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SCHOOL OF BIO AND CHEMICAL ENGINEERING

DEPARTMENT OF CENTRE FOR MOLECULAR AND NANOMEDICAL SCIENCES

UNIT – I - Ethical Aspects – SMB5303

Ethical principles underlined research involving human subjects

Any research using the human beings as subjects of medical or scientific research or experimentation shall bear in mind the following principles –

I. **Principles of essentiality** whereby, the research entailing the use of human subjects is considered to be absolutely essential after a due consideration of all alternatives in the light of the existing knowledge in the proposed area of research and after the proposed research has been duly vetted and considered by an appropriate and responsible body of persons who are external to the particular research and who, after careful consideration, come to the conclusion that the said research is necessary for the advancement of knowledge and for the benefit of all members of the human species and for the ecological and environmental wellbeing of the planet.

II. **Principles of voluntariness**, informed consent and community agreement whereby, research subjects are fully apprised of the research and the impact and risk of such research on the research subject and others; and whereby the research subjects retain the right to abstain from further participation in the research irrespective of any legal or other obligation that may have been entered into by such human subjects or someone on their behalf, subject to only minimal restitutive obligations of any advance consideration received and outstanding. Where any such research entails treating any community or group of persons as a research subject, these principles of voluntariness and informed consent shall apply, mutatis mutandis, to the community as a whole and to each individual member who is the subject of the research or experiment. Where the human subject is incapable of giving consent and it is considered essential that research or experimentation be conducted on such a person incompetent to give consent, the principle of voluntariness and informed consent shall continue to apply and such consent and voluntariness shall be obtained and exercised on behalf of such research subjects by someone who is empowered and under a duty to act on their behalf. The principles of informed consent and voluntariness are cardinal principles to be observed throughout the research and experiment, including its aftermath and applied use so that research subjects are continually kept informed of any and all developments in so far as they affect them and others. However, without in any way undermining the cardinal importance of obtaining informed consent from any human subject involved in any research, the nature and form of the consent and the evidentiary requirements to prove that such consent was taken, shall

depend upon the degree and seriousness of the invasiveness into the concerned human subject's person and privacy, health and life generally, and, the overall purpose and the importance of the research.

III. **Principles of non-exploitation** whereby as a general rule, research subjects are remunerated for their involvement in the research or experiment; and, irrespective of the social and economic condition or status, or literacy or educational levels attained by the research subjects kept fully apprised of all the dangers arising in and out of the research so that they can appreciate all the physical and psychological risks as well as moral implications of the research whether to themselves or others, including those yet to be born. Such human subjects should be selected so that the burdens and benefits ofthe research are distributed without arbitrariness, discrimination or caprice. Each research shall include an in-built mechanism for compensation for the human subjects either through insurance cover or any other appropriate means to cover all foreseeable and unforeseeable risks by providing for remedial action and comprehensive aftercare, including treatment during and after the research or experiment, in respect of any effect that the conduct of research or experimentation may have on the human subject and to ensure that immediate recompense and rehabilitative measures are taken in respect of all affected, if and when necessary.

IV. **Principles of privacy and confidentiality** whereby, the identity and records of the human subjects of the research or experiment are as far as possible kept confidential; and that no details about identity of said human subjects, which would result in the disclosure of their identity, are disclosed without valid scientific and legal reasons which may be essential for the purposes of therapeutics or other interventions, without the specific consent in writing of the human subject concerned, or someone authorised on their behalf; and after ensuring that the said human subject does not suffer from any form of hardship, discrimination or stigmatisation as a consequence of having participated in the research or experiment.

V. **Principles of precaution and risk minimisation** whereby due care and caution is taken at all stages of the research and experiment (from its inception as a research idea, its subsequent research design, the conduct of the research or experiment and its applicative use) to ensure that the research subject and those affected by it are put to the minimum risk, suffer from no irreversible adverse effects and, generally, benefit from and by the research or experiment; and that requisite steps are taken to ensure that both professional and ethical reviews of the research are undertaken at appropriate stages so that further and

specific guidelines are laid down, and necessary directions given, in respect of the conduct of the research or experiment.

VI. **Principles of professional competence** whereby, the research is conducted at all times by competent and qualified persons who act with total integrity and impartiality and who have been made aware of, and are mindful of, the ethical considerations to be borne in mind in respect of such research or experiment.

VII. **Principles of accountability and transparency** whereby, the research or experiment will be conducted in a fair, honest, impartial and transparent manner after full disclosure is made by those associated with the research or experiment of each aspect of their interest in the research, and any conflict of interest that may exist; and whereby, subject to the principles of privacy and confidentiality and the rights of the researcher, full and complete records of the research inclusive of data and notes are retained for such reasonable period as may be prescribed or considered necessary for the purposes of post-research monitoring, evaluation of the research, conducting further research (whether by the initial researcher or otherwise) and in order to make such records available for scrutiny by the appropriate legal and administrative authority, if necessary.

VIII. **Principles of the maximisation of the public interest and of distributive justice** whereby, the research or experiment and its subsequent applicative use are conducted and used to benefit all human kind and not just those who are socially better off but also the least advantaged; and in particular, the research subject themselves.

IX. **Principles of institutional arrangements** whereby, there shall be a duty on all persons connected with the research to ensure that all the procedures required to be complied with and all institutional arrangements required to be made in respect of the research and its subsequent use or application are duly made in a bonafide and transparent manner; and to take all appropriate steps to ensure that research reports, materials and data connected with the research are duly preserved and archived.

X. **Principles of public domain** whereby, the research and any further research, experimentation or evaluation in response to, and emanating from such research is brought into the public domain so that its results are generally made known through scientific and other publications subject to such rights as are available to the researcher and those associated with the research under the law in force at that time.

XI. **Principles of totality of responsibility** whereby the professional and moral responsibility, for the due observance of all the principles, guidelines or prescriptions laid down generally or in respect of the research or experiment in question, devolves on all

those directly or indirectly connected with the research or experiment including the researchers, those responsible for funding or contributing to the funding of the research, the institution or institutions where the research is conducted and the various persons, groups or undertakings who sponsor, use or derive benefit from the research, market the product (if any) or prescribe its use so that, inter alia , the effect of the research or experiment is duly monitored and constantly subject to review and remedial action at all stages of the research and experiment and its future use.

XII. **Principles of compliance** whereby, there is a general and positive duty on all persons, conducting, associated or connected with any research entailing the use of a human subject to ensure that both the letter and the spirit of these guidelines, as well as any other norms, directions and guidelines which have been specifically laid down or prescribed and which are applicable for that area of research or experimentation, are scrupulously observed and duly complied with. These 12 principles laid down under Statement on General Principles are common to all areas of biomedical research. The specific issues are mentioned under relevant topics.

Institutional Review Board (IRB)

The Independent Ethics Committee also referred to as Institutional Review Board (IRB) in many countries, serves as an independent representative and competent body to review, evaluate and decide on the scientific and ethical merits of research proposals. The primary purpose of this committee is to protect the rights, safety and wellbeing of human subjects who participate in a research project. The Ethics Committees are entrusted with the initial review of the proposed research protocols prior to initiation of the projects and also have a continuing responsibility of regular monitoring of the approved programmes till the same are completed. Such an ongoing review is in accordance with the Declaration of Helsinki and all the international guidelines for biomedical research.

Basic Responsibilities

The basic responsibility of an IEC is to ensure a competent review of all ethical aspects of the proposals received and free from any bias and influence that could affect their objectivity. IECs should ensure the scientific soundness of the proposed research projects through appropriate Scientific Review Committees and provide advice to the researchers on all aspects of the safety and welfare of the research participants. In smaller institutions the Ethics Committees may take up the

dual role of Scientific and Ethical Review, the scientific evaluation should ensure technical excellence of the proposed study.

The responsibilities of an IEC can be defined as follows:

1. To protect the dignity, rights and wellbeing of the potential research participants.
2. To ensure that universal ethical values and international scientific standards are expressed in terms of local community values and customs.
3. To assist in the development and the education of a research community responsive to local health care requirements.

Composition

IECs should be multidisciplinary and comprise of members from different sectors of society. Independence and competence are the two hallmarks of an IEC.

The number of persons in an Ethics Committee should have at least seven members; however a minimum of five persons is required to compose a quorum. Twelve to fifteen is the maximum recommended number.

The Chairperson of the Ethics Committee should preferably be from outside the institute to maintain the independence of the committee. The Member Secretary generally belongs to the same institution to conduct the business of the committee. Other's members should be a mix of medical/non-medical, scientific and non-scientific persons including lay public to reflect the different viewpoints. The composition may be as follows:

1. Chairperson
2. 1-2 basic medical scientists
3. 1-2 clinicians from various Institutes
4. One legal expert or retired judge
5. One social scientist/ representative of non-governmental voluntary agency
6. One philosopher/ethicist/theologian
7. One lay person from the community
8. Member Secretary

In any case, the ethics committee must include one member who is independent of the institution/trial site and one member whose primary area of interest/ specializiation is nonscientific. Also, there should be adequate gender representation of the Committee. Subject experts may be invited if required. Further, depending on the requirement of the research projects, for example HIV/AIDS,

genetic disorders etc, specific patient groups may also be represented in the committee. Members should be aware of local, social and cultural norms.

Only those Ethics Committee members who are independent of the sponsor and clinical trial should vote/provide opinion in matters related to the study.

Terms of Reference

The IEC members should be made aware of their roles and responsibilities as committee members. They should be kept aware of all the national and international developments and any change in the regulatory requirements should be brought to their notice. Each committee should have its own operating procedures which are updated from time to time.

Review Procedures

The Ethics Committee should review every research proposal on human subjects to evaluate the possible risks to the subjects. The EC should evaluate the adequacy of documents for ensuring privacy, confidentiality and justice issues. It should ensure that a research proposal has been scientifically reviewed before an ethical review is taken up. **The ethical review should be done through formal meetings and decisions not taken through circulation of proposals.**

The researcher should submit an appropriate application along with the study protocol. The protocol should include the following:

1. The title with signature of Principal Investigator (PI) and Co-investigators as attestation for conducting the study.
2. Clear research objectives and rationale for undertaking the investigation in human participants in the light of existing knowledge.
3. Recent curriculum vitae of the Investigators indicating qualification and experience.
4. Participant recruitment procedures and brochures, if any.
5. Inclusion and exclusion criteria.
6. Precise description of methodology of the proposed research, including sample size (with justification), type of study design (observational, experimental, pilot, random ized, blinded etc.), intended intervention, dosages of drugs, route of administration, duration of treatment and details of invasive procedures if any.
7. Plan to withdraw or withhold standard therapies in the course of research.
8. Plan for statistical analysis of the study.

9. Procedure for seeking and obtaining informed consent with sample of patient information sheet and informed consent forms in English and local languages.

10. Safety of proposed intervention and any drug or vaccine to be tested, including results of relevant laboratory, animal and human research.

11. For research involving more than minimal risk, an account of management of such risk or injury.

12. Proposed compensation and reimbursement of incidental expenses and management of research related and unrelated injury/ illness during and after research period.

13. An account of storage and maintenance of all data collected during the trial.

14. Plans for publication of results - positive or negative - while maintaining the privacy and confidentiality of the study participants.

15. A statement on probable ethical issues and steps taken to tackle the same like justification for washout of standard drug, or the use of placebo control.

16. All other relevant documents related to the study protocol like investigator's brochure for trial on drugs/ devices/ vaccines/ herbal remedies and statement of relevant regulatory clearances.

17. Agreement to comply with national and international Good Clinical Practices (GCP) protocols for clinical trials.

18. Details of Funding agency/ Sponsors and fund allocation.

19. For international collaborative study details about foreign collaborators and documents for review of Health Ministry's Screening Committee (HMSC) or appropriate Committees under other agencies/ authority like Drug Controller General of India (DCGI)

20. For exchange of biological material in international collaborative study a MoU/ Material Transfer Agreement between the collaborating partners.

21. A statement on conflict-of-interest (COI), if any.

Decision making process

The IEC should meet at periodically to review new proposals, evaluate the progress of ongoing tirals, review serious adverse event (SAE) reports and assess final reports of all research activities. The committee should have a previously scheduled agenda. The decision-making process is an important task and following points should be considered while doing so:

1. The decision to recommend/ reject/ suggest modification must be taken by a broad consensus after the quorum requirements are fulfilled.

2. A member having conflict-of-interest (COI) should submit in writing before the review meeting and it should also be recorded in the minutes.

3. If one of the members has her/his own proposal for review or has any COI then s/he should withdraw from the IEC while the project is being discussed not participate in the voting process.

4. A negative decision should be supported by clearly defined reason

5. It the IEC receives information that may affect the risk/benefit ratio, it may decide to reverse its positive decision on a study.

6. The IEC would order the trial be discontinued if it finds that the goals of the trial have already been achieved midway or unequivocal results are obtained.

7. In case of premature termination of study, notification should include the reasons for termination along with the summary of results conducted till date.

8. The IEC should be informed under following circumstances:

- Any amendment to the protocol with proper justification
- Serious and unexpected adverse events
- Any new information that may influence the study

1. The applicant/investigator may be invited to present the protocol or offer clarifications in the meeting if it deemed necessary.

2. Subject experts may be invited to express their views but should not take part in the voting process.

3. Meetings are to be minuted and should be approved and signed by the Chairperson.

Review Process:

Periodic review

The ongoing research may be reviewed at regular intervals of six months to one year as may be specified in the SOP of the ethics committee.

Continuing review

The IEC has the responsibility to continue reviewing approved projects for continuation, new information, adverse event monitoring, follow-up and if required later after completion.

Interim review

An interim review can be carried out by a sub-committee instead of waiting for the scheduled time of the meeting like re-examination of a proposal already examined by the IEC or any other matter; however, the IEC should decide the circumstances and the mechanism under which it is permitted.

Further, the decisions taken during interim review should be brought to the notice of the main committee.

Monitoring

Once a project is approved, it is the duty of the IEC to monitor the approved studies. The investigator must be asked to submit periodic status reports at appropriate intervals and this should be specified in the SOP of the IEC. The IEC reviews the SAE reports from the site as well as other sites and accordingly takes appropriate action.

Record keeping

According to written procedures, all documentation and communication of an IEC are to be dated, filed and preserved. Strict confidentiality is to be maintained during access and retrieval procedures. The following records should be maintained for the following:

1. constitution and composition of the IEC;
2. latest curriculum vitae of all IEC members (dated and signed);
3. standing operating procedures of the IEC;
4. national and International guidelines;
5. copies of protocols submitted for review;
6. all correspondence with IEC members and investigators regarding application, decision and follow up;
7. agenda of all IEC meetings;
8. minutes of all IEC meetings with signature of the Chairperson;
9. copies of decisions communicated to the applicants;
10. record of all notification issued for premature termination of a study with a summary of the reasons;
11. final report of the study including microfilms, CDs and Video recordings.

As per ICMR Guidelines, it is recommended that all records must be safely maintained after the completion/termination of the study for a period of 3 years if it is not possible to maintain the same for more than that due to resource crunch and lack of infrastructure.

Special considerations

All the above requirements are applicable to biomedical research as a whole, there are certain specific concerns applicable to specific areas of research which require additional safeguards/ protection and the IEC should take note of these specific considerations. For example, research involving children,

pregnant and lactating women, vulnerable participants and those with limited autonomy. In such instances, the observations and suggestions of IEC should give in writing in unambiguous terms.

Health and Human Services regulations (HHS)

Introduction

The Health Insurance Portability and Accountability Act of 1996 (HIPAA) required the Secretary of the U.S. Department of Health and Human Services (HHS) to develop regulations protecting the privacy and security of certain health information. To fulfill this requirement, HHS published what are commonly known as the HIPAA Privacy Rule and the HIPAA Security Rule. The Privacy Rule, or *Standards for Privacy of Individually Identifiable Health Information*, establishes national standards for the protection of certain health information. The *Security Standards for the Protection of Electronic Protected Health Information* (the Security Rule) establish a national set of security standards for protecting certain health information that is held or transferred in electronic form. The Security Rule operationalizes the protections contained in the Privacy Rule by addressing the technical and non-technical safeguards that organizations called "covered entities" must put in place to secure individuals' "electronic protected health information" (e-PHI). Within HHS, the Office for Civil Rights (OCR) has responsibility for enforcing the Privacy and Security Rules with voluntary compliance activities and civil money penalties.

Prior to HIPAA, no generally accepted set of security standards or general requirements for protecting health information existed in the health care industry. At the same time, new technologies were evolving, and the health care industry began to move away from paper processes and rely more heavily on the use of electronic information systems to pay claims, answer eligibility questions, provide health information and conduct a host of other administrative and clinically based functions.

Today, providers are using clinical applications such as computerized physician order entry (CPOE) systems, electronic health records (EHR), and radiology, pharmacy, and laboratory systems. Health plans are providing access to claims and care management, as well as member self-service applications. While this means that the medical workforce can be more mobile and efficient (i.e., physicians can check patient records and test results from wherever they are), the rise in the adoption rate of these technologies increases the potential security risks.

A major goal of the Security Rule is to protect the privacy of individuals' health information while allowing covered entities to adopt new technologies to improve the quality and efficiency of patient care. Given that the health care marketplace is diverse, the Security Rule is designed to be flexible

and scalable so a covered entity can implement policies, procedures, and technologies that are appropriate for the entity's particular size, organizational structure, and risks to consumers' e-PHI. This is a summary of key elements of the Security Rule and not a complete or comprehensive guide to compliance. Entities regulated by the Privacy and Security Rules are obligated to comply with all of their applicable requirements and should not rely on this summary as a source of legal information or advice.

Statutory and Regulatory Background

- The *Administrative Simplification* provisions of the Health Insurance Portability and Accountability Act of 1996 (HIPAA, Title II) required the Secretary of HHS to publish national standards for the security of electronic protected health information (e-PHI), electronic exchange, and the privacy and security of health information.

HIPAA called on the Secretary to issue security regulations regarding measures for protecting the integrity, confidentiality, and availability of e-PHI that is held or transmitted by covered entities. HHS developed a proposed rule and released it for public comment on August 12, 1998. The Department received approximately 2,350 public comments. The final regulation, the Security Rule, was published February 20, 2003. The Rule specifies a series of administrative, technical, and physical security procedures for covered entities to use to assure the confidentiality, integrity, and availability of e-PHI.

- The Security Rule applies to health plans, health care clearinghouses, and to any health care provider who transmits health information in electronic form in connection with a transaction for which the Secretary of HHS has adopted standards under HIPAA (the "covered entities") and to their business associates.

Business Associates

- The HITECH Act of 2009 expanded the responsibilities of business associates under the HIPAA Security Rule. HHS developed regulations to implement and clarify these changes.

- What Information is Protected
- Electronic Protected Health Information. The HIPAA Privacy Rule protects the privacy of individually identifiable health information, called protected health information (PHI), as explained in the Privacy Rule. The Security Rule protects a subset of information covered by the Privacy Rule, which is all individually identifiable health information a covered entity creates, receives, maintains

or transmits in electronic form. The Security Rule calls this information "electronic protected health information" (e-PHI). The Security Rule does not apply to PHI transmitted orally or in writing.

General Rules

- The Security Rule requires covered entities to maintain reasonable and appropriate administrative, technical, and physical safeguards for protecting e-PHI.

Specifically, covered entities must:

1. Ensure the confidentiality, integrity, and availability of all e-PHI they create, receive, maintain or transmit;
2. Identify and protect against reasonably anticipated threats to the security or integrity of the information;
3. Protect against reasonably anticipated, impermissible uses or disclosures; and
4. Ensure compliance by their workforce.

The Security Rule defines "confidentiality" to mean that e-PHI is not available or disclosed to unauthorized persons. The Security Rule's confidentiality requirements support the Privacy Rule's prohibitions against improper uses and disclosures of PHI. The Security rule also promotes the two additional goals of maintaining the integrity and availability of e-PHI. Under the Security Rule, "integrity" means that e-PHI is not altered or destroyed in an unauthorized manner. "Availability" means that e-PHI is accessible and usable on demand by an authorized person.

HHS recognizes that covered entities range from the smallest provider to the largest, multi-state health plan. Therefore, the Security Rule is flexible and scalable to allow covered entities to analyze their own needs and implement solutions appropriate for their specific environments. What is appropriate for a particular covered entity will depend on the nature of the covered entity's business, as well as the covered entity's size and resources.

Therefore, when a covered entity is deciding which security measures to use, the Rule does not dictate those measures but requires the covered entity to consider:

5. Its size, complexity, and capabilities,
6. Its technical, hardware, and software infrastructure,
7. The costs of security measures, and
8. The likelihood and possible impact of potential risks to e-PHI.

Covered entities must review and modify their security measures to continue protecting e-PHI in a changing environment.[7]

Risk Analysis and Management

- The Administrative Safeguards provisions in the Security Rule require covered entities to perform risk analysis as part of their security management processes. The risk analysis and management provisions of the Security Rule are addressed separately here because, by helping to determine which security measures are reasonable and appropriate for a particular covered entity, risk analysis affects the implementation of all of the safeguards contained in the Security Rule.
- A risk analysis process includes, but is not limited to, the following activities:
  - Evaluate the likelihood and impact of potential risks to e-PHI;
  - Implement appropriate security measures to address the risks identified in the risk analysis;
  - Document the chosen security measures and, where required, the rationale for adopting those measures; and
  - Maintain continuous, reasonable, and appropriate security protections.

  Risk analysis should be an ongoing process, in which a covered entity regularly reviews its records to track access to e-PHI and detect security incidents, periodically evaluates the effectiveness of security measures put in place, and regularly reevaluates potential risks to e-PHI.

  Administrative Safeguards
- Security Management Process. As explained in the previous section, a covered entity must identify and analyze potential risks to e-PHI, and it must implement security measures that reduce risks and vulnerabilities to a reasonable and appropriate level.
- Security Personnel. A covered entity must designate a security official who is responsible for developing and implementing its security policies and procedures.
- Information Access Management. Consistent with the Privacy Rule standard limiting uses and disclosures of PHI to the "minimum necessary," the Security Rule requires a covered entity to implement policies and procedures for authorizing access to e-PHI only when such access is appropriate based on the user or recipient's role (role-based access).
- Workforce Training and Management. A covered entity must provide for appropriate authorization and supervision of workforce members who work with e-PHI. A covered entity must train all workforce members regarding its security policies and procedures, and must have and apply appropriate sanctions against workforce members who violate its policies and procedures.
- Evaluation. A covered entity must perform a periodic assessment of how well its security policies and procedures meet the requirements of the Security Rule.

