intervention and the patients who receive placebo or no treatment will **not** be subject to any **risk** of serious or irreversible **harm**. Extreme care must be taken to **avoid abuse** of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the **outcome** of the study and to **share any benefits** that result from it, for example, **access to interventions** identified as **beneficial** in the study or to other appropriate care or benefits.

34. The physician must **fully inform** the patient which **aspects of the care** are **related** to the research. The **refusal** of a patient to participate in a study or the patient's **decision to withdraw** from the study must **never interfere** with the patient-physician **relationship**.

35. In the treatment of a patient, where proven interventions **do not exist** or have been **ineffective**, the physician, after seeking **expert advice**, with informed consent from the patient or a legally authorized representative, **may use** an unproven intervention if in the physician's judgment it offers **hope of saving life**, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its *safety* and *efficacy*. In all cases, **new information** should be **recorded** and, where appropriate, made **publicly available.**

Annex III

ICH GCP Efficacy Guidelines (Section E)

E1	Extent of Population Exposure to Assess **Clinical Safety** for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions
E2A	Definitions and Standards for **Expedited Reporting** (Clinical Safety Data Management)
E2B	Data Elements for Transmission of Individual Case **Safety Reports** (Data Management)
E2C	Clinical Safety Data Management: Periodic **Safety Update Reports** for Marketed Drugs Addendum to E2C: Periodic **Safety Update Reports** for Marketed Drugs **(in E2C(R1))**
E2D	Post-Approval Safety Data Management: Definitions & Standards for **Expedited Reporting**
E2E	Pharmacovigilance Planning
E2F	Development of Safety Update Reports
E3	Structure and Content of **Clinical Study Reports**
E4	**Dose-Response** Information to Support Drug Registration
E5	**Ethnic Factors** in the Acceptability of Foreign Clinical Data
E6	**Good Clinical Practice**
E7	Studies in Support of Special Populations: **Geriatrics**
E8	General Considerations of **Clinical Trials**
E9	**Statistical Principles** for Clinical Trials
E10	Choice of **Control Group** and Related Issues in Clinical Trials
E11	Clinical Investigation of Medicinal Products in the **Pediatric Population**
E12	Principles for Clinical Evaluation of New **Antihypertensive Drugs**
E14	The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for **Non-Antiarrhythmic Drugs**
E15	Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, **Genomic Data** and Sample Coding Categories
E16	**Genomic Biomarkers** Related to Drug Response: Context, Structure and Format of Qualification Submissions

Annex IV

KEY LEARNING POINTS

Overview of the Regulatory process

(Optional reading)

This part is included to **refresh** and enlarge the material, covered till now to establish the general picture and show it in a more systematic manner.

During the **clinical development** of a product **under an IND** (i.e. testing on humans of drug or biological product but not devices, which have different regulations), additional product process development and **testing/validation** are performed. Also, additional **preclinical** information is obtained regarding the safety and efficacy of the product **at the same duration** of application as during the expected phase of the clinical trial.

If there are certain **changes** to the product, the preclinical studies, or the clinical Protocols, FDA regulations require the Sponsors to submit an **amendment** to the IND. These include changes that affect the safety, scope, and scientific quality of the clinical Protocol, including its data and analyses, or the addition of a new Protocol.

Regarding the clinical development of a product, there are generally **three phases** of pre-marketing clinical research to examine the safety and efficacy of a drug or biological product and a **fourth phase** of post market surveillance when accelerated approval has been granted.

The first phase (**phase I** studies) consists of small, **dose escalation** studies that can include either patients with a particular disease or condition or normal volunteers with the primary goal to assess safety of the product using a particular route of administration. In addition, some phase I studies may examine pharmacokinetics and drug metabolism.

The Sponsor can request an **End-of-phase I meeting** to discuss the collected data and the drug development plan for further trials in next phase.

Phase II studies consist of one or more **moderately sized** clinical studies for a particular patient population. The primary goal of these studies is to provide preliminary **evidence** of efficacy at different dosing and supplementary data on safety.

Generally, the Sponsor **meets** with the FDA at the end of phase II studies to discuss the outcomes of the studies and the design and analysis plan for the final phase of clinical development.

Trials in the last phase of clinical development, **phase III,** are generally *larger studies* and are designed to evaluate the risk and benefit of a product in a particular patient population for a defined clinical indication.

The safety and efficacy data from these studies are generated to support **marketing approval** and to provide information to write the instructions for the use of the product for a particular indication.

Some key issues for the **design, conduct, and analysis** of clinical trials include:

- primary and secondary end points,
- study population,
- stratification by gender, age or other factor,
- randomization,
- blinding,
- sample size,
- participant adherence, and
- methods for study analysis

Information, gathered during the conduct of these clinical trials may affect product specifications and production, raise additional preclinical issues, and sometimes require additional clinical studies.