  Physical Safeguards
- Facility Access and Control. A covered entity must limit physical access to its facilities while ensuring that authorized access is allowed.

- Workstation and Device Security. A covered entity must implement policies and procedures to specify proper use of and access to workstations and electronic media. A covered entity also must have in place policies and procedures regarding the transfer, removal, disposal, and re-use of electronic media, to ensure appropriate protection of electronic protected health information (e-PHI).

Technical Safeguards

- Access Control. A covered entity must implement technical policies and procedures that allow only authorized persons to access electronic protected health information (e-PHI).
- Audit Controls. A covered entity must implement hardware, software, and/or procedural mechanisms to record and examine access and other activity in information systems that contain or use e-PHI.
- Integrity Controls. A covered entity must implement policies and procedures to ensure that e-PHI is not improperly altered or destroyed. Electronic measures must be put in place to confirm that e-PHI has not been improperly altered or destroyed.
- Transmission Security. A covered entity must implement technical security measures that guard against unauthorized access to e-PHI that is being transmitted over an electronic network.

Required and Addressable Implementation Specifications

- Covered entities are required to comply with every Security Rule "Standard." However, the Security Rule categorizes certain implementation specifications within those standards as "addressable," while others are "required." The "required" implementation specifications must be implemented. The "addressable" designation does not mean that an implementation specification is optional. However, it permits covered entities to determine whether the addressable implementation specification is reasonable and appropriate for that covered entity. If it is not, the Security Rule allows the covered entity to adopt an alternative measure that achieves the purpose of the standard, if the alternative measure is reasonable and appropriate.

Organizational Requirements

- Covered Entity Responsibilities. If a covered entity knows of an activity or practice of the business associate that constitutes a material breach or violation of the business associate's obligation, the covered entity must take reasonable steps to cure the breach or end the violation. Violations include the failure to implement safeguards that reasonably and appropriately protect e-PHI.
- Business Associate Contracts. HHS developed regulations relating to business associate obligations and business associate contracts under the HITECH Act of 2009.

Policies and Procedures and Documentation Requirements

- A covered entity must adopt reasonable and appropriate policies and procedures to comply with the provisions of the Security Rule. A covered entity must maintain, until six years after the later of the

date of their creation or last effective date, written security policies and procedures and written records of required actions, activities or assessments.

- Updates. A covered entity must periodically review and update its documentation in response to environmental or organizational changes that affect the security of electronic protected health information (e-PHI).

State Law

- Preemption. In general, State laws that are contrary to the HIPAA regulations are preempted by the federal requirements, which means that the federal requirements will apply. “Contrary” means that it would be impossible for a covered entity to comply with both the State and federal requirements, or that the provision of State law is an obstacle to accomplishing the full purposes and objectives of the Administrative Simplification provisions of HIPAA.

Enforcement and Penalties for Noncompliance

- Compliance. The Security Rule establishes a set of national standards for confidentiality, integrity and availability of e-PHI. The Department of Health and Human Services (HHS), Office for Civil Rights (OCR) is responsible for administering and enforcing these standards, in concert with its enforcement of the Privacy Rule, and may conduct complaint investigations and compliance reviews.
- Learn more about enforcement and penalties in the Privacy Rule Summary - PDF - PDF and on OCR's Enforcement Rule page.

Compliance Dates

- Compliance Schedule. All covered entities, except “small health plans,” must have been compliant with the Security Rule by April 20, 2005. Small health plans had until April 20, 2006 to comply.

FDA Regulations

The Food and Drug Administration (FDA or USFDA) is a government agency of the United States Department of Health and Human Services. The FDA is responsible for regulating and supervising the safety of foods, tobacco products, dietary supplements, prescription and non-prescription medication, vaccines, biopharmaceuticals, blood transfusions, medical devices, electromagnetic radiation emitting devices (ERED), veterinary products, and cosmetics. The FDA also enforces other laws, notably Section 361 of the Public Health Service Act and the associated regulations. Many of these regulations are not directly related to food or drugs. These include sanitation requirements on interstate travel and control of disease on products ranging from certain household pets to sperm donation for assisted reproduction.

Funding

The FDA regulates more than $1 trillion worth of consumer goods, about 25% of consumer expenditures in the United States. This includes $466 billion in food sales, $275 billion in drugs, $60 billion in cosmetics and $18 billion in vitamin supplements. Much of the expenditures is for goods imported into the United States; the FDA is responsible for monitoring a third of all imports.

Legal Authority

Most federal laws concerning the FDA are part of the Food, Drug and Cosmetic Act, (first passed in 1938 and extensively amended since) and are codified in Title 21, Chapter 9 of the United States Code. Other significant laws enforced by the FDA include the Public Health Service Act, parts of the Controlled Substances Act, the, as well as many others. in many cases these responsibilities are shared with other federal agencies.

Challenges and Opportunities Facing FDA

• Must maintain the balance of protecting and promoting public health. • US Consumers reliance on an effective FDA for protection from unsafe medical products and contaminated food. • Also charged with Promoting Public Health by – Guiding and supporting development and availability of safe and effective new medical technologies – As well as nutitious new food products • Determine Benefit versus Risk based on current available science information. FDA Mission • The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation. The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, sciencebased information they need to use medicines and foods to improve their health.

FDA Strategic Action Plan I. Strengthen FDA for Today and Tomorrow II. Improve Patient and Consumer Safety III. Increase Access to New Medical and Food Products IV. Improve the Quality and Safety of Manufactured Products and the Supply Chain Strategic Goal 1: Strengthen FDA for Today and Tomorrow • Strengthen the scientific foundation of FDA's regulatory mission • Cultivate a culture that promotes transparency, effective teamwork, and mutual respect, and ensures integrity and accountability in regulatory decision making. • Enhance partnerships and communications. • Strengthen FDA's base of operations. Strategic Goal 2: Improve Patient and Consumer Safety • Strengthen the science that supports product safety • Improve information systems for problem detection and public communication about product safety • Provide patients and consumers with better access to clear and timely risk-benefit information for medical products • Provide consumers

with clear and timely information to protect them from food-borne illness and promote better nutrition

Strategic Goal

3: Increase Access to New Medical and Food Products

• Objective 3.1: Increase the number of safe and effective new medical products available to patients. Improve information systems for problem detection and public communication about product safety

• Objective 3.2: Improve the medical product review process to increase the predictability and transparency of decisions using the best available science.

• Objective 3.3: Increase access to safe and nutritious new food products. Strategic Goal 4: Improve the Quality and Safety of Manufactured Products and the Supply Chain

• Objective 4.1: Prevent safety problems by modernizing science-based standards and tools to ensure highquality manufacturing, processing, and distribution. development of modern continuous manufacturing technologies, which present opportunities for remote automated monitoring; and • Objective 4.2: Detect safety problems earlier and better target interventions to prevent harm to consumers.

• Objective 4.3: Respond more quickly and effectively to emerging safety problems, through better information, better coordination and better communication. Implement New Import Safety Strategic

Framework

Implement New Import Safety Strategic Framework: FDA anticipates following a new direction in the future for regulating imports, as outlined in the Report to the President, Protecting American Consumers Every Step of the Way: A strategic framework for continual improvement in import safety. It is a risk-based strategy that shifts the focus from interdiction at the border to prevention with verification. It will utilize data from all points in the full import life cycle – from production, manufacture, transport, distribution, and consumption – to assist in targeting the highest risk imported products for review, and facilitating the entry of low-risk products. On November 6, 2007, the Action Plan for Import Safety (available at http://www.importsafety.gov/report/index.html) was released which provides specific short- and long-term recommendations to better protect consumers and enhance the safety of the increasing volume of imports entering the United States. Within two years, accomplishments will be made in the areas of foreign operations, border operations, imported products in domestic commerce, information technology, and applied science and technology. • Last year, the United States imported more than $2 trillion worth of products. These products were brought to the United States by roughly 825,000 importers, through over 300 ports of entry. All projections indicate that this volume will continue to rise, sharply, over the coming years as the scale and complexity of international trade multiplies.

Implement New Import Safety Strategic Framework

• Imports allow consumers to enjoy the benefits of a greater variety, availability, and affordability of goods in the marketplace. • The growth of imports, combined with an increased focus on security, places a greater burden on border officials. These officials must manage larger volumes of imports from countries which often have less-developed regulatory systems. In addition, they must consider more complex risk scenarios, use more sophisticated screenings and examinations, and employ new technologies to ensure product safety.

Conclusion

As FDA celebrates more than 100 years of service to the American people as the world's gold standard regulatory agency, it looks to the future. • FDA being a bridge, not a barrier • The products of explosive progress in science and technology have made that future a possibility and not just a promise but the pathway requires FDA to look ahead to being a bridge and not a barrier to the delivery of safe and nutritious food and life-saving medical and health products to the people we serve. • This strategic plan marks the path to achieve our vision for an organization that is dedicated to excellence as a science-based and science-led regulatory agency that provides global leadership in protecting public health.

Compensation for Injury

Definitions

When an injury occurs as a result of participation in a research study it is called a "research related injury" and these are sometimes inevitable. Such injuries may range from relatively minor harms (such as bruises due to a study procedure or vomiting due to a new drug) to major injuries (such as organ damage or temporary physical disability) to catastrophic injuries (such as permanent disability or death). Injuries can be physical, psychological/emotional, social or economic and may require only acute or emergency care, or long-term medical care.

Harm is defined as economic, physical, psychological and social damage. Economic Harm is financial loss resulting from participation in a research project, which may include direct losses such as amounts the claimant had to spend to try to mitigate problems and consequential economic losses resulting from lost income. Physical Harm is death, bodily injury to, illness or disease in any person. Psychological Harm is negative self-perception, emotional suffering (e.g., anxiety or shame), aberrations in thought or behaviour, or long-lasting intense psychological distress and fear, which in extreme cases might result into suicide. Disability is physical or mental impairment that substantially

limits one or more of the major life activities of such individual-including communication, walking, and self-care (such as feeding and dressing oneself) -and which is likely to continue indefinitely, resulting in the need for supportive services.

Compensation is defined as 'the act or process of making amends for something' or 'something, typically money, awarded to someone in recognition of loss, suffering or injury'.

Revised Indian compensation guidelines

The ICMR in collaboration with the Indian Society for Clinical Research (ISCR) and Forum for Ethics Committees in India (FERCI) had issued Draft Guidelines for Compensation to Participants for Research Related Injury in India in 2008 which would apply to all clinical research, whether sponsored by the pharmaceutical or medical device industry, government or academia or individual investigators.

Recently, in November 2011, the Drug Controller General of India (DCGI) published the new draft rules under the Drugs and Cosmetic Rules, 1945 (3rd Amendment, 2011) Rule 122 DAB for '*Compensation in case injury or death during the clinical trial*'. These draft rules mainly reiterate the ICMR guidelines on Compensation for research injuries with some important differences. The rule mandates that participants or family (as the case may be) be compensated for permanent injury or death occurring due to participation in clinical studies and that this should be responsibility of the Sponsor. It also states that all ICDs should incorporate this clause. A further step taken by the DCGI's office in August 2012 has been to circulate draft guidelines to determine the quantum of financial compensation to be paid in case of clinical trial related injury or death.[18] These guidelines describe the methods to be followed by the Ethics Committees for calculating the quantum of financial compensation to be paid in case of clinical trial related injury or death.

In the meantime, the ICMR has withdrawn its guidelines, in order to have a common standard in the country although it is likely that these will be re-issued later to apply to clinical research other than regulatory clinical trials covered by Schedule Y.

What to compensate for?

The CDSCO draft rules on compensation now state that compensation should be provided in case of research injury or death due to:

- Adverse effects of the investigational product/s.
- Departure from approved protocol, scientific misconduct or negligence by the Investigator/Sponsor/ CRO.

- Failure of an investigational product to provide intended therapeutic effect.
- Administration of placebo providing no therapeutic benefits.
- Adverse effects due to concomitant medications.
- Compensation be paid to a child injured *in utero* through the participation of the parent in a clinical trial.

Some of these points need further clarification as discussed later.

How much to compensate?

The moot question is how to quantify harm and leading from that how much to compensate? The DCGI draft rules on compensation for research related injuries mention that the quantum of compensation to be paid is to be decided by the EC within 30 days of the matter being referred to it. In case no formal claims are made by the trial subject, then the EC should review the SAE and recommend the amount of compensation. In case of any dispute or differences between the parties then the decision of the EC is final. Thus, the final responsibility lies with the EC. The recent draft guidance document released by the DCGI office describing calculation of the quantum of financial compensation to be paid in case of clinical trial related injury or death by Ethics Committees has listed certain parameters that need to be considered. These parameters are:

a. Age of the deceased

b. Income of the deceased

c. Seriousness and severity of the disease, the subject was suffering at the time of his/her participation into the trial and

d. Percentage of permanent disability.

A formula has been given to determine the amount of compensation in case of trial related death i.e., $C^{1} = A \times B\ (1 - F/100)$ wherein 'A' reflects the income of the deceased/injured per month from which a deduction (50 % in case of death and 40% in case of injury) should be made in regard to the amount which the deceased would have spent on himself by way of personal and living expenses. The balance, which is considered to be the contribution to the dependent family, constitutes 'A'. Multiplier 'B' depends on the age of the deceased and period of his/her active career. A table of multipliers (Annexure 1) has been provided from which an appropriate multiplier should be selected with reference to the age of the deceased.

In case of healthy participants, the actual calculation of the compensation amount would be C = (A × B). In case of diseased subjects/patients, C1 would be the compensation amount which would be a fraction of the amount arrived as 'C' depending on seriousness and severity of the disease. The disease seriousness and severity will be determined on a scale of 0 to 100 with 0 representing no risk

(i.e., healthy volunteers) and 100 representing fatality. 'F' is the risk factor of the trial participant which should be assessed by the Study Investigator study from the above-mentioned scale of 0 to 100. For the purpose of calculation of the compensation, 'F' should not be more than 50. Thus, the amount of compensation to be paid in such cases shall be arrived by using the formula: $C^1 = A \times B (1 – F/100)$

In case of trial related injuries, the amount of compensation to be paid shall be determined by the formula $C^2 = A \times B (1 – F/100) \times D/100$ wherein 'D' is the percentage disability caused to the participant due to the clinical trial.

Financial Interests

Many business considerations in clinical trial agreements grow out of FDA regulatory requirements. No-where is this more apparent than with the financial disclosure regulations in 21 CFR 54. These regulations are designed to help eliminate the potential for bias that may arise due to financial conflicts of interest. For example, if a sponsor compensates an investigator with an equity stake in the company or if an investigator has a proprietary interest in the investigational device, the investigator may be motivated to influence the outcome of the trial data rather than to remain impartial.

The regulations in 21 CFR 54 give the sponsor the option of certifying the absence of certain financial interests of the investigators or disclosing those financial interests. However, it is much more desirable for the sponsor to certify that the investigators have no financial interest. Doing so avoids raising a red flag for FDA.

When structuring the compensation for a clinical trial, sponsors should avoid creating any financial interests that would be disclosable. Sponsors should take care to include in their analysis all other financial arrangements they may have with the investigators, such as compensation for consulting services that investigators may have provided or will provide during the period covered by the financial disclosure regulations. If FDA is concerned about a potential bias from an investigator because of a financial interest, the agency has four options, which are presented in 21 CFR 54.5(c). These options are

• Auditing the clinical data.

• Requesting further analysis to determine whether there is investigator bias.

• Requesting that the sponsor con-duct further studies independently.

• Refusing to treat data as the basis of an FDA decision.

While the structure and amount of payments made by commercial sponsors vary, normally the budget includes per-subject payments by the sponsor to the institution or to the principal investigator. These payments are often tied to milestones, such as follow-up visits or completion of case report forms. Sponsors should consider making the last milestone payment based on final acceptance by the sponsor of all data pertaining to that subject. This gives the site incentive to finish its data submissions to the sponsor, which can often drag on at the end of a trial.

The budget exhibit should set forth conditions where payment will be denied, such as if the subject was ineligible to participate in the trial at time of enrollment or if the principal investigator failed to obtain informed consent. Some sponsors pay institutional review board (IRB) fees, start-up administrative fees, or other one-time fees. Fees can be nonrefundable or advances that are earned against subject follow-up payments. Sponsors may reimburse for study procedures or the cost of the device. In all cases, the sponsor must take care to avoid running afoul of healthcare fraud and abuse laws. Such laws include, but are not limited to, the federal Anti-Kickback Statute, Stark Laws, and False Claims Act. There may be similar state laws as well. In addition, the payment exhibit should make clear that it sets forth all payments and reimbursements that the sponsor will make for the trial.

Allocation of Risk

Indemnification. The parties involved in a clinical trial agreement face very real and significant exposure to liability because the trial involves testing humans. Particularly for devices that pose a significant risk, the trial could lead to injury or death. In today's litigious society, if a research subject in a clinical trial is injured or dies, often all parties will be sued, regardless of who or what caused the injury or death. To protect each party from liability created by the other parties, the clinical trial agreement typically includes a mutual indemnification by the sponsor and the institution. A mutual indemnity protects each party from the cost of defending a lawsuit in cases where it is not at fault.

The fairest approach to the mutual indemnity issue is for each side to be responsible for its own failures. On the sponsor side, if the device causes a subject's injury or death, the sponsor would indemnify the institution, the principal investigator, and their personnel from the costs of defending any resulting lawsuit.

Clinical trial agreements initiated by institutions may seek a wider indemnity from the sponsor, covering more than problems with the device. Sponsors should make clear that if a research subject is injured or dies, they will not indemnify if the institution, the principal investigator, or their personnel failed to follow the protocol, applicable laws or regulations, or were negligent or misused the device. Normally, institutions will agree to this condition, as it is a fair allocation of business risk. On the institution side, if the institution, principal investigator, or their personnel were at fault, the institution would indemnify the sponsor for the legal costs of defending a lawsuit where it may be named.

Often universities and large medical centers will refuse to indemnify the sponsor. In addition, some state laws prohibit public universities from indemnifying a sponsor. In such cases, the sponsor should still exclude from its indemnity obligations any losses caused by the institution's, the principal investigator's, or their personnel's failure to follow the protocol, applicable laws, or regulations, or their negligence or misuse of the device.

Insurance. Insurance provides each party with added assurance that the other will be able to meet its indemnification obligations. Historically, institutions have required the sponsor to maintain insurance, although sponsors are increasingly obtaining reciprocal insurance obligations from the institution. From the sponsor's perspective, corresponding institutional insurance is particularly important for small private hospitals, clinics, or physician's offices, because the sponsor has little assurance that they will be able to meet their indemnity obligations.

Limitation of Liability. It is generally good business practice to exclude each party's liability to the other parties for indirect and consequential damages arising out of the agreement, with the exception of damages attributable to a breach of confidentiality or the indemnification obligations. The term consequential damages refers to damages that do not flow directly and immediately from the act of

the offending party, but only from the consequences and results of such act. One common type of consequential damage is lost profits.

An exclusion of this liability protects the sponsor from negative fallout experienced by the institution or principal investigator, and a corresponding claim against the sponsor for lost profits, in the event of publicity relating to serious injury or death during the trial. Sponsors want to cap their liability for direct damages to an amount equal to what the sponsor has paid the institution or principal investigator during the trial. Universities and large medical centers are less receptive to liability caps, but often agree to a mutual exclusion of consequential damages, and sometimes to a liability cap, as long as it is clear that these provisions do not apply to the indemnification obligations. Smaller institutions may agree to both provisions more readily.

Parties to the Clinical Trial Agreement

As a best practice, three parties should sign the clinical trial agreement: the sponsor, the principal investigator, and the institution. However, there are some situations where a two-party clinical trial agreement may be necessary. If an institution employs the principal investigator, the institution may not want the principal investigator to be a formal party to a trial agreement. This should be acceptable to the sponsor under the theory that the institution, as the principal investigator's employer, is responsible for the principal investigator.

However, because so many provisions of the clinical trial agreement apply to the principal investigator, it is in the sponsor's interest to educate the principal investigator about the clinical trial agreement. To this end, the institution will normally be amenable to having the principal investigator sign a read and acknowledged signature block at the end of the clinical trial agreement. Note that if the principal investigator has staff privileges at the institution, but is not an institution employee, then the sponsor should press for the principal investigator to be a formal party to the clinical trial agreement. This is true even if the institution argues that the principal investigator's signature is unnecessary. The institution will likely lack sufficient authority to enter into the agreement on behalf of the principal investigator.

In cases when the principal investigator is not an employee of the institution, but has limited staff privileges, the institution may prefer not to use the same agreement signed by the investigator. Because the trial will be conducted on institution premises and will likely involve institution personnel and equipment, the sponsor should enter into a separate agreement with the institution to ensure that the institution bears responsibility for its personnel involved in the trial. In this case, the sponsor should sign one clinical trial agreement with the principal investigator and another clinical trial agreement with the institution. The sponsor should not have much difficulty convincing the institution to sign an agreement. Most institutions want to be indemnified by the sponsor if an injury or death of a research subject is caused by the sponsor's device.

The principal investigator usually appoints coinvestigators (or subinvestigators) to assist with the conduct of the trial. These people do not need to be parties to the trial agreement itself, but should sign an exhibit to the agreement in which, among other things, they agree to abide by the principal investigator's obligations in the clinical trial agreement. Educating the coinvestigators about the agreement requirements and having them sign an exhibit gives the sponsor an additional layer of protection.

Various additional parties may participate in the conduct of the trial, including interns, residents, staff physicians, independent study coordinators, contract research organizations (CROs), and core labs. With the exception of CROs and core labs, these ancillary parties do not typically sign documents that would make them responsible to the sponsor for their missteps in the trial. Nor would they assign to the sponsor the intellectual property (IP) that they develop during the trial. The sponsor needs to carefully consider who is involved in the trial. It also must ensure that the institution indemnifies and assigns IP to the sponsor on behalf of these ancillary parties.

In addition, if a CRO signs the clinical trial agreement on behalf of the sponsor, the sponsor should carefully review the clinical trial agreement before it is signed. Clinical trial agreements provided by CROs may pass through the institution's review process relatively quickly, but these agreements often do not adequately protect the sponsor's interests.

Regardless of the principal investigator's relationship with the institution, investigational device exemption regulations require investigators to sign an investigator agreement. This is a required

document that is separate from the clinical trial agreement. The applicable requirements are described in 21 CFR 812.43(c), 812.100, and 812.110. They include, for example, the investigator's commitment to conduct the trial in accordance with the protocol, FDA regulations, and FDA- or IRB-imposed conditions of approval. In addition, the investigator commits to supervising all device testing in humans. Sponsors often commingle the investigator agreement with the clinical trial agreement—and investigators can sometimes confuse the two. However, the investigator agreement should be a stand-alone document because it is subject to inspection by FDA; the clinical trial agreement is not.

Termination

Termination for Convenience. In commercial contracts, it is customary for the company that engages a service provider to have a right to terminate the agreement for convenience; the service provider does not have a corresponding right.

In a clinical trial context, other trial sites, communications with FDA, or other factors may affect the course of the trial, so the sponsor needs the right to terminate for convenience as well as the right to suspend the trial at any time. Some clinical trial agreements proffered by institutions include a mutual right to terminate the agreement for convenience. However, because the sponsor is investing a significant amount of time and money in the trial, the sponsor needs to be able to count on the institution's participation in the trial.

That said, the institution and principal investigator may legitimately fear that they could be forced to continue a trial when it appears advisable to terminate for health and safety reasons, but the sponsor disagrees. To address this, the parties should consider inserting a provision granting the principal investigator the right to terminate the trial if it presents an unreasonable risk of substantial harm to the research subjects or if the emergence of any adverse events is of such concern as to support termination.

Other sponsors allow the institution and principal investigator to terminate for any reason. The theory behind this is that they do not want people conducting a trial unwillingly—it could unfavorably affect the outcome.

Replacement of Principal Investigator. When setting up clinical trials, sponsors often select high-profile principal investigators to oversee the trials. If the principal investigator were to leave the institution, the sponsor might want to discontinue the trial or move it to another institution. To address this possibility, the clinical trial agreement should grant the sponsor approval rights over any replacement principal investigator as well as the right to terminate the agreement should the parties fail to agree upon a replacement principal investigator.

Competitive Devices

Some sponsors wish to prohibit the principal investigator and the institution, during the sponsor's trial, from working on trials for a competitive device. The parties should draft a noncompete clause in a manner narrow enough to pass muster with the courts. There is an exception if the device is used in a specialized field where only a handful of principal investigators possess sufficient expertise to conduct a clinical trial. In such a case, a noncompete clause is impractical because there is a high likelihood that the principal investigators would engage in trials on competitive devices. However, the sponsor can prohibit the investigator from enrolling subjects in competitive trials simultaneously to avoid enrollment bias.

Having a principal investigator work on competitive devices for multiple sponsors can create practical problems from a confidentiality and IP perspective, but device companies typically accept this as a reality of doing business in specialized device fields. In this situation, the confidentiality provision takes on a more critical role in protecting the sponsor's investment in its device, and the sponsor should confirm that it is drafted appropriately. With regard to IP, the sponsor should verify that the assignment provisions are sufficiently inclusive and clear. The sponsor should implement procedures to track any IP developed by the institution or principal investigator during the course of the trial.

FDA Inspections

Clinical trial agreements customarily include a right for the sponsor to inspect the clinical trial site so that the sponsor can monitor the conduct of the trial and obtain any information necessary to respond to FDA requests. If the principal investigator will perform any clinical trial work in an office

outside the institution, such as a private doctor's office, then the inspection right should extend to those facilities as well.

It is also standard to obligate the institution and principal investigator to notify the sponsor of any FDA inspection. Sponsors typically want to attend all FDA inspections related to the trial. If FDA inspects the trial site, the sponsor should request copies of all correspondence between FDA and the institution or principal investigator. Once again, the institution or principal investigator should not object to such requests. If FDA issues a Form FDA-483 Notice of Observations or similar warning letter to the institution or principal investigator, the sponsor should insist on a right of prior approval or review over any responses. Involvement in the response process will help the sponsor protect its investment in its device.

HIPAA

A trial agreement should state that the principal investigator must obtain subject authorizations that meet the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and any applicable state privacy laws. First, the investigator must obtain prior written authorization to use and disclose health information for research in accordance with HIPAA (HIPAA authorization). Second, the investigator must inform the sponsor of any failure to obtain a HIPAA authorization before a research subject's enrollment in the trial. Alternatively, a principal investigator can obtain an appropriate waiver by the IRB or by a properly constituted privacy board.

Many sponsors propose a form of HIPAA authorization, but institutions increasingly insist on using their own forms. Institutions' HIPAA authorizations address the needs of the institution and principal investigator, but often fail to sufficiently address the sponsor's interests. Sponsors want to ensure that they will have access to the trial data at the individual subject level, which would not be possible without a properly drafted HIPAA authorization. Further, sponsors want to ensure that the breadth of the disclosure allows them to use the trial data as desired. Whatever HIPAA authorization form the parties adopt; the sponsor should carefully vet the authorization with HIPAA counsel. In addition, the clinical trial agreement should prohibit the institution and the principal investigator from changing the HIPAA authorization without the sponsor's consent.

Parties may ask why it is necessary to include HIPAA language if the agreement contains a general obligation for the parties to comply with applicable laws. From the sponsor's perspective, it helps to ensure that the data generated through the trial are not encumbered by a HIPAA violation committed by the institution or the principal investigator. Although FDA has not issued a formal statement indicating that it would reject trial data obtained in violation of HIPAA, a sponsor would be in a much better position if it could show that it made good faith efforts to comply. The HIPAA language also helps to ensure that the sponsor or the sponsor's monitors may inspect subject records and other source data maintained by the institution. The trial data are the culmination of a vast investment of time and money by the sponsor in its device. Therefore, protecting the integrity of the trial data and ensuring that no legal barriers interrupt the flow of the data should be paramount.

Question bank

1. What are the ethical principles in research involving human subjects?
2. Explain about the FDA Regulations and their process?
3. How IRB is working, explain the committee composition and its importance?
4. What are the general procedures of the clinical trial? Explain it in detail.
5. Explain about Institutional Review board?
6. What are the process of HHS?
7. Mention about the FDA Regulations?
8. What are the role of IRB in reviewing clinical drug trail?
9. Mention the financial risk of clinical trial subjects?
10. What are the general principles involved in human subjects?
11. How will you select the subject, balancing benefits and risk of drugs?
12. What is Multi institutional trail? why it is necessary?
13. Explain the legal authorities of IRB?

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UNIT – II - History of Good Clinical Practices – SMB5303

International Conference on Harmonisation

ICH denotes for "International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human consumption". ICH's logo has been contrived with a view to symbolizing the letters "I", "C", "H" in a manner which embodies the letters in an outline human form. The main colour of the logo is blue, a colour often used with healthcare. ICH mission: ICH's mission is to make suggestions towards accomplishing greater harmonisation in the interpretation and application of technical Guidelines and requirements for medicinal product registration. History of ICH: Since ICH's origin in 1990, the ICH process has step by step evolved. ICH's first 10 years saw substantial progress in the growth of Tripartite ICH Guidelines on Safety, Quality and Efficacy topics (QSEM). Work was also undertaken on a number of important multidisciplinary subjects, which admitted MedDRA (Medical Dictionary for Regulatory Activities) and the CTD (Common Technical Document).

As the second tenner the exploitation of ICH Guidelines continued, but with more care given to the following need to:

- Maintain already present Guidelines as science and technology continued to develop;
- Expand communication and spreading of information on ICH Guidelines with non-ICH regions became a key focus;
- Provide the implementation of ICH Guidelines in ICH's own regions;

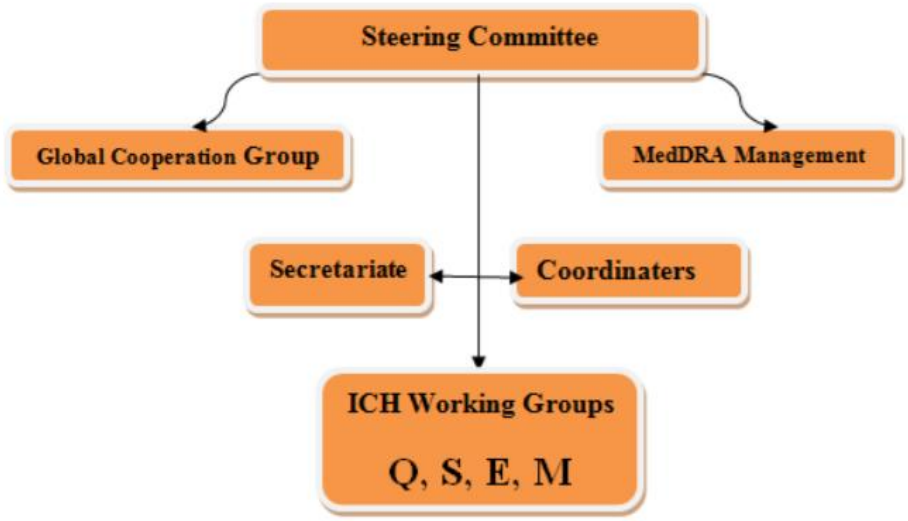
Entering into its third tenner of activity, ICH's attention is directed towards continuing the benefits of harmonisation outside the ICH regions. Training, active participation of nonICH regions in Guideline exploitation is seen as key in this effort.

Organisation

a. ICH Steering Committee and its subgroups The ICH Steering Committee and its sub-groups are constituted of representatives from 6 parties that represent the regulatory bodies and research-based industry in the USA, Japan and the European Union.

Region	Regulatory Body	Research Based Industry
Japan	**MHLW** - Ministry of Health, Labour and Welfare	**JPMA** - Japan Pharmaceutical Manufacturers Association
Europe	**EU** - European Union	**EFPIA** - European Federation of Pharmaceutical Industries and Associations
USA	**FDA** - Food and Drug Administration	**PhRMA** - Pharmaceutical Research and Manufacturers of America

The ICH Observers have been affiliated with the ICH process from the starting to act as a link with non-ICH countries. These non-voting members who are component of the ICH Steering Committee and its sub group include the European Free Trade Association (EFTA), World Health Organization (WHO), and Canada.



ICH Expert Working Groups (EWGs) / Implementation Working Groups (IWGs)

Each of the official 6 ICH members (EFPIA, EU, MHLW, JPMA, PhRMA & FDA) and the ICH perceivers (WHO, EFTA & Health Canada) appoint official representatives to each ICH Working Group. The official membership of ICH Expert Working Groups shall be comprised of one Topic Leader and one Deputy Topic Leader for ICH members and one representative per ICH Observer (EFTA, Health Canada, WHO). Experts are constituted by the ICH regional Coordinators.

Depending on the subject under harmonisation, other specialist may also be invited by the ICH Steering Committee to nominate one representative to take part to the ICH Working Groups. If accepted by the Steering Committee, one expert can be called from: ICH Regional Pharmacopeias, ICH Interested members (World Self Medication Industry - WSMI, International Generic Pharmaceutical Alliance - IGPA, International Pharmaceutical Excipients Council – IPEC, Biotechnology Industry and Active Pharmaceutical Ingredient Industry - API) as well as Regional Harmonisation Initiatives (RHIs), Individual Drug Regulatory Authorities (DRAs) and Department of Health (DoH) from non ICH member countries.

WORK PRODUCTS

Guidelines: ICH has originated over 50 harmonised Guidelines aiming at eliminating gemination in the development and registration process, so that a single set of reports can be generated to demonstrate the quality, safety and efficacy of a new pharmaceutical product. ICH has also developed Questions and Answers (Q&A) when additional guidance and advice were considered required helping the interpretation of certain harmonised tripartite Guidelines.

CTD: The Common Technical Document (CTD) describes the common format for the formulation of a well-integrated CTD for applications that will be submitted to regulatory bodies.

eCTD: The Electronic Common Technical Document (eCTD) has been prepared for the electronic submission of the Common Technical Document (CTD) from applicant to drug regulator, in order to provide international electronic communication through the provision of Electronic Standards for the Transfer of Regulatory Information (ESTRI).

MedDRA: The Medical Dictionary for Regulatory Activities (MedDRA) Terminology has also been developed under the aegis of international conference on harmonization.

PROCESS OF HARMONISATION

The ICH Steering Committee is responsible for the administration of ICH. This includes determining on the adoption of every ICH project, whether a new issue, maintenance of an existing Guideline, or a specific implementation works. Each harmonisation action is started by a Concept Paper which is a short summary of the proposal. As per the category of harmonisation activity a Business Plan may also be needed. Any ICH member or Observer is welcomed to give a proposal for a new ICH implementation activity.

The ICH Steering Committee determines on the adoption of every ICH task and then supports the creation of a EWG/IWG. ICH harmonisation activities categorised into four types. They are Formal ICH Procedure, Questions & Answers Procedure, Revision Procedure and Maintenance Procedure.

a. Formal ICH Procedure:

A formal ICH procedure is started with the approval by the SC of a Concept Paper and Business Plan. An Expert Working Group (EWG) with membership as specified by the Concept Paper is afterwards established. At the same time, a Rapporteur (and co-Rapporteur) is officially assigned by the Steering committee and a Regulatory Chair is officially assigned the three regulatory parties of the Steering committee. The EWG works to develop a draft Guideline and bring it through the various steps of

the procedure which end in Step 5 and the implementation in the ICH regions of a Harmonised Tripartite Guideline.

Step 1: Consensus building

The process of unanimity starts when the Steering Committee acquires a Concept Paper as a new topic. Step 1 is started when the EWG begin the preparation of a unanimity draft of the technical document, depending on the objectives set out in the Concept Paper. Work is conducted via e-mail, telephonic conferences and web conferences. If supported by the Steering committee, the EWG will also meet face to face at the 2 years SC meetings. Meanwhile reports on the progress of the draft technical document are made to the SC on a regular interval. When consensus is reached among all six party EWG members, the EWG will sign the Step 1 Experts sheet. The Step 1 Technical Document with EWG signatures is then presented to the Steering Committee to request acceptance under Step 2a of the ICH process. Step 2a: Confirmation of six-party unanimity on the technical document: Step 2a is reached when the Steering Committee accepts based on the report of the EWG, that there is enough scientific consensuses on the technical issues for the Technical Document to proceed to the next stage of regulatory consultation. The unanimity text approved by the Steering Committee is signed-off by the Steering Committee as the Step 2a Final Technical Document.

Step 2b: Espousal of the draft Guideline:

Based on the technical document, the three ICH regulatory members will take the actions they deem essential to develop the "draft Guideline". The unanimity text approved by the three regulatory ICH members is signed-off by the three regulatory ICH members as Step 2b Draft Guideline. Step 3: Regulatory consultation and Discussion:

Step 3 occurs in three separate stages:

Stage I: Regional regulatory consultation: The Guideline being the scientific unanimity leaves the ICH process and becomes the subject of normal varied regulatory consultation in the three regions. In the European union it is published as a draft Committee for Medicinal Products for Human Use (CHMP) Guideline, in Japan it is interpreted and issued by MHLW for internal and external consultation and in the USA it is issued as draft guidance in the Federal Register. Regulatory authorities and industry associations in non ICH areas may also annotate on the draft consultation documents by furnishing their comments to the ICH Secretariat.

Stage II: Discussion of regional consultation comments: After receiving all comments from the consultation process, the EWG works to handle the comments received and reach unanimity on what is called the Step 3 Experts Draft Guideline. If the Rapporteur was from an industry member, until Step 2b a new Rapporteur from a regulatory party is appointed, preferably from the same area as the

previous Rapporteur. The same procedure depicted in Step 1 is used to address the consultation results. The draft document to be formulated as a result of the Step 3 phase is called Step 3 Experts Draft Guideline.

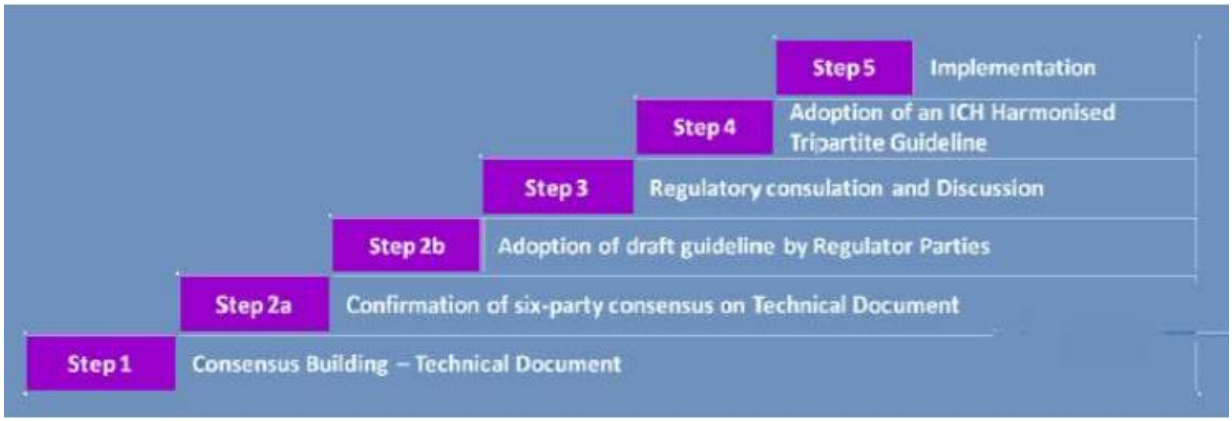
Stage III: Finalisation of Step 3 Experts Draft Guideline

After due consideration of the consultation results by the EWG, unanimity is reached amongst the experts from the three regulatory ICH members on a revised version of the Step 2b Final Draft Guideline, the Step 3 Experts Draft Guideline is signed by the EWG experts of the three regulatory ICH members. The Step 3 Document with regulatory EWG signatures is presented to the Steering Committee to request acceptance as Step 4 of the ICH process.

Step 4: Acceptance of an ICH Harmonised Tripartite Guideline:

Step 4 is completed when the Steering Committee accepts, on the basis of the report from the Regulatory Chair and the regulatory Rapporteur of the EWG, that there is sufficient unanimity on the draft guideline. Step 4 is reached when the Step 4 Final Document is signed-off by the SC signatories for the regulatory members of ICH as an ICH Harmonised Tripartite Guideline at Step 4 of the ICH procedure.

Step 5: Implementation: After completing Step 4, the harmonised tripartite Guideline moves immediately to the final step of the process that is the regulatory execution or Step 5. Step 5 is accomplished according to the same national/regional procedures that apply to other regional regulatory requirements, in the, USA, Japan and the European Union.



Quality Guidelines

S.No.	Guidelines
1	**Q1A-Q1F Stability:** Q1A: Stability testing of new drug substances and products Q1B: Stability testing: photostability testing of new drug substances and products Q1C Stability testing for new dosage forms Q1D Bracketing and matrixing designs for stability testing of new drug substances and products Q1E Evaluation of stability data Q1F Stability data package for registration applications in climatic zones III and IV
2	**Q2 Analytical validation:** Validation of analytical procedures
3	**Q3A-Q3D Impurities:** Q3A Impurities in new drug substances Q3B Impurities in new drug products Q3C Impurities: Guidelines for residual solvents Q3D Impurities: Guidelines for elemental impunities
4	**Q4A-Q4B Pharmacopeias:** Q4A: Pharmacopeial Harmonization Q4B Evaluation and recommendation of pharmacopeial texts for use In the ICH regions
5	**Q5A-Q5E Quality of biotechnological products:** Q5A Viral safety evaluation of biotechnology products derived from cell lines of human or animal origin Q5B Analysis of expression construct in cells used for production of r-DNA derived protein products Q5C Stability testing of biotechnological/ biological products Q5D Derivation and characterization of cell substrates used for production of biotechnological/ biological products Q5E comparability of biotechnlogical / biological products subject to changes in their manufacturing process
6	**Q6A-Q6B Specifications:** Q6A Test procedures and acceptance criteria for new drug substances and new drug products: Chemical substances Q6B Test procedures and acceptance criteria for biotechnological/ biological products
7	Q7 Good manufacturing practices for Active pharmaceutical ingredients
8	Q8 Pharmaceutical development
9	Q9 Quality risk management
10	Q10 Pharmaceutical quality system
11	Q11 Development and manufacture of drug substances (Chemical entities and biological entities)

Safety guidelines:

ICH has prepared a comprehensive set of safety guidelines to reveal potential risks like carcinogenicity, reprotoxicity and genotoxicity. A recent finding has been a non-clinical testing schema for determining the QT interval prolongation liability.

S.No.	Guidelines
1	**S1A-S1C Carcinogenicity studies:** S1: Rodent carcinogenicity studies for human Pharmaceuticals S1A: Need for carcinogenicity studies of Pharmaceuticals S1B: Testing for carcinogenicity of Pharmaceuticals
2	**S2 Genotoxicity studies** S2 (R1) Guidance on genotoxicity testing and data interpretation for Pharmaceuticals intended for human use
3	**S3A-S3B Toxicokinetics and pharmacokinetics:** S3A note for guidance on toxicokinetics: The assessment of systemic exposure in toxicity studies S3B Pharmacokinetics: Guidance for repeated dose tissue distribution studies
4	**S4 Toxicity testing:** S4 Duration of chronic testing in animals (Rodent and non rodent toxicity testing)
5	**S5 Reproductive toxicology:** S5 Detection of toxicity to reproduction for medicinal products and toxicity to male fertility
6	**S6 Biotechnological products:** S6 Preclinical safety Evaluation of biotechnology derived Pharmaceuticals
7	**S7-S7B Pharmacology studies:** S7A Safety pharmacology studies for human Pharmaceuticals S7B The non clinical evaluation of the potential for delayed ventricular repolarization by human Pharmaceuticals
8	**S8 Immunological Studies:** S8 Immunotoxicity studies for human Pharmaceuticals.
9	**S9 Nonclinical evaluation for anti cancer Pharmaceuticals**
10	**S10 Photosafety evaluation of Pharmaceuticals**

Efficacy guidelines:

The Efficacy guidelines are concerned with the design, carrying, and safety and reporting of clinical trials. It also gives information related to novel types of medicines derived from biotechnological methods and the use of pharmacogenomics techniques to produce better targeted drug.