After completion of the phase III or **pivotal studies**, the Sponsor again meets with the FDA to discuss a marketing application submission.

At any stage in the clinical development of the product, different issues or need of changes may arise that require additional product development work, preclinical studies, or additional clinical data.

The **content and format** of IND applications is specified in 21 CFR 312.23. They must include:

- a table of content
- introduction, incl. biological rationale and general investigational plan;
- chemistry, manufacturing and control information (**CMC**);
- pharmacology and **toxicology** information;
- previous **human experiences** and other relevant information,
- **Protocol** and **Investigator's brochure**

Once the original IND is submitted, the FDA has 30 days to review and notify the submitter or Sponsor whether or not the trial has been placed on Clinical Hold. This **initial review** is aimed primarily at an evaluation of the **safety** of the product for human clinical trials.

During those 30 days, the Sponsor **may *not* initiate** the clinical trial. If in this time frame FDA has not expressed any safety concerns regarding the study, or the Sponsor does not hear from

the FDA, then the IND is allowed to proceed. (In Canada a *No objection letter* should be received to start the study)

However, if the FDA has some **concerns** about the IND, it may be placed on **clinical hold.** A **Clinical Hold Notice** is issued to notify the Sponsor that the clinical trial(s) **may *not* begin** until certain deficiencies are resolved.

Phase I studies may be placed on **Clinical Hold** for any of five reasons:

1. Subjects would be exposed to unreasonable risk of illness or injury.
2. There is insufficient information to assess the risk to subjects.
3. The Investigator's Brochure is inadequate.
4. The clinical investigators are not qualified to carry out the study.
5. The study of a life-threatening disease excludes eligible men and women with reproductive potential (21 CFR 312.42)

Phase II and III studies may be put on **clinical hold** for any of the reasons discussed above. They may also be placed on hold if the study design is inadequate to achieve the stated purpose of the study.

If the IND is placed on **Clinical Hold**, the Sponsor is notified immediately *by phone*. This notification is followed with a *letter* that specifically states the deficiencies. FDA provides advice on the appropriate corrective actions. It is then up to the Sponsor to correct the deficiencies and notify the FDA of the corrections in a Clinical Hold Response Letter.

Once the Sponsor submits a complete **response** to the clinical hold, the FDA then has another 30 days to review the information in the clinical hold response letter but there is **no automatic release** from clinical hold.

In this case, if the Sponsor does not hear from the FDA in 30 days after sending the response to the clinical hold, the clinical trial still **cann*ot* start**. When the review is finished, the Sponsor is **notified** that the trial(s) may proceed, or that there are continuing deficiencies.

If **major changes** are made to the product or in the clinical Protocol, the FDA regulations also require that the Sponsor files an **IND amendment.** These include changes in **product formulation** and changes in the **Protocol** that affect *safety*, scientific *quality*, or the *scope* of the clinical trial.

The Sponsor must also file an **annual report** that includes all **changes** and **results** of the study.

Several mechanisms are available to **accelerate** the drug development process, such as:

- **Expedited review** for severe and life-threatening illnesses (21 CFR 312 Subpart E);
- **Accelerated approval** (21 CFR 314.510 Drugs and 601.41 Biologics), and
- **Fast track** development programs.

1. Expedited review procedures to speed-up the development, evaluation, and marketing of new therapies intended to treat persons with **life-threatening** and **severely debilitating** illnesses, which have **no acceptable alternatives** are described in Subpart E of 21 CFR 312

Under the Subpart E regulations for investigational new drugs, drug development is considered a **continuous process** from early preclinical and clinical studies through submission of a marketing application, which includes **early consultations**, submissions of treatment Protocols, and risk–benefit analysis considerations for review of marketing applications as specified in Subpart E of 21 CRF 312.

The regulations emphasize the critical nature of this close **early communication** between the Agency and a sponsor, outline procedures such as **pre-IND** and end of **phase I meetings** as methods to improve the efficiency of preclinical and clinical development, and focus on efforts by the Agency and the sponsor to reach early **agreement on the design** of the major clinical efficacy studies that will be needed to support approval. These provisions have been included and *expanded* in the **Fast Track** Program.

2. The Fast Track Guidance for *unmet medical needs* was originally developed in 1998 and was revised in 2004. The purpose of this program is to facilitate the development of new drugs and biological projects and to expedite the review of new drugs and biologics, that are intended to treat serious and life threatening conditions and that **demonstrate the potential** to address unmet medical needs.

In the guidance, the Agency defined an **unmet medical need** as a "medical need that is not addressed adequately by an existing therapy."