S.No	Guidelines
1	E1 Clinical safety for drugs used in long term treatment
2	E2A-E2F Pharmacovigilance
3	E3 Clinical study reports
4	E4 Dose response studies
5	E5 Ethnic factors
6	E6 Good clinical practice
7	E7 Clinical trials in geriatric population
8	E8 General Consideration for clinical trials
9	E9 Statistical principles for clinical trials
10	E10 choice of control group in clinical trials
11	E11 Clinical trials in paediatric population
12	E12 Clinical evaluation by therapeutic category
13	E14 Clinical evaluation
14	E15 Definitions in pharmacogenetics/ Pharmacogenomics
15	E16 Qualification of genomic biomarkers
16	E17 Multi regional clinical trails
17	E18 Genomic sampling methodologies

Multidisciplinary Guidelines:

These guidelines contain topics which are unique, and do not fit into one of the Quality, Safety and Efficacy guidelines category. Multidisciplinary Guidelines describes about Common Technical Document (CTD), medical terminology (MedDRA), and the development of Electronic Standards for the Transfer of Regulatory Information (ESTRI).

S.No.	Guidelines
1	M1-MedDRA terminology :(Medical dictionery for regulatory activities)
2	M2 Electronic standerds
3	M3 Non clinical safety studies
4	M4 Common technical document
5	M5 Data elements and standers for drug dictionaries
6	M6 Gene therapy
7	M7 Genotoxic impurities
8	M8 Electronic common technical document (eCTD)

The Nuremberg Code (1947)

Permissible Medical Experiments The great weight of the evidence before us to effect that certain types of medical experiments on human beings, when kept within reasonably well-defined bounds, conform to the ethics of the medical profession generally. The protagonists of the practice of human experimentation justify their views on the basis that such experiments yield results for the good of society that are unprocurable by other methods or means of study. All agree, however, that certain basic principles must be observed in order to satisfy moral, ethical and legal concepts:

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 so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come 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 with impunity.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results justify the performance of the experiment.

4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

5. No experiment should be conducted where there is an a priori reason to believe that death or 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 skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.

9. During the course of the experiment 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 probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him, that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

GCP - 13 Principles

- Ethics Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).

- Trial risk vs trial benefit Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.

- Trial participants the rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

- Information on the Medicinal Product The available non-clinical and clinical information on an Investigational Product should be adequate to support the proposed clinical trial.

- Good quality trials Clinical trials should be scientifically sound, and described in a clear, detailed protocol.

- Compliance with the study protocol A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion.

- Medical decisions The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.

- Trial staff Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).

- Informed consent Freely given informed consent should be obtained from every subject prior to clinical trial participation.

- Clinical trial data All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.

- Confidentiality The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

- Good Manufacturing Practice Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.

- Quality assurance Systems with procedures that assure the quality of every aspect of the trial should be implemented.

ICMR

The Indian Council of Medical Research (ICMR) is the apex body under the Department of Health Research (DHR), Ministry of Health and Family Welfare, Government of India for formulation, coordination and promotion of biomedical research in India, and is well recognised globally for its landmark initiatives in formulating ethical guidelines for biomedical research. One year after the release of the Belmont Report in 1979, ICMR had issued a Policy Statement related to ethical aspects of human research in 1980. In line with the advances in medical research, ICMR updated the ethical guidelines in 2000 and then in 2006. The third revision had become overdue since a number of

scientific and technical advances had been made and were posing serious challenges to ethical review and conduct of research. The need was felt to elaborate on existing guidance as well as to have additional guidance on topics such as, responsible conduct of research, public health and socio-behavioural research, conduct of research during emergency situations, use of stored biological material and data and others. In October 2015, the first meeting of the Core Advisory Group* set up by ICMR (Annex. 2.B) decided on the topics to be included in the latest revision and the approach to involve a variety of stakeholders in the process of revision. In order to ensure the widest possible participation, the core group appointed a sub-committee for each of the 12 identified topics, comprising of 48 members (Annex. 2.B). They were drawn from various research organisations and included trained bioethicists and ethics committee members, clinician and researchers, sponsors and the public. Following a series of meetings, an initial draft capturing the latest national requirements and global standards was circulated for comments and was posted on the ICMR website for a period of eight weeks to obtain comments from the public. Efforts were made to consult with stakeholders from across the country to ensure responsiveness to health needs while accommodating our varied socio-cultural ethos. The WHO-Country Office India partnered with the ICMR Bioethics Unit and supported two consultation programmes at the regional and national levels. The regional consultation programme was organised on October 4, 2016, at Bangalore and was attended by the relevant stakeholders from across various regions of the country, who provided valuable suggestions. At the National Consultation meeting held on December 14, 2016, in New Delhi, representatives of various public and private institutions, the relevant government departments and agencies, members of the Central Ethics Committee on Human Research (CECHR), international agencies, and others provided relevant feedback. Comments received from all these sources, through public consultation, both regional and national, were extensively discussed for updating of the draft document. In addition, a number of separate expert group meetings were held to get the relevant advice in specific areas such as ethical review procedures, public health research, socio-behavioural research, human genetic testing and research, clinical trials, new technologies, etc. The National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, 2017, were released on October 12, 2017 by the Hon'ble Union Minister of Health and Family Welfare at ICMR. It is a detailed document covering a wide range of topics in which the existing chapters have been updated and new sections of current importance.

The general principles in the present document have been simplified for easy understanding (Sec 1). The principles of social responsibility and environmental protection have been added in order to stress the need for protecting social and cultural harmony and conserving our limited resources in the

conduct of biomedical and health research. In the General Ethical Issues section (Sec 2), the addition of the topic of risk categorisation will help ethics committees (EC) conduct a more objective benefit-risk assessment. The earlier version of the Ethical Guidelines had separate chapters on transplantation and assisted reproductive technologies, which were dropped in this version because they are more applicable to medical practice rather than to research. Some topics dealt with in brief in the earlier version have been expanded into complete sections, such as those on informed consent, vulnerability, biological materials and biobanking. Newer sections were created to cover areas like the responsible conduct of research (including publication ethics), public health research, socio-behavioural research, and research during humanitarian disasters and emergencies.

Another important inclusion in the revised guidelines is the introduction of research using datasets which has now been added to the section on biological materials and Biobanking since the basic ethical requirements for both are common. The chapters on ethical review procedures, clinical trials, and genetics research have also been also elaborated considerably, and will be helpful for researchers as well as for ethics committees (EC) in their day-to-day functioning. Guidance was needed for researchers in the country regarding the responsible conduct of research (RCR) since there is a lack of formal education/ training on this. The newly created section on RCR will help the scientist understand the measures required for data acquisition, management and sharing, collaboration (both national and international), responsible authorship and publication ethics (Sec 3). In the section on Ethical review procedures (Sec 4), each EC member's affiliation, qualifications, role and responsibilities have been described to remove the existing confusion about their appointment, composition of the committee, and quorum. It is hoped that the document will help, especially the non-medical members, to have greater clarity about their roles and responsibilities and make their participation at EC meetings more meaningful and effective beyond just fulfilling quorum requirements.

In addition, efforts have been made to harmonise and explain the differences between regulatory and non-regulatory/academic clinical trials. Clear guidance has been given regarding the setting up of independent ethics committees with special reference to when and how the services of other ECs can be utilised. Review of multicentre research has been a challenge in view of the varied requirements put forth by the different participating ECs. For the first time in India, the guidelines have proposed that a common EC may be identified from the participating sites to act as the main designated EC (Sec 4.2). This can have representatives from ECs of other participating sites and a common review can be carried out. It is hoped that this would greatly reduce the time and effort required for reviewing a common proposal at multiple sites and would help to initiate a dialogue among the concerned ECs

and build an EC network with communication channels. In the long run, this would help to streamline and strengthen ethical review systems in the country. The Guidelines advise ECs to undertake regular monitoring of research and explain conditions when site monitoring may be essential. Institutions are now requested to make adequate provision (manpower, infrastructure, funds) to run the ethics committee office smoothly. EC work should no longer be regarded as a part-time voluntary activity but as an essential function requiring protected time of the member secretary for efforts to improve EC efficiency. The Guidelines have explained the need for building quality EC systems, laying down conflict of interest policies, and stressed the need for registration of an EC as well as its participation in national or international recognition or accreditation programmes.

In our country, ethics is, unfortunately, still not part of the existing teaching curriculums in both the medical and non-medical streams. This influences both the quality of output in biomedical and health research and the protection of human participants for which the ethical conduct of research is essential. The ICMR National Ethical Guidelines document sets the standards for the ethical requirements to be followed in biomedical research in India. It is expected that all biomedical and health research in the country should follow this guidance which will go a long way towards improving the quality and outcomes of research.

General Principles

1.1.1 Principle of essentiality whereby after due consideration of all alternatives in the light of existing knowledge, the use of human participants is considered to be essential for the proposed research. This should be duly vetted by an ethics committee (EC) independent of the proposed research.

1.1.2 Principle of voluntariness whereby respect for the right of the participant to agree or not to agree to participate in research, or to withdraw from research at any time, is paramount. The informed consent process ensures that participants' rights are safeguarded.

1.1.3 Principle of non-exploitation whereby research participants are equitably selected so that the benefits and burdens of the research are distributed fairly and without arbitrariness or discrimination. Sufficient safeguards to protect vulnerable groups should be ensured.

1.1.4 Principle of social responsibility whereby the research is planned and conducted so as to avoid creation or deepening of social and historic divisions or in any way disturb social harmony in community relationships.

1.1.5 Principle of ensuring privacy and confidentiality whereby to maintain privacy of the potential participant, her/his identity and records are kept confidential and access 4 INDIAN COUNCIL OF MEDICAL RESEARCH Statement of General Principles is limited to only those authorized. However, under certain circumstances (suicidal ideation, homicidal tendency, HIV positive status, when required by court of law etc.) privacy of the information can be breached in consultation with the EC for valid scientific or legal reasons as the right to life of an individual supersedes the right to privacy of the research participant.

1.1.6 Principle of risk minimization whereby due care is taken by all stakeholders (including but not limited to researchers, ECs, sponsors, regulators) at all stages of the research to ensure that the risks are minimized and appropriate care and compensation is given if any harm occurs.

1.1.7 Principle of professional competence whereby the research is planned, conducted, evaluated and monitored throughout by persons who are competent and have the appropriate and relevant qualification, experience and/or training.

1.1.8 Principle of maximization of benefit whereby due care is taken to design and conduct the research in such a way as to directly or indirectly maximize the benefits to the research participants and/or to the society.

1.1.9 Principle of institutional arrangements whereby institutions where the research is being conducted, have policies for appropriate research governance and take the responsibility to facilitate research by providing required infrastructure, manpower, funds and training opportunities.

1.1.10 Principle of transparency and accountability whereby the research plan and outcomes emanating from the research are brought into the public domain through registries, reports and scientific and other publications while safeguarding the right to privacy of the participants. Stakeholders involved in research should disclose any existing conflict of interest and manage it appropriately. The research should be conducted in a fair, honest, impartial and transparent manner to guarantee accountability. Related records, data and notes should be retained for the required period for possible external scrutiny/ audit.

1.1.11 Principle of totality of responsibility whereby all stakeholders involved in research are responsible for their actions. The professional, social and moral responsibilities compliant with ethical guidelines and related regulations are binding on all stakeholders directly or indirectly.

1.1.12 Principle of environmental protection whereby researchers are accountable for ensuring protection of the environment and resources at all stages of the research, in compliance with existing guidelines and regulations.

Clinical Trials in India

Drug development is a process that calls for utmost care. An error can cause fatal result. Clinical trials are developed in such a way that it not only helps the discovery of new drugs but also ensures safety profile of such drugs.

A clinical trial in simple terms can be defined as a set of practice that helps certify a new drug molecule as safe and efficacious before reaching the market.

To determine the safety and efficacy of drug research on humans is always warranted, but one needs to be cautious and vigilant as to how the players in this field undertake the process. Adherence to the principles of good clinical practices or GCPs, including adequate human subject protection universally recognized as a critical requirement to the conduct of research involving human subjects. Most countries have adopted good clinical practice principles as laws or regulations. In India, compliance with GCP guidelines issued by the Central Drugs Standard Control Organization or the CDSCO is recommended.

APPLICABLE LAWS AND REGULATORY FRAMEWORK-

Clinical trials, in addition to national laws, are governed by –

- Guidelines and directives at international level like EU regulations and directives,
- ICH– Good Clinical Practices (GCP) guidelines,
- Recommendations of World Medical Association Declaration of Helsinki,
- Guidelines for Good Pharmacoepidemiology Practices and ICMR (Indian Council of Medical Research) guidelines.

These guidelines, recommendations and opinions are considered as "*soft law*" and are not legally binding but play an important role in regulating these clinical trials. Most of the multi -national corporations carrying out clinical trials worldwide voluntarily and as a good practice follow these guidelines and recommendations.

These guidelines and directives primarily aim at-

- protecting the subject from taking undue risk in participating in a clinical trial;

- Enforce both voluntary consent to research and the continual assessment of risk and benefit.

In India, Central Drugs Standard Control Organization (CDSCO) (headed by Director Control General of India) is the primary authority and "Drugs and Cosmetics Act, 1940" (along with the rules framed there under) is the principal legislation for the regulation of clinical trials. Schedule Y of the Drugs and Cosmetics Rules, 1945 ("Rules") provides for the detailed conditions, and compliances relating to clinical trials in India.
The legislative framework governing medical research in India are:

- Drugs and Cosmetics Act 1940 (Schedule Y)
- Drugs And Cosmetics (II Amendment) Rules, 2005
- ICMR guidelines, DBT guidelines
- Medical Council of India Act – 1956, (amended in the year 2002)
- Central Council for Indian Medicine Act 1970
- Guidelines for Exchange of Biological Material (MOH order, 1997)
- Right to Information Act 2005
- The Constitution of India
- The Biomedical Research on Human Subjects (regulation, control and safeguards) Acts, rules and codes of ethics of professional bodies regulating the practice of medicine in India, such as the Medical Council of India, Department of Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homoeopathy (AYUSH). Bill – 2005

Apart from these legislation's, The Indian Council of Medical Research or the ICMR, which was established with a view to foster a research culture, improve and develop infrastructure and foster community support, plays a significant role in controlling clinical trials in India.

The Drugs and Cosmetics Act and The Medical Council of India Act state that all clinical trials in India should follow the ICMR guidelines of 2000. The ICMR has a mechanism of review for its own institutions, and so do other government agencies.

The Drugs Controller General of India or the DCGI is responsible for regulatory approvals of clinical trials in India. The DCGI's office depends on external experts and other government agencies for advice. The ICMR has a Central Ethics Committee on Human Research. This committee audits the functioning of this Institutional Ethics Committee or the IEC. The amended Schedule Y of Drugs and

Cosmetic Rules order the composition of the IEC as per the ICMR guidelines. Compliance with GCP guidelines issued by the Central Drugs Standard Control Organization or the CDSCO is recommended.

DRUG AND COSMETIC RULES–

Schedule Y of the Drugs and Cosmetics Act -1940 was amended in the year 2005. Earlier, we required that all foreign drugs be retested at one phase below the highest phase of testing abroad. Now parallel global clinical trials have come. Schedule Y now permits concomitant phase 2 and phase 3 trials. India can become part of global trials. But even then, phase 1 has to be repeated for safety.

New chemical entities cannot be administered to human subjects in a clinical trial without permission from the Drugs Controller General of India. Such permission may be obtained by submitting to the DCGI an application for a clinical trial. The application must include-

- a protocol for the study,
- a draft of the Informed Consent Document,
- a list of proposed investigators who have agreed to participate in the study, and
- background information about the drug in accordance with Schedule Y of the Drugs & Cosmetics Rules.

It takes almost 12 weeks to obtain permission for a clinical trial for most investigatory drugs. The duration may be longer for drugs with special significance to the healthcare concerns of the country or those that may be considered controversial since these are liable to be referred to the Indian Council of Medical Research for comments. If clinical supplies are to be imported, a "Test-Import License" must also be applied for. Import and manufacture of clinical trial supplies is governed by Rules 33 & 34 and provisions contained in Part X-A of the rules.

CHANGING REGULATION IN INDIA

A major threat India faces in this area is its low literacy levels, which has always kept regulators skeptical about the possibility of the volunteers being not adequately informed about the risks they are undertaking. However, compliance to International Conference on Harmonization-Good Clinical Practice or ICH-GCP norms, trained investigators, a growing population of experienced monitors and exposure to international protocols seem to provide some relief to such issues but at the same time a lot of issues needs to be addressed.

1. CLINICAL TRIALS REGISTRATION

The Clinical Research Organizations or the CROs use to operate using a voluntary process administered by the Indian Council of Medical Research along with World Health Organization. As this process has proved insufficient, the DGCI came up with plans for mandatory registration of CROs in a central registry.4 The Clinical Trials Registry- India (CTRI), hosted at the ICMRs National Institute of Medical Statistics (NIMS), is a free and online public record system for registration of clinical trials being conducted in India that was launched on 20th July 2007 5Initiated as a voluntary measure, since 15th June 2009, trial registration in the CTRI has been made mandatory by the Drugs Controller General (India) (DCGI)

2. SWASTHIYA ADHIKAR MANCH INDORE AND ORS. VS MINISTRY OF HEALTH OF HEALTH AND FAMILY WELFARE AND ORS.-

In February 2012, a non-governmental organization (Swasthiya Adhikar Manch) filed a public interest lawsuit complaining about unregulated clinical trials of new drugs conducted in India by multinational pharmaceutical companies. On January 3,2013 the Supreme Court heard the complaint and castigated the Union government "for being negligent in curbing illegal clinical trials despite the deaths of at least 2,374 persons who had undergone the dubious testing for unregistered drugs between 2007 and 2012. The apex court said that the government has gone into deep slumber on the issue and has failed to put in place proper mechanisms to stop rackets of multinational companies, which are conducting illegal clinical trials. A bench of justices R.M. Lodha and A.R. Dave said in its interim order that all clinical trials will be done under the supervision of the Health Secretary at the Center.

3. RECENTAMENDMENTS–

Recently on 30th January 2013, just after the interim order was passed by the apex court in the above-mentioned matter, the Government of India came out with certain amendments to Schedule Y of the Rules with a view to tighten the norms relating to the conduct of clinical trials especially in terms of taking informed consents from the trial subjects and providing them or their legal representatives (as the case may be) compensation in case of any trial related injury or death. The amendment has imposed complete and ultimate liability on the sponsor of the clinical trial to reimburse any cost incurred by the trial subjects for the medical treatment of "*any injury*" suffered by the trial subjects

as well as financial compensation for such injury or death. Further in case the sponsor fails to provide the proper medical treatment and/ or the financial compensation as per the orders of the licensing authority to the trial subjects (or their representatives as the case may be), then the authority may cancel or suspend the license of the sponsor to carry out the clinical trials and may even debar it from carrying any clinical trial in future in India. The amendment also mandates GCP compliance and adverse event reporting. The amendment has certainly acted as a deterrent on the multi-national corporations and is a negative catalytic agent to the prospects of clinical trials in India.

- **Insertion of Rule 122- DAB in the Drugs and Cosmetics Rule, 1945 (called as The Drugs and Cosmetics (First Amendment) Rules, 2013.**

Rule 122-DAB (1) lays down the requirement of providing free medical management as long as required, in the case of an injury occurring to a clinical trial subject. Further if the injury suffered by the trail subject is related to the clinical trial conducted on such subject, he or she shall also be entitled for financial compensation as per order of the Licensing Authority. In case the clinical trial results in the death of the subject, financial compensation, as per the order of the Licensing authority, has to be compensated to the nomiee (s) of the deceased subject. The preceding subsections of the Rule explain the circumstances which is considered as a "direct nexus" to an immediate cause to the injury/death, consequences of non-payment of compensation, etc.

2. Insertion of Rule 122 DAC in the Drugs and Cosmetics Rule, 1945 (called as The Drugs and Cosmetics (Second Amendment) Rules, 2013.

Rule 122 DAC specifies the prerequisites required for a clinical trial to be considered as adequate so as to grant permission by the Licensing Authority to be conducted on any human body. Further the rule lays down the power of the Licensing Authority to impose any additional conditions to be fulfilled in case of grant of permission in respect of any specific clinical trial, as it is deem fit.

3. Insertion of Rule 122 DD in the Drugs and Cosmetics Rule, 1945 (called as The Drugs and Cosmetics (Third Amendment) Rules, 2013.

Rule 122 DD deals with mandatory registration of the Ethics Committee and specifies that no Ethics Committee shall review and accord its approval to a clinical trial protocol without prior registration with the Licensing Authority as defined in clause (b) of rule 21 and describes the procedure of such registration to be made by filling an application to be made to the Licensing Authority in accordance with the requirements as specified in the Appendix VIII of Schedule Y of the Rule and the procedure thereof.

PRESENT SCENARIO

The Supreme Court on July26, 2013 directed the Union government to come up with a new regulatory regime for clinical trials that reflects the concerns of all stakeholders, including those who volunteer to undergo the tests at the risk of adverse health effects and even death.
The Swasthiya Adhikar Manch's petition filed as a public interest litigation, came on top of criticism faced by the government for poor regulation of clinical trials conducted by foreign companies.
The Supreme Court bench also instructed the government to take suggestions from the National Human Rights Commission and activists groups such as Swasthya Adhikar Manch (which translates roughly as Right to Health Forum), one of the petitioners.
The health ministry has been directed to file an affidavit detailing its compliance with Friday's order within six weeks from july26 ,2013.
The government proposals included-

- registration of ethics committees.
- a provision to suspend or revoke their registration in case of misconduct.
- regular inspections during clinical trials, and medical treatment and compensation for those adversely affected, serious adverse impact caused by negligence will result in penalties.

As India is approaching towards globalization in the recent developments in the pharmaceutical sector occurring worldwide, India portrays to be a prospective hub for many big foreign Pharmaceutical Companies for drug innovation, based on its comparatively low cost and skill base, so as to exploit this opportunity for the betterment of the country. However, all these while India was failing to implement a rigid and stricter vigilance mechanism on the Pharmaceutical Companies who conduct such clinical trial at the cost of the lives of some vulnerable and poor individuals who are not even aware that in our Country there is existence of "right" to lead a safe and healthy life. To conclude, with the insertion of the rules and the active effort of government in hearing and examining the PIL filed by Swasthiya Adhikar Manch has brought ray of hope to many of those vulnerable ones and it is expected that the concept of Good Clinical Practices (GCP) will be a reality and not just on papers.

Question Bank

1. Explain the principles of ICH-GCP.

2. Explain the general statement about the principles of ICMR.

3. Write about the Good clinical practices that followed in India.

4. How does Indian GCP differ from ICH-GCP.

5. What are all regulatory requirements and procedures in MHRA?

6. Write about the principles of human experimentation.

7. Name the experiments done by Nazi.

8. Write about the objectives of ICH-GCP.

9. Explain the declaration of Helsinki.

10. Explain the committee member's composition in ICMR.

11. Explain the sections of ICH-GCP Guidelines.

12. Give an idea about ethical guidelines on human participants by ICMR.

SATHYABAMA
INSTITUTE OF SCIENCE AND TECHNOLOGY
(DEEMED TO BE UNIVERSITY)
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SCHOOL OF BIO AND CHEMICAL ENGINEERING

DEPARTMENT OF CENTRE FOR MOLECULAR AND NANOMEDICAL SCIENCES

UNIT – III - International Regulatory bodies and Guidelines – SMB5303

USFDA

FDA • The Food and Drug Administration (FDA or USFDA) is a government agency of the United States Department of Health and Human Services. The FDA is responsible for regulating and supervising the safety of foods, tobacco products, dietary supplements, prescription and non-prescription medication, vaccines, biopharmaceuticals, blood transfusions, medical devices, electromagnetic radiation emitting devices (ERED), veterinary products, and cosmetics. The FDA also enforces other laws, notably Section 361 of the Public Health Service Act and the associated regulations. Many of these regulations are not directly related to food or drugs. These include sanitation requirements on interstate travel and control of disease on products ranging from certain household pets to sperm donation for assisted reproduction.

Funding • The FDA regulates more than $1 trillion worth of consumer goods, about 25% of consumer expenditures in the United States. This includes $466 billion in food sales, $275 billion in drugs, $60 billion in cosmetics and $18 billion in vitamin supplements. Much of the expenditures is for goods imported into the United States; the FDA is responsible for monitoring a third of all imports.

Legal Authority • Most federal laws concerning the FDA are part of the Food, Drug and Cosmetic Act, (first passed in 1938 and extensively amended since) and are codified in Title 21, Chapter 9 of the United States Code. Other significant laws enforced by the FDA include the Public Health Service Act, parts of the Controlled Substances Act, the, as well as many others. in many cases these responsibilities are shared with other federal agencies.

Challenges and Opportunities Facing FDA • Must maintain the balance of protecting and promoting public health. • US Consumers reliance on an effective FDA for protection from unsafe medical products and contaminated food. • Also charged with Promoting Public Health by – Guiding and supporting development and availability of safe and effective new medical technologies – As well as nutitious new food products • Determine Benefit versus Risk based on current available science information.

FDA Mission • The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation’s food supply, cosmetics, and products that emit radiation. The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health.

FDA Strategic Action Plan I. Strengthen FDA for Today and Tomorrow II. Improve Patient and Consumer Safety III. Increase Access to New Medical and Food Products IV. Improve the Quality and Safety of Manufactured Products and the Supply Chain Strategic Goal 1: Strengthen FDA for Today and Tomorrow • Strengthen the scientific foundation of FDA's regulatory mission • Cultivate a culture that promotes transparency, effective teamwork, and mutual respect, and ensures integrity and accountability in regulatory decision making. • Enhance partnerships and communications. • Strengthen FDA's base of operations.

Strategic Goal 2: Improve Patient and Consumer Safety • Strengthen the science that supports product safety • Improve information systems for problem detection and public communication about product safety • Provide patients and consumers with better access to clear and timely risk-benefit information for medical products • Provide consumers with clear and timely information to protect them from food-borne illness and promote better nutrition

Strategic Goal 3: Increase Access to New Medical and Food Products • Objective 3.1: Increase the number of safe and effective new medical products available to patients. Improve information systems for problem detection and public communication about product safety • Objective 3.2: Improve the medical product review process to increase the predictability and transparency of decisions using the best available science. • Objective 3.3: Increase access to safe and nutritious new food products. Strategic Goal 4: Improve the Quality and Safety of Manufactured Products and the Supply Chain • Objective 4.1: Prevent safety problems by modernizing science-based standards and tools to ensure highquality manufacturing, processing, and distribution. development of modern continuous manufacturing technologies, which present opportunities for remote automated monitoring; and • Objective 4.2: Detect safety problems earlier and better target interventions to prevent harm to consumers. • Objective 4.3: Respond more quickly and effectively to emerging safety problems, through better information, better coordination and better communication. Implement New Import Safety Strategic Framework • Implement New Import Safety Strategic Framework: FDA anticipates following a new direction in the future for regulating imports, as outlined in the Report to the President, Protecting American Consumers Every Step of the Way: A strategic framework for continual improvement in import safety. It is a risk-based strategy that shifts the focus from interdiction at the border to prevention with verification. It will utilize data from all points in the full import life cycle – from production, manufacture, transport, distribution, and consumption – to assist in targeting the highest risk imported products for review, and facilitating the entry of low-risk products. On November 6, 2007, the Action Plan for Import Safety was released which provides specific short- and long-term recommendations to better protect consumers and enhance the safety

of the increasing volume of imports entering the United States. Within two years, accomplishments will be made in the areas of foreign operations, border operations, imported products in domestic commerce, information technology, and applied science and technology.

• Last year, the United States imported more than $2 trillion worth of products. These products were brought to the United States by roughly 825,000 importers, through over 300 ports of entry. All projections indicate that this volume will continue to rise, sharply, over the coming years as the scale and complexity of international trade multiplies.

Implement New Import Safety Strategic Framework • Imports allow consumers to enjoy the benefits of a greater variety, availability, and affordability of goods in the marketplace. • The growth of imports, combined with an increased focus on security, places a greater burden on border officials. These officials must manage larger volumes of imports from countries which often have less-developed regulatory systems. In addition, they must consider more complex risk scenarios, use more sophisticated screenings and examinations, and employ new technologies to ensure product safety.

• As FDA celebrates more than 100 years of service to the American people as the world's gold standard regulatory agency, it looks to the future. • FDA being a bridge, not a barrier • The products of explosive progress in science and technology have made that future a possibility and not just a promise but the pathway requires FDA to look ahead to being a bridge and not a barrier to the delivery of safe and nutritious food and life-saving medial and health products to the people we serve. • This strategic plan marks the path to achieve our vision for an organization that is dedicated to excellence as a science-based and science-led regulatory agency that provides global leadership in protecting public health.

Food, Drug, and Cosmetic Act

The Federal Food, Drug, and Cosmetic Act (FD&C Act) requires that every cosmetic product and its individual ingredients be substantiated for safety and that product labeling be truthful and not misleading. Cosmetic manufacturers are responsible for ensuring that products comply with the law before they are marketed. This process includes analyzing a cosmetic ingredient's testing and safety data. If the manufacturer is unable to substantiate the safety of a product, the law requires the product to carry a conspicuous warning stating that its safety has not been substantiated.

The law provides severe penalties for products that do not meet these standards. Specifically, the law gives FDA the authority:

- Ban or restrict cosmetic ingredients for safety reasons

- Mandate warning labels
- Inspect manufacturing facilities
- Issue warning letters
- Seize unsafe or misbranded products
- Enjoin unlawful activities
- Prosecute and jail violators
- Work with cosmetic manufacturers in implementing nationwide product recalls
- Collect samples for examination and analysis as part of cosmetic plant inspections, import inspections, and follow-up to complaints of adverse reactions
- Conduct research on cosmetic and personal care products and ingredients to address safety concerns

In addition to the Food, Drug, and Cosmetics Act, the Fair Packaging and Labeling Act authorizes FDA to require ingredient labeling of cosmetic and personal care products sold to consumers. Detailed FDA regulations govern where and how ingredients must be listed on the package.

Cosmetics are among the safest of all consumer products sold in the U.S. Their continued safety is ensured by FDA's regulatory program and additional safety measures undertaken by the cosmetic and personal care products industry in addition to decades of safe use by consumers who trust and enjoy them every day.

NEW DRUG APPROVAL PROCEDURE IN INDIA

The new drug approval is of two phase process - the first phase for clinical trials and second phase for marketing authorization of drug. Firstly, non-clinical studies of a drug are completed to ensure efficacy and safety, and then application for conduct of clinical trials is submitted to the competent authority of the concerned country. Thereafter, the clinical trials can be conducted (phase I to phase IV). These studies are performed to ensure the efficacy, safety and optimizing the dose of drug in human beings. After the completion of clinical studies of the drug, then an application to the competent authority of the concerned country for the approval of drug for marketing is submitted. The competent authority review the application and approve the drug for marketing only if the drug is found to be safe and effective in human being or the drug have more desirable effect as compare to the adverse effect.

Even after the approval of new drug, government should monitor its safety due to appearance of some side effects, when it is used in larger population. The interactions with other drugs, which were not assessed in a pre-marketing research trial and its adverse effects (in particular populations) should also be monitored.

DRUG APPROVAL PROCESS IN OTHER COUNTRY

Drug Approval Process In USA

In 1820, the new era of USA drug regulation was started with the establishment of U.S. Pharmacopoeia. In 1906, Congress passed the original Food and Drugs Act, which require that drugs must meet official standards of strength and purity. However, in 1937, due to sulphanilamide tragedy, the Federal Food, Drug and Cosmetic Act (of 1938) was enacted and added new provisions that new drugs must be shown safe before marketing. Further, in 1962, the Kefauver-Harris Amendment Act was passed which require that manufacturers must prove that drug is safe and effective (for the claims made in labeling).

The Food and Drug Administration (FDA) is responsible for protecting and promoting public health. Like general drug approval process, FDA's new drug approval process is also accomplished in two phases: clinical trials (CT) and new drug application (NDA) approval. FDA approval process begins only after submission of investigational new drug (IND) application. The IND application should provide high quality preclinical data to justify the testing of the drug in humans. Almost 85% of drugs are subjected to clinical trials, for which IND applications are filed. The next step is phase-I clinical trials (1-3 years) on human subjects (~100). The drug's safety profile and pharmacokinetics of drug are focused in this phase. Phase II trials (2 years) are performed if the drug successfully passes phase I. To evaluate dosage, broad efficacy and additional safety in people (~300) are the main objective of the phase II. If evidence of effectiveness is shown in phase II, phase III studies (3-4 years) begins. These phase III concerns more about safety and effectiveness of drug from data of different populations, dosages and its combination with other drugs in several hundred to about 3,000 peoples. A new drug application (NDA) can be filed only when the drug successfully passes all three phases of clinical trials and includes all animal and human data, data analyses, pharmacokinetics of drug and its manufacturing and proposed labelling. The preclinical, clinical reports and risk-benefit analysis (product's beneficial effects outweigh its possible harmful effects) are reviewed at the Center for Drug Evaluation and Research by a team of scientists. Generally approval of an NDA is granted within two years (on an average), however, this process can be completed from two months to several years. The innovating company is allowed to market the drug after the approval of an NDA and is

considered to be in Phase IV trials. In this phase, new areas, uses or new populations, long-term effects, and how participants respond to different dosages are explored. Figure 1 represents the new drug approval process of FDA.

Drug Approval Process in Europe

In European Union (EU), the medical products were approved for marketing at the National level initially. The mutual recognization procedure was introduced in 1983 and a single national review in case of pharmaceutical/medicinal product for marketing authorizations in all EU's countries was made feasible. The primary aim of this procedure was to create a united standard for product review among national regulatory authorities. In 1987, for high-technology or biologically derived products, the concertration procedure was established by directive 87/22, in which product assessment should be completed by Committee for Proprietary Medicinal Products (CPMP) besides the the normal national regulatory review. Further, in 1993, by council regulation (EEC) 2309/93, the concertration procedure was replaced with centralised procedure, by which all the high-tech and biologically derived product was reviewed and granted EU's wide marketing authorization by the EU's CPMP.

Similarly, the drug approval process in European countries is also accomplished in two phases: clinical trial and marketing authorization. A clinical trial application (CTA) is filed to the competent authority of the state to conduct the clinical trial within EU. The competent authority of that member state evaluates the application. The clinical trials are conducted only after the approval. The purpose and phases of clinical trials are similar as specified in FDA drug approval process. Figure 2 represent the clinical trial authorization process in EU.

After completing of all three phases of clinical trial, marketing authorization application is filed including all animal and human data, its analyses, as well as pharmacokinetics, manufacturing and proposed labelling. In the EU's countries, the company have a choice of following regulatory procedures:

Centralized Procedure

The Committee for Human Medicinal Products (CHMP) evaluate the applications received by the EMEA. In view of the applicant's preference, CHMP contracts out assessment work in one of the member states (the "rapporteur"). After the complete assessment, the CHMP deliver opinion to EU Commission within 210 days. The EU Commission requests comments from other member states, if a positive opinion from CHMP is received. The other member states can respond in about 28 days. When a licence is recommended, a European Public Assessment Report (EPAR) is produced and marketing authorisation is issued. This authorisation is valid throughout the European Union and is

for five years, however, the extension can be applied to the EMEA three months before the expiration of this period. Figure 3 represent the centralized procedure for marketing authorization.

Decentralised Procedure

In order to obtain marketing authorizations in several member states, the centralised procedure is not mandatory; in such case the decentralized procedure is to be used. An application is submitted to competent authorities of each of the member states, where a marketing authorization is to be sought. The information like quality, efficacy, safety, administrative information shall be submitted and a list of all Concerned Member States (CMSs) and one member state to act as Reference Member State (RMS). A draft assessment report on the medicinal product is prepared and the CMSs and the RMS validate the application within a time frame of 14 days. The RMS prepare draft summary of product characteristics, labeling and package leaflet within 120 days. This report can be approved within 90 days. However, if a medicinal product is supposed to cause potential serious risk to public health, CMS(s) will inform to other CMS, RMS and applicant and further decision in this regard is taken within 30 days. Within 60 days of the communication of the points of disagreement, all member states reach to an agreement on the action to be taken. After reaching to an agreement of the member states, the RMS records the agreement and informs to the applicant. However, if the member states could not reach an agreement, then CHMP intervenes and take a final decision keeping in view of the written or oral explanations of the applicant. Figure 4 represent the decentralized procedure for marketing authorization in EU.

National Procedure

This type of authorization is granted on country-by-country basis by the competent authorities, in each member state. Products only intended for one market and not obliged to use the centralized procedure.

History of Drug Regulation in India

Every government has the responsibility to provide access to the safe, effective and quality medication to its people. Therefore, it enacts specific laws to regulate every aspect of the drugs i.e., manufacture, sale, distribution, import and clinical research in humans. These regulatory measures are dynamic and ever evolving in consonance with the developing technologies. In India, there is broadening of regulation, Since independence, from mere manufacture and sale to newer aspects like import, clinical research and adverse drug reaction monitoring. Indian drug regulatory system has been built on the basis of principles enshrined in documents of ministry of Chemicals and Fertilizers, Department of Chemicals and Petrochemicals.

Quite evolved, though, history of drug Regulation dates back to the British Rule in India when majority of the drugs were imported from abroad. In early decade of 20th century, many unscrupulous foreign manufacturers flooded the Indian market with spurious and adulterated drugs. In response to widespread 'Gigantic Quinine Fraud'; the Government, then, formed a Drug inquiry committee under Sir Ram Nath Chopra also known as 'Chopra Committee' whose recommendations later on tabled amidst growing protest in legislative assembly as 'The Drug Bill' later on amended to the Drugs and Cosmetic Act 1940 (D and C Act) and Drugs and Cosmetic rules of 1945. This would be the central legislation that regulates India's drug and cosmetic import, manufacture, distribution and sale. This also established the Central Drugs Standard Control Organization (CDSCO), and the office of its controller, the Drugs Controller General (India) (DCG(I)). The CDSCO in the Directorate General of Health services, is a division in Ministry of Health and Family welfare, Government of India, headed by Drug Controller General of India (DCGI). It has four zonal, three sub-zonal and seven port/airport offices and six laboratories to carry out its activities.

The Drugs and Cosmetic Act, 1940 came into force from 1st April 1947. Later on, government, in 1962, extended the regulatory provisions to the cosmetics, and finally the Act came to known as Drugs and Cosmetic Act 1940. Drugs and Cosmetic Act has been divided in Chapters, Rules and Schedules and is amended from time to time to control the safety, efficacy and quality of the drugs. It is an act to regulate the import, manufacture, distribution and sale of the drugs and cosmetics. Manufacture and sale is under the respective states governments and union territories through their respective drug control organization, whereas setting standard, import, marketing authorization and monitoring of adverse drug reactions of a new drug is under Central Government.

Under Chapter Two of this Act, one statutory board and a committee have been framed called Drugs Technical Advisory Board (DTAB) and Drug Consultative Committee (DCC) separately for Modern Scientific System of Medicine and Indian traditional system of Medicine and a provision of Central Drug Laboratory at Central Research Institute, Kasauli for testing drugs has been made in this act. DTAB comprises of technical experts who advises central and state governments on technical matters of Drug regulation. Amendment, if any, to Drug and Cosmetic are made after consulting this board. Drug Consultative Committee, which has central and state Drug Control officials as its members, ensures drug control measures in all over India. It is an advisory body for the Central Government, the State Government and DTAB.

The Indian government, realizing the potential of clinical research for new therapies, has modified and amended Schedule Y to the Drug and Cosmetics Rules of 1945. Schedule Y establishes a set of

guidelines and requirements for clinical trials. However, Schedule Y was written with the generics industry in mind but increase entry of foreign pharmaceutical companies after the introduction of strict patent rules in the area of clinical research led the government to introduce many changes. The government recognized the importance of their regulation and thus developed Ethical and Regulatory Guidelines. The Indian Council of Medical Research (ICMR) issued the Ethical Guidelines for Biomedical Research on Human Subjects in 2000 and CDSCO released Indian Good Clinical Practice (GCP) guidelines in 2001.

Current Drug Regulatory Procedures

The Central Drugs Standard Control Organization (CDSCO) under Ministry of Health and Family Welfare (MoH and FW) prescribes standards for ensuring safety, efficacy and quality of drugs, cosmetics, diagnostics and devices in India. It also regulates the market authorization of new drugs and clinical trials standards; supervises drug imports and approves license to manufacture. The Department of Chemical and Petrochemicals of Ministry of Chemicals and Fertilizers through National Pharmaceutical Pricing Authority (NPPA) sets or revise the prices of drugs; maintains data on production, exports and imports; and enforces and monitors the availability of medicines and also gives opinions to parliament on the related issues. It also ensures administration of Drug Policy, 1986 (updated in 2002); Drug (Price Control) Order, 1995 and Pharmaceutical Policy, 2002.

There are two main ministries which regulate the drugs in India; the Ministry of Health and Family Welfare concerned with public health and the Ministry of Chemicals and Fertilizers on Industrial policy. Other ministries, though indirect, also have a role in regulation process; Ministry of Environment and Forests, Ministry of Finance, Ministry of Commerce and Industry and the Ministry of Science and Technology. Regulation of Patents, drug exports is governed by Department of Industrial Policy and Promotion and Directorate General of Foreign Trade under the aegis of Ministry of Commerce and Industry and the Ministry of Chemical and Fertilizers respectively. Licensing and quality control and distribution maintained by CDSCO, MoH and FW, Department of Biotechnology, Ministry of Science and Technology (DST) and Department of Environment and Forests especially after the decline of vulture population.

Medicines and Healthcare products Regulatory Agency

The Medicines and Healthcare products Regulatory Agency, an executive agency of the Department of Health and Social Care, exists to enhance and improve the health of millions of people every day through the effective regulation of medicines and medical devices, underpinned by science and research. We deliver this through three distinct yet complimentary business centres: the MHRA

regulatory centre, the National Institute for Biological Standards and Control (NIBSC) and the Clinical Practice Research Datalink (CPRD). With a range of interesting specialist opportunities on offer, with plenty of scope to develop your career within a leading and multifaceted scientific organisation, why not consider a career with us at our offices in central London or Hertfordshire.

Structure

The MHRA is divided into three main centres:

- MHRA Regulatory – the regulator for the pharmaceutical and medical devices industries
- Clinical Practice Research Datalink – oversees clinical primary care data for research
- National Institute for Biological Standards and Control – responsible for the standardisation and control of biological medicines

The MHRA has several independent advisory committees which provide the UK Government with information and guidance on the regulation of medicines and medical devices. There are currently eight such committees:

- Advisory Board on the Registration of Homeopathic Products
- Herbal Medicines Advisory Committee
- The Review Panel
- Independent Scientific Advisory Committee for MHRA database research
- Medicines Industry Liaison Group
- Innovation Office
- Blood Consultative Committee
- Devices Expert Advisory Committee

Clinical Trial of an Investigational Medicinal Product (CTIMPs)

A CTIMP is any study that will generate new information about the safety and/or efficacy of one or more medicinal products. A medicinal product is a substance presented in a pharmacological form with the intention of affecting a clinical or physiological outcome. A product that a CTIMP generates information about is referred to as an Investigational Medicinal Product (IMP).

This includes studies of licenced medicinal products, if they will be used in any way other than as described in their licence or if new information will be generated.

This includes studies where the medicinal product is not the subject of the study but new information will or may be generated - due to its use as a control, for example.

Application

Applications to the MHRA are generated via IRAS. For a CTIMP, selecting option 1 on filter question 2 will open follow-up filter questions and will add Section B1 to the main form. The details required by the MHRA will be recorded in this form and then downloaded. Once this has been reviewed by Research Governance, we will submit it to the MHRA - usually in parallel with the REC/HRA application.

Safety reporting

The Clinical Trial regs require that strict Safety Reporting be observed for CTIMPs - regardless of the perceived risk of the study or the licensing status of the product.

Inspection

The MHRA are required to inspect organisations conducting CTIMPs. This will either take the form of a routine inspection, usually of a Sponsor, during which they will inspect a number of studies from the Sponsor's portfolio; or a triggered inspection, where a concern has been raised about the conduct of an organisation, or a specific study.

European Medicines Agency

The European Medicines Agency (EMA) is an agency of the European Union (EU) in charge of the evaluation and supervision of medicinal products. Prior to 2004, it was known as the European Agency for the Evaluation of Medicinal Products or European Medicines Evaluation Agency (EMEA).

The EMA was set up in 1995, with funding from the European Union and the pharmaceutical industry, as well as indirect subsidy from member states, its stated intention to harmonise (but not replace) the work of existing national medicine regulatory bodies. The hope was that this plan would not only reduce the €350 million annual cost drug companies incurred by having to win separate approvals from each member state but also that it would eliminate the protectionist tendencies of Sovereign states unwilling to approve new drugs that might compete with those already produced by domestic drug companies.