When there is available therapy for the condition, the **Fast track** drug development program would address **unmet medical needs**, if it was evaluated to potentially achieve any of the following:

- **Improved effects** on **serious outcomes** of the condition that are **affected** by alternative therapies
- **Effects on serious outcomes** of the condition, **not affected** or **not known** to be affected by the alternatives therapies
- Ability to provide benefits in patients, who are **unable to tolerate** or are **unresponsive** to alternative agents, or ability to be effective **in combination** with other critical agents, that **can't be combined** with available therapy
- Ability to provide **similar benefits**, to those of alternative therapies, while **avoiding serious toxicity**, which is present in existing therapies, or avoiding **less serious toxicity**, that is **common** and **causes discontinuation** of treatment of a serious disease
- Ability to provide benefits, **similar** to those of alternatives, but with **improvement in some factors**, such as *compliance* or *convenience*, that is shown to lead to improved effects on serious outcomes.

The **Fast Track Guidance** describes:

- the **definitions** for serious and life threatening conditions and
- the **potential** to address **unmet needs**,
- the process of **designation**, and
- the programs for **expediting** the development and review of new drugs and biologics.

3. Accelerated approval (21 CFR 314.510 and 601.41) is an FDA approval based on a **surrogate end-point** that is **reasonably likely** to predict clinical benefits, or **clinical effects**, that are **not the desired benefit**, but are **reasonably likely** to *predict* such benefit.

If a product is approved by **Accelerated Approval** and made commercially available, the Sponsor **must conduct** a **phase IV** (post marketing) study to **validate** the surrogate end-point and **prove** the clinical benefit.

There are also a number of **Expanded Access Programs** that are available under IND, including "**Parallel track**" and **Treatment IND** (21 CFR 312.34 and 312.35).

4. The Parallel Track Policy developed by the U.S. Public Health Service was in response to the **AIDS/HIV** epidemic to permit wider availability of **experimental agents**.

Under this policy, **patients with AIDS**, whose condition prevents them from participating in controlled clinical trials, can receive investigational drugs shown in preliminary studies to be **potentially useful**. It can also be used for other clinical conditions when appropriate.

In 1987 FDA created a special **"AA" priority category** to classify all applications for **potential AIDS therapies** and to ensure that these products receive the highest **priority in the review** process.

While the **Parallel Track Policy** is still technically available, it has *not* been used since 1994 because **Treatment INDs** have proven to be a **more practical** mechanism to provide treatment access.

5. The Treatment IND, 21 CFR 312.305(a), revised and expanded in Oct. 2009, allows:

- the **treatment use** of a drug or biologic, that is **not approved** for marketing, but is made available for clinical investigation ***outside of*** **a clinical trial** under a **treatment Protocol**, or

- treatment of an investigational new drug application (IND) for ***serious*** *or* ***immediately life threatening*** *disease* conditions in patients, for whom ***no*** **comparable** or **satisfactory alternative** therapy is available.

The **Treatment IND** is generally made available under a **treatment Protocol**, or **Treatment investigational new drug application** (IND), when the drug/biologic is **already *well into* phase III** investigation, or all clinical trials have been **completed**, after the **accumulation** of adequate safety data and there is **evidence of likely effectiveness**; however, it can also be made available in earlier phases if appropriate.

According to 21 CFR 312.305(a) regulations, the investigational drug can be used in a **Treatment IND**, only if the following **criteria** are met:

- The patient(s) to be treated have a **serious** or immediately life-threatening disease or condition, and there is ***no* comparable or satisfactory alternative** therapy to *diagnose*, *monitor*, or *treat* the disease or condition;
- The **potential benefit** for the patient **justifies** the potential risks of the treatment use and those potential risks are **not unreasonable** in the context of the disease or condition to be treated; and
- The investigational drug for the requested use **will not interfere** with the initiation, conduct, or completion of clinical investigations, which could support marketing approval of the expanded access use, or will not compromise the potential development of the **expanded access** use.

Further, in accord with 21 CFR 312.320, FDA must determine that:

- The drug is being investigated in a **controlled clinical trial** under an **IND** application, designed to support a marketing application for the **expanded access use**, or all clinical trials of the drug have been **completed**;
- The sponsor is actively **pursuing marketing approval** of the drug for the **expanded access use** with due diligence; and
- When the expanded access use is for a *serious disease* or condition, there is **sufficient clinical evidence** of *safety* and *effectiveness* to support the expanded access use.

  Such evidence consists of **data from phase III trials**, but could also consist of **compelling** (non-questionable) data from completed **phase II trials**; or
- When the expanded access is for an *immediately life-threatening* disease or condition, the available **scientific evidence**, taken as a whole, provides a reasonable basis to conclude that the drug **may be effective** for the expanded access use and **would not expose** patients to an *unreasonable* and *significant* **risk** of illness or injury.

  This **evidence** would ordinarily consist of clinical data from phase III or phase II trials, but could be based on more preliminary clinical evidence.