The EMA was founded after more than seven years of negotiations among EU governments and replaced the Committee for Proprietary Medicinal Products and the Committee for Veterinary Medicinal Products, though both of these were reborn as the core scientific advisory committees. The agency was located in London prior to the United Kingdom's vote for withdrawal from the European Union, relocating to Amsterdam in March 2019.

Operations

The EMA operates as a decentralised scientific agency (as opposed to a regulatory authority) of the European Union and its main responsibility is the protection and promotion of public and animal health, through the evaluation and supervision of medicines for human and veterinary use. More specifically, it coordinates the evaluation and monitoring of centrally authorised products and national referrals, develops technical guidance and provides scientific advice to sponsors. Its scope of operations is medicinal products for human and veterinary use including biologics and advanced therapies, and herbal medicinal products. The agency is composed of the Secretariat (ca. 600 staff), a management board, seven scientific committees (human, veterinary and herbal medicinal products, orphan drugs, paediatrics, advanced therapies and pharmacovigilance risk assessment) and a number of scientific working parties. The Secretariat is organised into five units: Directorate, Human Medicines Development and Evaluation, Patient Health Protection, Veterinary Medicines and Product Data Management, Information and Communications Technology and Administration. The Management Board provides administrative oversight to the Agency: including approval of budgets and plans, and selection of Executive Director. The Board includes one representative of each of the 27 Member States, two representatives of the European Commission, two representatives of the European Parliament, two representatives of patients' organisations, one representative of doctors' organisations and one representative of veterinarians' organisations. The Agency decentralises its scientific assessment of medicines by working through a network of about 4500 experts throughout the EU. The EMA draws on resources of over 40 National Competent Authorities (NCAs) of EU Member states.

Committees

Medicinal products for human use

A single evaluation is carried out through the Committee for Medicinal Products for Human Use (CHMP). If the Committee concludes that the quality, safety and efficacy of the medicinal product is sufficiently proven, it adopts a positive opinion. This is sent to the European Commission to be transformed into a marketing authorisation valid for the whole of the EU. A special

type of approval is the paediatric-use marketing authorisation (PUMA), which can be granted for medical products intended exclusively for paediatric use.

The CHMP is obliged by the regulation to reach decisions within 210 days, though the clock is stopped if it is necessary to ask the applicant for clarification or further supporting data.

Orphan medicinal products

The Committee on Orphan Medicinal Products (COMP) administers the granting of orphan drug status since 2000. Companies intending to develop medicinal products for the diagnosis, prevention or treatment of life-threatening or very serious conditions that affect not more than five in 10,000 persons in the European Union can apply for 'orphan medicinal product designation'. The COMP evaluates the application and makes a recommendation for the designation which is then granted by the European Commission.

Centralised marketing authorisations

The centralised procedure allows companies to submit a single application to the agency to obtain from the European Commission a centralised (or "community") marketing authorisation (MA) valid in all European Union member states and in Iceland, Liechtenstein and Norway. The centralised procedure is compulsory for all medicines derived from biotechnology and other high-tech processes, as well as for human medicines for the treatment of HIV/AIDS, cancer, diabetes, neurodegenerative diseases, auto-immune and other immune dysfunctions, and viral diseases, and for veterinary medicines for use for growth or yield enhancers. It is also compulsory for advanced-therapy medicines such as gene-therapy, somatic cell-therapy or tissue-engineered medicines and for orphan medicines (for rare diseases). The centralised procedure is also open to products that bring a significant therapeutic, scientific or technical innovation, or is in any other respect in the interest of patient or animal health. As a result, the majority of genuinely novel medicines are authorised through the EMA.

For products eligible for or requiring centralised approval, a company submits an application for a marketing authorisation to the EMA.

Comparison with other regulatory agencies

The EMA is roughly parallel to the drug part of the U.S. Food and Drug Administration (FDA), but without centralisation. The timetable for product approval via the EMA's centralised procedure of 210 days compares well with the average of 500 days taken by the FDA to evaluate a product.

Brazil: Overview of regulatory affairs Good Laboratory practices (GLP)

Overview

As per ResNo9, ResNo61, and ResNo176, the National Health Surveillance Agency (Agência Nacional de Vigilância Sanitária (ANVISA)) is the regulatory authority responsible for clinical trial oversight, approval, and inspection of drugs to be registered in Brazil. ANVISA grants permission for clinical trials to be conducted in accordance with the provisions of ResNo9, ResNo61, and ResNo176.

LawNo9.782 states ANVISA is an independent administrative agency linked to the Ministry of Health (MOH) that is responsible for regulating, controlling, and supervising products and services involving public health risks. LawNo9.782 and ResNo61 explain that the goods and products under the agency's purview include medicines for human use and their active ingredients, immunobiologicals and their active substances, and blood and blood derivatives.

As indicated in LawNo9.782 and ResNo61, ANVISA is headed by a Collegiate Board of Directors composed of up to five (5) members, one of whom serves as the Chief Executive Officer. Among the Collegiate Board's key responsibilities are its role in defining ANVISA's strategic guidelines and proposing governmental policies and directives to the Minister in support of the agency's sanitary surveillance objectives.

LawNo9.782 and ResNo61 further indicate that ANVISA has an Advisory Board and an Ombudsman. Per ResNo61 and BRA-36, the Advisory Board's main objectives include requesting information and proposing guidelines and technical recommendations to the Collegiate Board to be addressed by ANVISA, and providing opinions on proposed governmental policies. According to BRA-35, the Ombudsman's Office acts independently from the Collegiate Board and the Advisory Board. The Ombudsman's activities, as described in ResNo61, include receiving and registering criticisms, complaints, claims, and suggestions from users and participating in the monitoring and evaluation of ANVISA's customer service policy. Refer to LawNo9.782, ResNo61, BRA-36, and BRA-35 for detailed Collegiate Board, Advisory Board, and Ombudsman responsibilities.

As delineated in ResNo61, ANVISA oversees five directorates including the Sanitary Authorization and Registration Board, the directorate responsible for granting approval to conduct clinical trials for drugs to be registered in Brazil. Per ResNo61 and ResNo176, the Sanitary Authorization and Registration Board oversees the administration of the General Management of Medicines and Biological Products (Gerência-Geral de Medicamentos e Produtos Biológicos (GGMED)). The

GGMED coordinates and supervises the organizational units responsible for the regulation of active pharmaceutical ingredients, medicines, and biological products, and manages the implementation of international cooperation activities aimed at regulating active pharmaceutical inputs, medicines, and clinical research involving human beings. The Coordination of Clinical Research on Drugs and Biologicals (Coordenação de Pesquisa Clínica em Medicamentos e Produtos Biológicos (COPEC)) is an administrative unit operating within GGMED that evaluates the processes and petitions related to clinical research on drugs and biological products, and issues technical opinions with the goal of granting approval to initiate clinical research in Brazil. See ResNo61 and ResNo176 for detailed information on ANVISA's organizational structure and administrative units.

Per BRA-55, ANVISA has successfully completed the Pharmaceutical Inspection Co-operation Scheme (PIC/S) qualification process to modernize its regulatory instruments and inspection processes. Refer to BRA-55 for additional information.

Please note: Brazil is party to the Nagoya Protocol on Access and Benefit-sharing (BRA-63), which may have implications for studies of investigational products developed using certain non-human genetic resources (e.g., plants, animals, and microbes). For more information, see BRA-81.

ANVISA's vision is to achieve legitimation in society as an integral part of the Brazilian Unified Health System, via a nimble, modern, transparent, and domestic and international benchmark in health surveillance and regulation. ANVISA's mission is "to protect and promote public health and to intervene in the risks caused by the production and use of products regulated by health surveillance. This mission must be carried out in coordination with states, municipalities and the Federal District, according to the Brazilian Unified Health System principles, to improve the quality of life of the population." The agency is also responsible for health control in ports, airports, and borders, as well as for establishing relations with the Ministry of International Affairs and with foreign organisms and institutions to deal with international affairs regarding health surveillance. ANVISA was accepted as a new regulatory member of the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). As part of the objective to extend its global outreach, ICH, in November 2016, welcomed ANVISA from Brazil and the Ministry of Food and Drug Safety (MFDS) from South Korea as the first new regulatory Members, together with the Biotechnology Innovation Organization (BIO) as a new industry association Member. There are now 13 members and 22 observers.

Responsibilities

ANVISA is responsible for drug registration and licensure of pharmaceutical laboratories and other companies inside the pharmaceutical production flow. The agency is also responsible for establishing regulations applicable to clinical trials (with regards to drugs Chemistry, Manufacturing, and Control (CMC) and subject safety). In conjunction with the Health Ministry and other ministries members, ANVISA works with the Chamber of Drug Market Regulation (CMED) to regulate drug pricing. Ethical human clinical trials are in turn regulated by an Ethics Committee (EC) linked to the Health Ministry. Together with states and local municipalities, the agency inspects factories, monitors the quality of drugs, exercises post-marketing surveillance, takes pharmacovigilance actions, and regulates drug promotion and marketing. Moreover, ANVISA evaluates patent requests related to pharmaceutical processes and products, in partnership with the National Industrial Property Institute (INPI). ANVISA's values encompass ethics and responsibility as a public agency, the capacity for interaction and integration, management excellence, knowledge as a source of action, transparency, and accountability.

Regulatory submission process

Companies need to understand the regulatory structure as well as their requirements to initiate product development in a new country. For the past five years, ANVISA has updated their regulations and developed numerous guidance. The primary challenge to successfully submitting an ANVISA regulatory file is directly associated with bio/pharmaceutical companies' lack of knowledge of the process. Currently, ANVISA's website is presented in two languages: Portuguese (the native language in Brazil) and English. However, the English version is limited in contents and does not contain all the relevant information that is presented in the Portuguese version. Companies that do not have a regulatory presence in Brazil may be dependent on regulatory professionals with specific expertise in that market. To facilitate the better understanding of the ANVISA process, the registration procedure is compared to a more familiar registration system used by the U.S. Food and Drug Administration (FDA).

Conducting a clinical trial in brazil

Brazil has become a large market and more attractive to the pharmaceutical industry, thus the desire to entering this market became more evident. It is helpful to know the regulatory institutions that are involved with the clinical trials conducted in Brazil and to be awared of related documents.

Institutions involved in the approval process

In Brazil, three different institutions: CONEP (Central), CEP (local committee), and ANVISA, are responsible for reviewing and approving regulatory documents to initiate a clinical study in this region. The CONEP and ANVISA processes happen in parallel.

Approval process

The regulatory approval process typically passes through 2 ethical evaluations: the institutional CEP and CONEP. The Coordinating Ethics Committee (EC) submits the multicenter research center research protocol for CONEP for review, and approval would apply to all sites. CONEP submission requires the protocol, the ICF, investigator's brochure, Power of Attorney, protocol approved a letter from Coordinating EC, and all other documents submitted to the Coordinating EC. ANVISA has separate departments for drugs and devices: COPEC is the Coordination of Clinical Research with Drugs, and Biological Products and COPEA is the Coordination of Clinical Research with Devices and Food. ANVISA evaluates the clinical dossier of drug development rather than each trial. For individual clinical protocol, a simple submission package must be submitted when phase I, II or III trials in Brazil is to be performed; however, for phase IV, only a notification to ANVISA is required. According to their guidance, it could take from 90 to 180 days for ANVISA to review the dossier before the study can be initiated.

Recent updated resolutions

In Brazil, it is required that all Active Pharmaceutical Ingredients (APIs) and drug products manufactured or imported are registered with the agency. The regulatory system though established but yet is quite complex. The drug registration is valid for five years and may be revalidated for equal and successive periods of time. Their regulatory requirements and guidelines are written in the format called "resolution". As a new ICH member, ANVISA strives to revise many of their resolutions and bring them up-to-date, especially those topics that have corresponding ICH guidelines. However, many of these updated guidelines contain higher level of details with concrete structure, thus making it difficult to embrace the risk-based approached as compared to the original ICH countries. Below are some examples of recent distributed resolutions.

Question bank:

1. What are all regulatory requirements and procedures in MHRA?

2. How to develop the new drug? What is the process to approve the new drug and its principle in India?

3. What are the GLP's Standard operation procedures?

4. Describe about the Mutual recognition procedures?

5. Give details about FDA?

6. Give a detail about food and cosmetic act.

7. What are the regulatory law for approving new drug?

8. Describe about Schedule Y.

9. What are the MHRA and give some examples.

10. Details about the EMEA?

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SCHOOL OF BIO AND CHEMICAL ENGINEERING

DEPARTMENT OF CENTRE FOR MOLECULAR AND NANOMEDICAL SCIENCES

UNIT – IV - Intellectual Property Rights – SMB5303

INTRODUCTION

- **Intellectual property (IP)** is a term referring to the creation of the intellect (the term used in studies of the human mind) for which a monopoly (from greek word Monos means single-pole in to sell) is assigned to designated owners by law.
- Some common types of intellectual property rights (IPR), in some foreign countries intellectual property rights, are referred to as ***industrial property***, copyright, patent, and trademarks, trade secrets all these cover music, literature and other artistic works, discoveries and inventions and words, phrases, symbols, and designs.
- Intellectual Property Rights are legal rights, which result from intellectual activity in industrial, scientific, literary & artistic fields.
- These rights Safeguard creators and other producers of intellectual goods & services by granting them certain time-limited rights to control their use.
- Protected IP rights like other property can be a matter of trade, which can be owned, sold, or bought. These are intangible and non-exhausted consumption.

BASIC CONCEPT IN IPR

- Intellectual property is an intangible creation of the human mind, usually expressed or translated into a tangible form that is assigned certain rights of property.
- Examples of intellectual property include an author's copyright on a book or article, a distinctive logo design representing a soft drink company and its products, unique design elements of a website, or a patent on the process to manufacture chewing gum.
- Intellectual property rights (IPR) can be defined as the rights given to people over the creation of their minds. They usually give the creator an exclusive right over the use of his/her creations for a certain period of time.

- Intellectual property (IP) refers to creations of the mind: inventions, literary and artistic works, and symbols, names, images, and designs used in commerce.

TYPES OF IPR

1. Patents
2. Trademarks
3. Copyrights and related rights
4. Geographical indications
5. Industrial designs
6. Trade secrets
7. Layout design for integrated circuits
8. Protection of new plant variety

PATENTS

- A patent is an exclusive right granted for an invention, which is a product or a process that provides a new way of doing something or offers a new technical solution to a problem. It provides protection for the invention to the owner of the patent. The protection is granted for a limited period, i.e. 20 years.
- Patent protection means that the invention cannot be commercially made, used, distributed, or sold without the patent owner's consent. A patent owner has the right to decide who may - or may not - use the patented invention for the period in which the invention is protected.
- The patent owner may permit to, or license, other parties to use the invention on mutually agreed terms. The owner may also sell the right to the invention to someone else, who will then become the new owner of the patent.

- ❖ Once a patent expires, the protection ends, and an invention enters the public domain, that is the owner no longer holds exclusive rights to the invention, which becomes available for commercial exploitation by others.
- ❖ All patent owners are obliged, in return for patent protection, to publicly disclose information on their invention in order to enrich the total body of technical knowledge in the world.
- ❖ Such an ever-increasing body of public knowledge promotes further creativity and innovation in others. In this way, patents provide not only protection for the owner but valuable information and inspiration for future generations of researchers and inventors.

TRADEMARKS

- A trademark is a distinctive sign that identifies certain goods or services as those produced or provided by a specific person or enterprise. It may be one or a combination of words, letters, and numerals.
- They may consist of drawings, symbols, three-dimensional signs such as the shape and packaging of goods, audible signs such as music or vocal sounds, fragrances, or colors used as distinguishing features.
- It provides protection to the owner of the mark by ensuring the exclusive right to use it to identify goods or services or to authorize another to use it in return for payment.
- It helps consumers identify and purchase a product or service because its nature and quality, indicated by its unique trademark, meets their needs.
- Registration of a trademark is prima facie proof of its ownership giving the statutory right to the proprietor.
- Trademark rights may be held in perpetuity. The initial term of registration is for 10 years; thereafter it may be renewed from time to time.

- **Mark** includes *"Device, brand, heading, label, ticket, name, signature, word, letter, numeral, shape of goods, packaging, the combination of colors, and any combination thereof."*
- **Brand** refers to a name, term, sign, symbol, or design, or a combination of them, intended to identify the goods or services of one seller or group of sellers and to differentiate them from those of competitors. E.g. McDonald for restaurants, Cycle brand agarbattis, *etc*.
- **Brand Name** is that part of a brand that can be vocalized-the utterable.
- **Brand Mark** is that part of a brand that can be recognized but is not utterable, such as symbol, design or distinctive coloring, or lettering.
- **Device** refers to pictorial representations – e.g. animals, birds, landscape buildings, etc.
- **Letter** as a mark is the identity created out of letterforms and has its inbuilt strength of distinctiveness and individuality – e.g. IBM, GM, ELBEE, 3M *etc*

TRADEMARKS TERMS EXPLANATION

- ✓ **Numerals** can be registered as a trademark upon evidence of user, e.g. 555, 501
- ✓ **Symbols** may take the shape of brand or logos. A logo is a visual depiction of a manufacturer or company and gives an identity to it. E.g. B.M.W., Maruti, Benz etc.
- ✓ **Label and ticket** mean a composite mark containing various features incl. devices, words, usually painted on paper and attached to the goods themselves.
- ✓ **Name** is the words signifying a name, surname or a personal name or an abbreviation thereof
- ✓ **Color** – a combination of colors can be considered as a trademark-e.g. color combinations used in drug capsules.
- ✓ **Sound** – sound or a sequence of sound can be registered as a trademark – e.g. 'the roar of the lion' sound has been registered by MGM pictures; the 'Tarzan Yell" has been registered as Edgar Rice Burroughs Inc.

- ✓ **Smell** – Registration of smell as a trademark has been permitted as a trademark. A smell reminiscent of roses applied to tyres was registered for Sumitomo tyres – the smell of fresh-cut grass for the tennis ball, etc.
- ✓ **Containers** fall within the definition of a trademark.
- ✓ 'Collective mark' means a trade mark distinguishing the goods or services of members of an association of persons (not being a partnership), who is the proprietor of the mark from those of others.
- ✓ 'Service' means service of any description which is made available to potential users and includes the provisions of services in connection with the business of any industrial or commercial matters such as banking, communication, education, financing, insurance, chit funds, real estate, transport, storage, material treatment, processing, supply of electrical or other energy, boarding, lodging, entertainment, amusement, construction, repair, conveying of news or information and advertising. A mark identifying such a service is called a service mark.
- ✓ "Certification trade mark" means a mark capable of distinguishing the goods or services in connection with which it is used in the course of trade which is certified by the proprietor of the mark in respect of origin, material, mode of manufacture of goods, or performance of services, quality, accuracy or other characteristics from goods and services not so certified. (e.g. wool mark, ISO 9001, etc.)

TRADEMARKS REGISTRATION

- δ Trademark and Service mark are used before registration.
- δ Registration of a trademark is not a compulsory requirement of the law. The Controller-General of Patents, Designs, and Trade Marks Act, appointed by the central government is

the Registrar of Trade Marks. A Register of Trade Marks shall be kept in offices, Regd. Trade Marks details shall be entered into the register.

- δ Once Trade Mark is accepted, allotted should advertise it in the prescribed manner.
- δ The registration of a trademark, if valid, gives its proprietor the exclusive right to the use of the trademark in relation to the goods or services in respect of which the trademark is registered and to obtain relief in respect of infringement of the trademark.
- δ Trademark registration is for 10 years from the date of registration and can be renewed every 10 years consecutively. Failure to renew is the removal of the trademark from the register.
- δ If the earlier trademark being a well-known trademark and the trademark sought to be registered is identical with or similar to an earlier trademark and the goods or services are dissimilar and the use of the mark would take unfair advantage of or be detrimental to the distinctive character or repute of the earlier trademark.
- δ If the use of the trademark in India is liable to be prevented because of any law protecting an unregistered trademark used in the course of trade or because of the law of copyright.

GROUNDS FOR REFUSAL OF REGISTRATION

- β Marks devoid of distinctive character
- β Descriptive marks
- β Generic marks
- β Marks of such a nature as to deceive or cause confusion
- β Marks containing any matter which is likely to hurt the religious susceptibilities of any class or section of the Indian citizens
- β Marks containing scandalous or obscene matter
- β Marks prohibited under the Emblems and Names (Prevention of Improper use) Act, 1950

- β Marks consisting exclusively of the shape of the goods which results from the nature of the goods themselves (e.g. apple design for a package of apples, round shape for tennis balls, etc.)
- β Marks consisting exclusively of the shape of the goods which is necessary to obtain technical results.
- β If there exists a likelihood of confusion with the earlier trademark because of the fact of the trademark being identical with the earlier trademark and similarity of goods and services or being similar to the earlier trademark and identical or similar goods and services.

COPYRIGHTS AND RELATED RIGHTS

- ❖ Copyright is a monopoly right restraining others from exercising that right that has been conferred on the owner of the copyright.
- ❖ It is a negative right meaning thereby that it is prohibitory in nature. It is a right to prevent others from copying or reproducing the work.
- ❖ The object of copyright is to encourage authors, composers, and artists to create original works by rewarding them the exclusive right for a specific period to reproduce the works for publishing and selling them to the public. The moral basis of copyright law rests in the eighth commandment “Thou shall not steal”.
- ❖ Copyright is not a single right. It is a bundle of rights in the same work. For e,g. in the case of a literary work, copyright consists of reproduction in print media, the right of dramatic and cinematographic versions, the right of translation, adaptation, abridgment, and the right of public performance.
- ❖ Copyright consists not merely of the right of reproduction. It also consists of the right to works derived from the original work, rights like the right of public performance, the recording right, and the broadcasting right. Such related rights are called “neighbouring rights”.

- To secure copyright protection, the author must have bestowed upon the work "sufficient judgment, skill, and labor or capital". It is immaterial whether the work is wise or foolish, accurate or inaccurate or whether it has literary merit or not. Copyright protects the skill and labour employed by the author in his work.
- The owner of a copyright has no monopoly in the subject matter. Others are at liberty to produce the same result provided they do so independently and though they are not first in the field, their work is nonetheless 'original'.
- There is no copyright in ideas. Copyright subsists only in the material form to which the ideas are translated. Since there is no copyright in ideas or information, it is no infringement of copyright to adopt the ideas of another or to publish information derived from another, provided there is no copying of the language in which those ideas have or that information has been previously embodied.
- Copyright subsists in "original literary, dramatic, musical and artistic works; cinematographic films and sound recordings".
- Literary work includes computer programs, tables, compilations included. Computer databases. Dramatic work includes any piece for recitation, choreographic work, or entertainment in a dumb show, the scenic arrangement or acting form of which is fixed in writing or otherwise but does not include cinematographic film.
- Music work means a work consisting of music and includes any graphical notation of such work, but does not include any works or action intended to be sung, spoken, or performed with the music.
- Artistic work means a painting, a sculpture, a drawing (incl. diagram, map, chart, or plan), an engraving or a photograph, whether or not any such work possesses artistic quality; a work of 'architecture' means any building or structure having an artistic character or design or any model for such building or structure.

- The cinematographic film means any work of usual recording on any medium produced through a process from which a moving image may be produced by any means and includes a sound recording accompanying such visual recording and 'cinematograph' shall be construed as including any work produced by any process analogous to cinematography including video films.
- Sound recording means a recording of sounds from which such sounds may be reproduced regardless of the medium on which such recording is made or the method by which the sounds are produced.
- The word 'original' does not mean that the work must be an expression of original or inventive thought. It only means the work must not be copied from another work, that is, it should originate from the author.
- To qualify for copyright in India, the work should satisfy the following conditions:-
  - ✓ The work is first published in India;
  - ✓ Where the work is first published outside India, the author at the date of publication must be a citizen of India. If the publication was made after the author's death, the author must have, at the time of death, being a citizen of India.
  - ✓ In the case of unpublished work the author, on the date of making of the work, is a citizen of India or domiciled in India.

TERM (Period) OF COPYRIGHT

- In the case of any literary, dramatic, musical, or artistic work (other than a photograph), a lifetime of the author + 60 years.
- In the case of a photograph, cine films, sound recording, and Govt. Work, 60 years from the beginning of the calendar year next following the year in which the work is first published.

- In the case of broadcasters/performers, reproduction rights shall subsist until 25 years from the calendar year next following the year in which the broadcast/performance is made.

COPYRIGHT - OWNERSHIP

The author in relation to various categories of works is as follows:-

- Literary or dramatic work – author of the work
- Musical work – composer
- Artistic work – Artist
- Photograph – Photographer
- Cinematograph film – Film producer
- Sound recording – the producer
- Literary, dramatic, musical, or artistic work which is computer generated – the person who causes the work to be created.
- Normally the author of the work will be the first owner, subject to the following exceptions.

COPYRIGHT – OWNERSHIP: EXCEPTIONS

- Where a work is made by the author in the course of his employment by the proprietor of a newspaper/magazine/ periodical for publication therein, then such proprietor will be the first owner.
- Where a photograph is taken or a painting or a portrait drawn or an engraving or cine film made for consideration at the instance of any person, then such person shall be the first owner.
- When a work is made in the course of the author's employment under a contract of service/apprenticeship, the employer will be the first owner.
- Where any person has delivered any address or speech in public, that person will be the first owner of the copyright.

- In the case of Government work, the government is the first owner.

GEOGRAPHICAL INDICATIONS

- GI are signs used on goods that have a specific geographical origin and possess qualities that derive from their place of production and are influenced by specific local factors, such as climate and soil.
- They may also highlight specific qualities of a product, which are due to human factors that can be found in the place of origin of the products, such as specific manufacturing skills and traditions.
- A geographical indication points to a specific place or region of production that determines the characteristic qualities of the product that originates therein. The product must derive its qualities and reputation from that place.
- The place of origin may be a village or town, a region or a country. It is an exclusive right given to a particular community hence the benefits of its registration is shared by all members of the community.
- Recently the GIs of goods like Chanderi Sarees, Kullu Shawls, and Wet Grinders, etc have been registered. Keeping in view the large diversity of traditional products spread all over the country, the registration under GI will be very important in the future growth of the tribes/communities / skilled artisans associated with developing such products.

INDUSTRIAL DESIGNS

- Industrial designs refer to creative activity, which results in the ornamental or formal appearance of a product, and design right refers to a novel or original design that is accorded to the proprietor of a validly registered design.

- δ Industrial designs are an element of intellectual property. Under the TRIPS Agreement, minimum standards of protection of industrial designs have been provided. As a developing country, India has already amended its national legislation to provide for these minimal standards.
- δ The essential purpose of design law is to promote and protect the design element of industrial production. It is also intended to promote innovative activity in the field of industries.
- δ The existing legislation on industrial designs in India is contained in the New Designs Act, 2000 and this Act will serve its purpose well in the rapid changes in technology and international developments.
- δ India has also achieved a mature status in the field of industrial designs and in view of the globalization of the economy, the present legislation is aligned with the changed technical and commercial scenario and made to conform to international trends in design administration.
- δ This replacement Act is also aimed to enact a more detailed classification of design to conform to the international system and to take care of the proliferation of design-related activities in various fields.

TRADE SECRETS

- η It may be confidential business information that provides an enterprise a competitive edge may be considered a trade secret.
- η Usually, these are manufacturing or industrial secrets and commercial secrets. These include sales methods, distribution methods, consumer profiles, and advertising strategies, lists of suppliers and clients, and manufacturing processes. Contrary to patents, trade secrets are protected without registration.

- η A trade secret can be protected for an unlimited period of time but a substantial element of secrecy must exist, so that, except by the use of improper means, there would be difficulty in acquiring the information.
- η Considering the vast availability of traditional knowledge in the country the protection under this will be very crucial in reaping benefits from such type of knowledge.
- η The Trades secret, traditional knowledge are also interlinked/associated with the geographical indications.

THE LAW GOVERNING TRADE SECRETS

- ★ Trademarks, copyrights, and patents are all subject to extensive federal statutory schemes for their protection, there is no federal law relating to trade secrets, and no registration is required to obtain trade secret protection.
- ★ Most trade secret law arises from common law principles, namely, judge-made case law.
- ★ The first reported trade secret case in the United States was decided in 1837 and involved manufacturing methods for making chocolate.
- ★ In 1939, the Restatement of Torts (a wrongful act or an infringement of a right) adopted a definition of a trade secret, and many states relied on that in developing their body of case law, leading to greater consistency in the development of trade secrets law.
- ★ Additionally, in 1979, the National Conference of Commissioners on Uniform State Laws drafted the Uniform Trade Secrets Act (UTSA) to promote uniformity among the states with regard to trade secrets law.
- ★ The UTSA was amended in 1985.

DETERMINATION OF TRADE SECRET STATUS

- η The extent to which the information is known outside the company
- η The extent to which the information is known within the company

- The extent of the measures taken by the company to maintain the secrecy of the information
- The extent of the value of the information to the company and its competitors
- The extent of the expenditure of time, effort, and money by the company in developing the information
- The extent of the ease or difficulty with which the information could be acquired or duplicated by other

TRADE SECRET LITIGATION

- If a trade secret is disclosed in violation of a written confidentially agreement, and the parties cannot resolve the dispute themselves, an action for breach of contract may be brought, similar to any other breach of contract action.
- The plaintiff may add other causes of action as well, for example, for misappropriation in violation of a state trade secret law. If no written agreement exists, the plaintiff must rely upon case law or state statutes protecting trade secrets, or both.
- To protect itself against a lawsuit by another alleging trade secret violation, companies should require new employees who will have access to confidential information to acknowledge in writing that accepting employment with the new company does not violate any other agreement or violate any other obligation of confidentiality to which the employee may be subject.
- If grounds for federal jurisdiction exist (the parties have diverse citizenship and the claim exceeds $75000), the action may be brought in federal court.
- The UTSA [Uniform Trade Secrets Act] provides that an action for misappropriation must be brought within three years after the misappropriation is discovered or reasonably should have been discovered.
- In federal court, the action will be governed by the Federal Rules of Civil Procedure relating

to federal civil actions generally.

- Most states have rules relating to civil procedure that are modeled substantially after the Federal Rules of Civil Procedure and likewise govern litigation.
- If the defendant has a cause of action to assert against the plaintiff relating to the trade secret, it must be asserted by way of a counterclaim in the litigation so that all disputes between the parties relating to the information can be resolved at the same time.
- After the complaint, answer, and counterclaim have been filed, various motions may be made. Discovery will commence. The plaintiff and defendant will take depositions to obtain testimony from those who may have information about the case.
- Ultimately, if the matter cannot be resolved by private agreement, it will proceed to trial. The trade secret owner must prove misappropriation by a preponderance of the evidence. Either party may request a jury trial; otherwise, a judge will render the decision. Appeals may follow.
- One of the difficult issues in trade secret litigation arises from the fact that the trade secret sought to be protected often must be disclosed in the litigation so the judge or jury can evaluate whether the information is sufficiently valuable that it affords its owner a competitive advantage.
- Similarly, the owner's methods of protecting the information often must be disclosed so the fact-finder can determine whether the owner has taken reasonable measures to protect the alleged trade secrets.
- The dilemma faced by trade secrets owners is that they must disclose the very information they seek to protect.
- As technology progresses and the value of certain communication and entertainment inventions increases, trade secret litigation is becoming an increasingly common and high-stakes occupation.

LAYOUT DESIGN FOR INTEGRATED CIRCUITS

- ✓ Semiconductor Integrated Circuit means a product having transistors and other circuitry elements, which are inseparably formed on a semiconductor material or an insulating material or inside the semiconductor material and designed to perform an electronic circuitry function. The Semiconductor Integrated Circuits Layout Design Act 2000 is to provide protection of Intellectual Property Right (IPR) in the area of Semiconductor Integrated Circuit Layout Designs and for matters connected therewith or incidental thereto.
- ✓ The main focus of the SICLD Act is to provide for routes and mechanisms for the protection of IPR in Chip Layout Designs created and matters related to it.
- ✓ The SICLD Act empowers the registered proprietor of the layout design an inherent right to use the layout design, commercially exploit it and obtain relief in respect of any infringement. The initial term of registration is for 10 years; thereafter it may be renewed from time to time.
- ✓ Department of Information Technology Ministry of Communications and Information Technology is the administrative ministry looking after its registration and other matters.

CONCEPT RELATED PATENTS

TYPES OF PATENT

UTILITY PATENT

- η If you have a new, useful invention that is not obvious to others in the field of invention, you may qualify for a utility patent. Utility patents are grouped into five categories: a process, a machine, manufacture, a composition of matter, or an improvement of an existing idea.
- η Often, an invention will fall into more than one of the categories. For instance, computer software can usually be described both as a process (the steps that it takes to make the computer do something) and as a machine (a device that takes information from an input device and moves it to an output device).

- η Regardless of the number of categories in which an invention falls, only one utility patent may be issued on it.
- η Among the many types of creative works that might qualify for a utility, patents are biological inventions; new chemical formulas, processes, or procedures; computer hardware and peripherals; computer software; cosmetics; electrical inventions; electronic circuits; food inventions; housewares; machines; and magic tricks. If you acquire a utility patent, you can stop others from making, using, selling, and importing the invention.
- η A utility patent lasts for 20 years from the date that the patent application is filed.

DESIGN PATENT

- δ If you create a new and original design that ornaments a manufactured device, you may qualify for a design patent.
- δ Design patents are granted for any new or original ornamental design for an article of manufacture. A design patent protects only the appearance of the article and not the article itself. An inventor can easily register both a utility patent and a design patent.
- δ A design patent is granted for product designs-for example, an IKEA chair, Keith Haring wallpaper, or a Manolo Blahnik shoe. You can even get a design patent for a computer screen icon. There are strings attached to a design patent, too.
- δ As noted, the design must be ornamental or aesthetic; it can‘t be functional. Once you acquire a design patent, you can stop others from making, using, selling, and importing the design. You can enforce your design patent for only 14 years after it‘s issued.

PLANT PATENT

- β The least frequently issued types of the patent are plant patents-granted for any asexually or sexually reproducible plants (such as flowers) that are both novel and nonobvious.

- This may include cultivating different types of plants to create mutants or hybrids and also newly found seedlings. This patent protects the owner by keeping other individuals or businesses from creating the type of plant or profiting from the plant for at least 20 years from the date of the application

TANGIBLE AND INTANGIBLE PROPERTY

Property is an external thing that can be owned or possessed. Property can be divided into two categories: tangible and intangible. The word tangible refers to something that has a definable physical form that can be felt or touched. The word intangible refers to something that cannot be perceived by the senses.

TANGIBLE PROPERTY

- In law is, literally, anything which can be touched, and includes both real property (or, in civil law systems, immovable property) and personal property (or moveable property), and stands in distinction to intangible property.
- In English law and some Commonwealth legal systems, items of tangible property are referred to as choices in possession (or a chose in possession in the singular). However, some property, despite being physical in nature, is classified in many legal systems as intangible property rather than tangible property because the rights associated with the physical item are of far greater significance than the physical properties.
- Principally, these are documentary intangibles. For example, a promissory note is a piece of paper that can be touched, but the real significance is not the physical paper, but the legal rights which the paper confers, and hence the promissory note is defined by the legal debt rather than the physical attributes.
- A unique category of property is money, which in some legal systems is treated as tangible property and in others as intangible property. Whilst most countries legal tender is expressed

in the form of intangible property ("The Treasury of Country X hereby promises to pay to the bearer on demand...."), in practice banknotes are now rarely ever redeemed in any country, which has led to banknotes and coins being classified as the tangible property in most modern legal systems.

- ♣ The tangible property consists of real property and personal property. Real property is the property that does not move, such as land and the things that are attached to or built on that land. Personal property is a property that can be moved or any other tangible property that can be owned. Personal property is also called chattels.
- ♣ Chattels that are attached to the land and that cannot be removed without damaging the land are called fixtures. Examples of fixtures are built-in bookcases and ceiling fans.

GLOBAL PERSPECTIVE OF PATENT SYSTEM

- ✓ In the United States, patent infringement lawsuits filed by non-practicing entities continue to rise. A non-practicing entity (NPE) is an entity that does not manufacture products themselves and broadly includes universities, individual inventors, research institutions, and speculators who purchase patents from others.
- ✓ According to Patent Freedom, based on the largest patent holdings, the top 5 NPEs are Intellectual Ventures, Interdigital, Round Rock Research LLC, Wisconsin Alumni Foundation, and Rock star Consortium LLC. Some refer to many or all NPEs as “patent trolls” arguing these patent holders wait until another party brings a product to market and then jump out from “under a bridge” to a demand a toll (namely, a license fee and/or royalty).
- ✓ We at the BRIC Wall Blog thought it would be interesting to examine patent troll activity in countries other than the U.S. and Europe. In this post, we examine patent troll activity in Australia, Brazil, Canada, China, India, Japan, and Russia.

ROLE OF INTERNATIONAL ORGANIZATION

1. WIPO (WORLD INTELLECTUAL PROPERTY ORGANIZATION)

- The World Intellectual Property Organization (WIPO) was established in 1970.
- The Organization became a specialized agency of the United Nations in 1974.
- The Director-General is Francis Gurry.
- Based in Geneva, with an international staff of some 1,300 employees, WIPO counts 184 Member States – more than 90 percent of the world‘s countries.
- WIPO is dedicated to developing a balanced and accessible international intellectual property (IP) system, which rewards creativity, stimulates innovation, and contributes to economic development while safeguarding the public interest.

Strategic Goals

- Balanced Evolution of the International Normative Framework for IP.
- Provision of Premier Global IP Services.
- Facilitating the Use of IP for Development.
- Coordination and Development of Global IP Infrastructure.
- World Reference Source for IP Information and Analysis.
- International Cooperation on Building Respect for IP.
- Addressing IP in Relation to Global Policy Issues.
- A Responsive Communications Interface between WIPO, its Member States, and All Stakeholders.
- An Efficient Administrative and Financial Support Structure to Enable WIPO to Deliver its Programs.

Core Tasks of WIPO

- δ Developing international IP laws and standards.
- δ Delivering global IP protection services.
- δ Encouraging the use of IP for economic development.
- δ Promoting a better understanding of IP.
- δ Providing a forum for debate.

Functions of WIPO

- δ Harmonize national intellectual property legislation and procedures.
- δ Provide services for international applications for industrial property rights.
- δ Exchange intellectual property information.
- δ Provide legal and technical assistance to developing and other countries.
- δ Facilitate the resolution of private intellectual property disputes.
- δ Marshal information technology as a tool for storing, accessing, and using valuable intellectual property information.

2. EPO (EUROPEAN PATENT ORGANIZATION)

- δ A controllable, accountable Organization.
- δ Governed by a body where all 30 member states are equally represented.
- δ After the publication of the application, full transparency.
- δ After the publication of the application, multiple intervention mechanisms available (submissions of third parties, oral proceedings, opposition)
- δ The final say on infringement and validity remains with national courts.
- δ Committed to European patent law standards and decisions of the European political leadership.

The Role and Functions of the EPO

- δ European Patent Office, the executive branch of the European Patent Organization
- δ Implementing the European Patent Convention
- δ The overriding principle: patents stimulate innovation and economy
- δ Giving effect to the decisions of the political leadership.

Role of EPO in granting patent

- δ In carrying out its mission.
- δ Set patent protection standards.
- δ Set a benchmark for best patent practice.
- δ Help to promote a knowledge-based society in Europe.
- δ Stand out as a model international public service organization.

3. WTO (WORLD TRADE ORGANIZATION)

- δ WTO was born on 1st January 1995 with the main objective to improve the welfare of people of member countries. Its main function is to ensure that trade flows as smoothly, predictably & freely as possible.
- δ **Breetonwood Conference 1944**: To overcome recession after post World War II group of 44 nations met in Breetonwood, New Hampshire, England to discuss the establishment of an organization; this will help to restore international trade.
- δ **General Agreement on Tariffs & Trade (GATT Agreement):** GATT was established in 1948 in Geneva.

INDIAN PATENT ACT 1970

1. History of Patent Acts in India

In India, the grant of patents is governed by the patent act 1970 and rules 1972 which is operative in the whole of India.

- ✓ 1856: Act for the protection of inventions on the basis of British law of 1852
- ✓ 1859: Patent monopolies called exclusive privileges (14 years)
- ✓ 1872: Patents and Designs Act
- ✓ 1883: Protection of Inventions Act
- ✓ 1888: Inventions and Designs Act
- ✓ 1911-1947: Modern patent era by Patents and Designs Act. The first time an authority call Controller General of Patents appointed
- ✓ 1959: Justice Ayyangar‘s report
- ✓ 1967: Patent Act bill introduced in the Parliament
- ✓ 1970: The Patents Act passed by the parliament
- ✓ 1972: The Patents Act-1970 came into force on April 20, 1972
- ✓ 1994: Amendment by ordinance to include Exclusive Marketing Rights (EMR‘s)
- ✓ 1999: Amendment passed by the parliament. New patent amendment bill referred to select committee
- ✓ 2003: Patents Act 1970 with the second amendment comes into force
- ✓ 2005: Patent Act 1970 (2005 Amendment) comes in to force from 1-1-2005

2. Purpose of getting a patent

To enjoy exclusive rights over the invention. The patent is to ensure commercial returns to the inventor for the time and money spend in generating a new product.

3. Patent Law - Salient Features

- Both product and process patent provided
- Term of patent – 20 years
- Examination on request
- Both pre-grant and post-grant opposition
- Fast track mechanism for disposal of appeals
- Provision for protection of biodiversity and traditional knowledge
- Publication of applications after 18 months with facility for early publication
- Substantially reduced time-lines

4. Safeguards in the Patent Law

- Compulsory license to ensure availability of drugs at reasonable prices
- Provision to deal with a public health emergency
- Revocation of patent in the public interest and also on security considerations

5. Patentable Inventions: Invention must

- Relates to a process or product or both
- Be new (novel)
- Involves an inventive step
- Be capable of industrial application
- Not fall under section 3 and 4

6. Procedure for grant of Patent

- Applying for a patent
- Examination of application

- ❖ Acceptance of the application
- ❖ Opposition to grant of patent
- ❖ Grant and sealing of patents

APPLICATIONS OF IPR

- ✓ An intellectual property right is a government right is granted by the government of India for maintaining the quality and standard of drug or drug-related products or services.
- ✓ An intellectual property right is important to maintain the quality, purity, and safety of drug products.
- ✓ The intellectual property right is important for the determination of product stability and safety.
- ✓ The intellectual property right is applicable for industrial, Pharmaceutical, analytical, chemical, drug development, drug synthesis, and Manufacturing industries.
- ✓ The intellectual property right is applicable for companies, industries, Businesses, and marketing.
- ✓ An intellectual property right is applicable for the industrial, scientific, literary, artistic fields.
- ✓ The intellectual property right is applicable to NDA, ANDA, and INDA analysis of Drug Products or Pharmaceutical Formulations.
- ✓ The intellectual property right is applicable for testing, analysis, characterizing, drug properties, and drug quality.
- ✓ The intellectual property right is an exclusive right is granted by the government of India for the protection of the invention of the inventor.
- ✓ It is applicable for Protection of originality or novelty of work of author has a function of copyright.

- ✓ It acts as certification as well as an identification mark for identification of the product in would wide market has the function of a trademark.
- ✓ It is important for maintaining the protection of patent or business-oriented data as a function of Trade secrets.
- ✓ It is applicable for maintaining the utility, designing, and Novelty of Patented data.
- ✓ It is applicable for the determination of the law of the Indian system or Indian legal system.
- ✓ It is important for determining simple ornamental or industrial designing and Layout oriented semiconductor devices.
- ✓ It is Applicable for determination of Anticipation of data as well as Patent data under prior art or not is conducted by IPR.
- ✓ It is having an important application for the Indian Patent act 1970, and also the determination of Amendment of the patent act in 1999, 2002, 2005, and 2006.
- ✓ It is applicable for the determination of Patent filling and Patent Granting Processes.
- ✓ It is applicable for the determination of Patent Revocation and Patent Infringements.
- ✓ It is applicable for the determination of Commercialization and Patent Licensing Processes.

CONCLUSION

- ♣ Intellectual Property Right is Government Right is granted by the Government of India. The intellectual Property right is concerned with intellectual activity in industrial, scientific, literary & artistic fields.
- ♣ These rights Safeguard creators and other producers of intellectual goods & services by granting them certain time-limited rights to control their use. The rights are given to people over the creation of their minds.
- ♣ They usually give the creator an exclusive right over the use of his/her creations for a certain period of time. It is an exclusive right is granted by the government for the protection of

Novelty as well as Originality of Patent oriented Data and Maintaining Quality, Safety, Efficacy, and Standard or Certification of the drug, Any Product, and Services.

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QUESTION BANK

1. Why do we need an IP system?
2. What is IP?
3. What categories does IP fall into?
4. What are the characteristics of IP?
5. What is exclusivity of IP?
6. What is the territoriality principle of IP?
7. Does IP protection have a time limit?
8. Does IP infringement always give rise to criminal liability?
9. What remedies are available to redress IP infringement?
10. How does the international community coordinate IP protection?
11. How is IP administered around the world?
12. What international treaties comprehensively protect IP rights

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SCHOOL OF BIO AND CHEMICAL ENGINEERING
DEPARTMENT OF CENTRE FOR MOLECULAR AND NANOMEDICAL SCIENCES

UNIT – V - Clinical Trial Application Requirements – SMB5303

INVESTIGATIONAL NEW DRUG APPLICATIONS (INDA)

INTRODUCTION

- The investigational New Drug (IND) program is the means by which a pharmaceutical company obtains permission to start human clinical trials and to ship an experimental drug across state lines (usually to clinical investigators) before a marketing application for the drug has been approved.
- An investigational new drug (IND) application is to provide the data showing that it is reasonable to begin tests of a new drug on humans.
- The IND application is also the vehicle through which a sponsor advances to the next stage of drug development known as clinical trials.
- Current Federal law requires that a drug be the subject of an approved marketing application before it is transported or distributed across state lines (Clinical Investigators).
- Because a sponsor will probably want to ship the investigational drug to clinical investigators in many states, it must seek an exemption from that legal requirement.
- The IND application is the means through which the sponsor technically obtains this exemption from the FDA.
- During a new drug's early preclinical development, the sponsor's primary goal is to determine if the product is reasonably safe for initial use in humans and if the compound exhibits pharmacological activity that justifies commercial development.
- When a product is identified as a viable candidate for further development, the sponsor then focuses on collecting the data and information necessary to establish that the product will not expose humans to unreasonable risks when used in limited, early-stage clinical studies.
- FDA's role in the development of a new drug begins when the drug's sponsor (usually the manufacturer or potential marketer), having screened the new molecule for pharmacological activity and acute toxicity potential in animals, wants to test its diagnostic or therapeutic potential in humans.

- At that point, the molecule changes in legal status under the Federal Food, Drug, and Cosmetic Act and becomes a new drug subject to specific requirements of the drug regulatory system.

CLASSIFICATION OF IND

1. Commercial: Permits sponsor to collect data on clinical safety and effectiveness needed for application for marketing in the form of NDA.

2. Research (non-commercial): Permits the sponsor to use the drug in research to obtain advanced scientific knowledge of the new drug, no plan to market the product.

TYPE'S OF IND APPLICATIONS

1. Investigator IND application
2. Emergency Use IND application
3. Treatment IND application
4. Screening IND application

1. Investigator IND application

- Application is submitted by a physician, who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed.
- A physician might submit a research IND application.
- An unapproved drug.
- An approved product for a new indication.
- An approved product in a new patient population.

2. Emergency Use IND application

- The application allows the FDA to authorize the use of an experimental drug in an emergency situation that does not allow time for submission of an IND application, in accordance with 21CFR, Sec. 312.23 or Sec. 312.20.
- It is also used for patients who do not meet the criteria of an existing study protocol, or if an approved study protocol does not exist.
- In such a case, FDA may authorize the shipment of the drug for a specified use in advance of submission of an IND application.

3. Treatment IND application

- Application is submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place.
- A drug that is not approved for marketing, maybe under clinical investigation for a serious or immediately life-threatening disease condition in patients for whom no comparable or satisfactory alternative drug or other therapy is available.
- In the case of a serious disease, a drug ordinarily may be made available for treatment use during phase III investigations or after all clinical trials have been completed.
- In the case of an immediately life-threatening disease, a drug may be made available for treatment use earlier than phase III, but ordinarily not earlier than phase II.

4. Screening IND application

- Filed for multiple, closely related compounds to screen for the preferred compounds or formulations.
- The preferred compound can then be developed under a separate IND.

- Used for screening different salts, esters, and other drug derivatives that are chemically different, but pharmacodynamically similar.

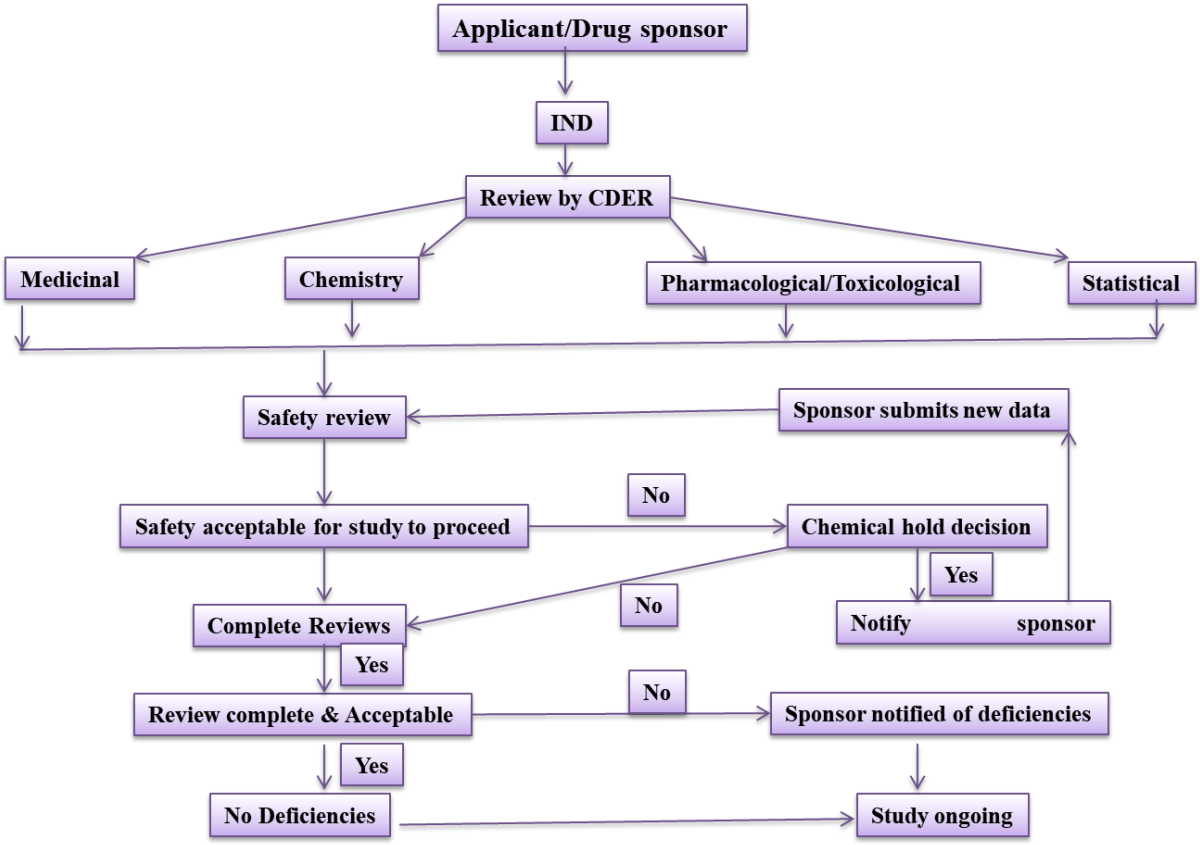

Figure 2. IND review process flowchart

CONTENTS OF IND APPLICATIONS

1. Animal pharmacology and toxicology studies: Preclinical data to permit an assessment as to whether the product is reasonably safe for initial testing in humans.

2. Manufacturing information: Information about the composition, manufacturer, stability, and controls used for manufacturing the drug substance and the drug product. This information is assessed to ensure that the company can adequately produce and supply consistent batches of the drug.

3. Clinical protocols and investigator information: Detailed protocols for proposed clinical studies to assess whether the initial-phase trials will expose subjects to unnecessary risks.

RESOURCES FOR IND APPLICATIONS

The following resources include the legal requirements of an IND application, assistance from CDER to help you meet those requirements, and internal IND review principles, policies, and procedures

i. Pre-IND Consultation Program

ii. Guidance Documents for INDs

iii. Laws, Regulations, Policies, and Procedures

iv. Code of Federal Regulations (CFR)

v. Manual of Policies and Procedures (MaPPs)

i). Pre-IND Consultation Program

- CDER's Pre-Investigational New Drug Application (IND) Consultation Program fosters early communications between sponsors and new drug review divisions to provide guidance on the data necessary to warrant IND submission.
- The review divisions are organized generally along with therapeutic class and can each be contacted using the designated Pre-IND Consultation List.

ii). Guidance Documents for INDs

- Guidance documents represent the Agency's current thinking on a particular subject.
- These documents provide FDA review staff and applicants/sponsors with guidelines to the processing, content, and evaluation/approval of applications and also to the design, production, manufacturing, and testing of regulated products.
- They also establish policies intended to achieve consistency in the Agency's regulatory approach and establish inspection and enforcement procedures.

- Because guidance's are not regulations or laws, they are not enforceable, either through administrative actions or through the courts.
- An alternative approach may be used if it satisfies the requirements of the applicable statute, regulations, or both.
- For information on a specific guidance document, please contact the originating office.

iii). Laws, Regulations, Policies, and Procedures

- The mission of the FDA is to enforce laws enacted by the U.S. Congress and regulations established by the Agency to protect the consumer's health, safety, and pocket.
- *The Federal Food, Drug, and Cosmetic Act* is the basic food and drug law of the U.S.
- The law is intended to assure consumers that foods are pure and wholesome, safe to eat, and produced under sanitary conditions; that drugs and devices are safe and effective for their intended uses; that cosmetics are safe and made from appropriate ingredients; and that all labelling and packaging is truthful, informative, and not deceptive.

iv). Code of Federal Regulations (CFR)

- The final regulations published in the Federal Register, are collected in the Code of Federal Regulations (CFR).
- The CFR is divided into 50 titles that represent broad areas subject to Federal regulations.
- The FDA's portion of the CFR interprets the Federal Food, Drug, and Cosmetic Act and related statutes.
- Section 21 of the CFR contains most regulations about food and drugs.
- The regulations document all actions of all drug sponsors that are required under Federal law.

v). Manual of Policies and Procedures (MaPPs)

- CDER's *Manual of Policies and Procedures* are approved instructions for internal practices and procedures followed by CDER staff to help standardize the new drug review process and other activities.
- All MAPPs are available for the public to review for a better understanding of office policies, definitions, staff responsibilities, and procedures.

IND REVIEW & REPORT

During this time, FDA has an opportunity to review the IND application for safety to assure that research subjects will not be subjected to unreasonable risk.

i. Medical Review

ii. Chemistry Review

iii. Pharmacology/Toxicology review

iv. Statistical analysis

v. Safety review

i). Medical Review

- During the IND application review process, the medical reviewer evaluates the clinical trial protocol to determine if (i). the participants will be protected from unnecessary risks. (ii). the study design will provide data relevant to the safety and effectiveness of the drug.
- Under Federal regulations, proposed phase I studies are evaluated almost exclusively for safety reasons.
- Since the late 1980s, FDA reviewers have been instructed to provide drug sponsors with greater freedom during phase I, as long as the investigations do not expose participants to undue risks.

- In evaluating phase II and III investigations, however, FDA reviewers also must ensure that these studies are of sufficient scientific quality to be capable of yielding data that can support marketing approval.

ii). Chemistry Review

- They address issues related to drug identity, manufacturing control, and analysis.
- The reviewing chemist evaluates the manufacturing and processing procedures for a drug to ensure that the compound is adequately reproducible and stable.
- At the beginning of the Chemistry and Manufacturing section, the drug sponsor should state whether it believes the chemistry of either the drug substance or the drug product, or the manufacturing of either the drug substance or the drug product, present any signals of potential human risk.
- If so, these signals should be discussed, with steps proposed to monitor for such risks.
- In addition, sponsors should describe any chemistry and manufacturing differences between the *drug product proposed for clinical use* and the *drug product used in the animal toxicology trials* that formed the basis for the sponsor's conclusion that it was safe to proceed with the proposed clinical study.

iii). Pharmacology/Toxicology review

- This team is staffed by pharmacologists and toxicologists who evaluate the results of animal testing and attempt to relate animal drug effects to potential effects in humans.
- The regulations do not further describe the presentation of these data, in contrast to the more detailed description of how to submit toxicology data.
- A summary report, without individual animal records or individual study results, usually suffices.

- An integrated summary of the toxicology effects of the drug in animals and *in-vitro* the particular studies needed depends on the nature of the drug and the phase of human investigation.
- When species specificity, immunogenicity, or other considerations appear to make many or all toxicological models irrelevant, sponsors are encouraged to contact the agency to discuss toxicological testing.

iv). Statistical analysis

The purpose of these evaluations is to give the medical officers a better idea of the power of the findings to be extrapolated to the larger patient population in the country.

v). Safety review

- Following a review of an initial IND application submission, CDER has 30-calendar-days in which to decide if a *clinical hold is necessary* (i.e. if patients would be at unacceptable risk or if CDER doesn't have the data to make such a determination).
- Generally, Drug Review Divisions do not contact the sponsor if no concerns arise with drug safety and the proposed clinical trials.
- The sponsor is notified about the deficiencies through a *Clinical Hold.*
- A clinical hold is issued by the FDA to the sponsor to delay a proposed clinical investigation or to suspend a clinical investigation.

CONCLUSION

- ♣ The data obtained during animal studies and human clinical trials of IND becomes part of NDA.
- ♣ 30 days after an IND is submitted to the FDA, if the sponsor has not heard anything from the FDA it can be assumed that the drug is not on a clinical hold and clinical trials may be started.

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NEW DRUG APPLICATIONS (NDA)

INTRODUCTION

- For decades, the regulation and control of new drugs in the United States has been based on the New Drug Application (NDA).
- Since 1938, every new drug has been the subject of an approved NDA before U.S. commercialization.
- The data gathered during the animal studies and human clinical trials of an Investigational New Drug (IND) becomes part of the NDA.
- When the Food, Drug, and Cosmetic Act (FD&C Act) was passed in 1938, NDAs were only required to contain information about the investigational drug's safety.
- In 1962, the Kefauver-Harris Amendments to the FD&C Act required NDAs to contain evidence that a new drug was effective for its intended use as well, and that the established benefits of the drug outweighed its known risks.
- The NDA was again the subject of change in 1985 when the FDA completed a comprehensive revision of the regulations pertaining to NDAs.
- While this revision, commonly called the NDA Rewrite, modified content requirements, it was mainly intended to restructure the ways in which information and data are organized and presented in the NDA to easily access FDA reviews.

NDA CLASSIFICATIONS

CDER classifies new drug applications with a code that reflects both the type of drug being submitted and its intended uses. The numbers 1 through 7 are used to describe the type of drug.

1. New Molecular Entity
2. New Salt of Previously Approved Drug (not a new molecular entity)
3. New Formulation of Previously Approved Drug (not a new salt OR a new molecular entity)
4. New Combination of Two or More Drugs

5. Already Marketed Drug Product - Duplication (i.e., new manufacturer)
6. New Indication (claim) for Already Marketed Drug (includes switching marketing status from prescription to OTC)
7. Already Marketed Drug Product - No Previously Approved NDA

FUNDAMENTALS OF NDA SUBMISSION

As outlined in Form FDA-356h, Application to Market a New Drug for Human Use or as an Antibiotic Drug for Human Use, NDAs can consist of as many as 15 different sections:

1. Index
2. Labelling
3. Application Summary
4. Chemistry, Manufacturing, and Control
5. Nonclinical Pharmacology and Toxicology
6. Human Pharmacokinetics and Bioavailability
7. Microbiology (for anti-microbial drugs only)
8. Clinical Data
9. Safety data (typically submitted 120 days after the NDA's submission)
10. Statistical
11. Case Report Tabulations
12. Case Report Forms
13. Patent Information
14. Patent Certification; and
15. Other Information. (e.g. the marketing history of the drug (if any) outside the U.S., a concluding discussion of benefit/risk considerations and proposed additional studies or post-marketing surveillance plans, etc.)

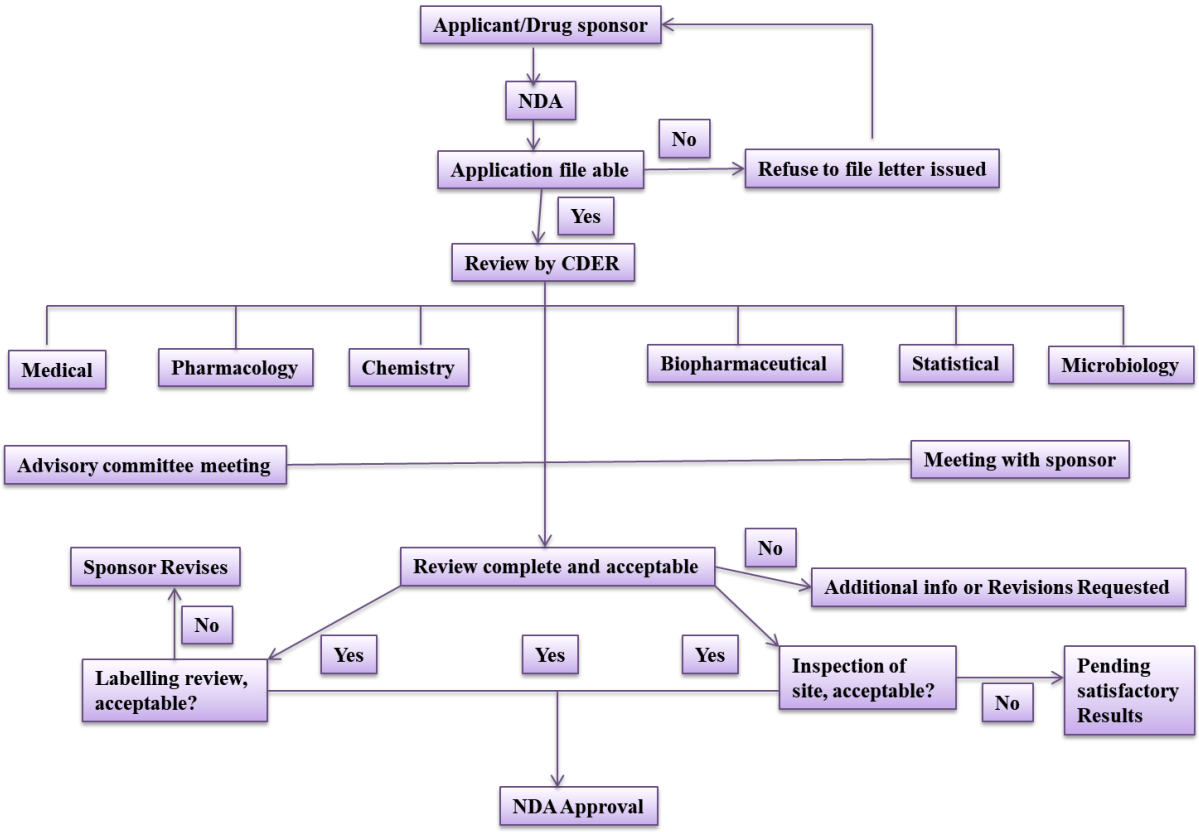

Figure 3. NDA approval process flowchart

NDA CONTENT AND FORMAT REQUIREMENTS

- ❖ NDA must provide all relevant data and information that a sponsor has collected during the product's research and development.
- ❖ The FDA has numerous guidelines that relate to NDA content and format issues. These guidelines can be obtained from CDER's Drug Information Branch (DIB).
- ❖ The following letter codes describe the review priority of the drug:

  S - Standard review: For drugs similar to currently available drugs.

  P - Priority review: For drugs that represent significant advances over existing treatments

GENERAL REQUIREMENTS

- ✓ The new (present) NDA regulations require that an application be submitted in two copies:

  (a) An archival copy that serves as a permanent record of the submission, and

(b) A review copy.

- ✓ The review copy is made up of several separate technical volumes, each tailored to the needs of the disciplines involved in the review.
- ✓ Both the archival and review copies are submitted in hard copy, the regulations permit an application to submit the archival copy as microfiche
- ✓ The NDA application form (FORM NDA 356 h) consists of: Twelve items (including index) deals with the safety and efficacy features of drug product, two are concerned with patent information

INDEX

A comprehensive index by volume number & page number to the summary, the technical sections & the supporting information.

LABELLING

It must include all draft labelling that is intended for use on the product container, cartons, or packages, including the proposed package insert

CONCLUSION

- ✓ It has been suggested that the summary consists of 50 - 200 pages. The summary should discuss all aspects of the application and needs to be written at approximately the level of detail required for publication and meet the editorial standards applied by referred scientific and medical journals.
- ✓ It is advantageous to provide data in the summary in tabular and graphic form with a clear explanation of any terminology used in the tabulations or graphics.

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ABBREVIATED NEW DRUG APPLICATIONS (ANDA)

INTRODUCTION

- An Abbreviated New Drug Application (ANDA) contains data which when submitted to FDA's CDER, Office of Generic Drugs, provides for the review and ultimate approval of a generic drug product.
- Once approved, an applicant may manufacture and market the generic drug product to provide a safe, effective, low-cost alternative to the public.
- All approved products, both innovator and generic, are listed in FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book).
- "A drug product that is comparable to a brand/reference listed drug product in dosage form, strength, route of administration, quality and performance characteristics, and intended use".
- It is termed "abbreviated" because they are generally not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness.

BASIC GENERIC DRUG REQUIREMENTS

- ✓ Same active ingredient(s)
- ✓ Same route of administration
- ✓ Same dosage form
- ✓ Same strength
- ✓ Same conditions of use
- ✓ Inactive ingredients already approved in a similar NDA

GOAL OF ANDA

- To reduce the price of the drug.
- To reduce the time development.
- Increase the bioavailability of the drug in comparison to references list drug.

GENERIC DRUG APPROVAL

- In 1970 FDA established the ANDA as a mechanism for the review and approval of generic versions.
- Before 1978, generic product applicants were required to submit complete safety and efficacy through clinical trials.
- Post-1978, applicants were required to submit published reports of such trials documenting safety and efficacy.
- Neither of these approaches was considered satisfactory and so originated Hatch Waxman Act in 1984.

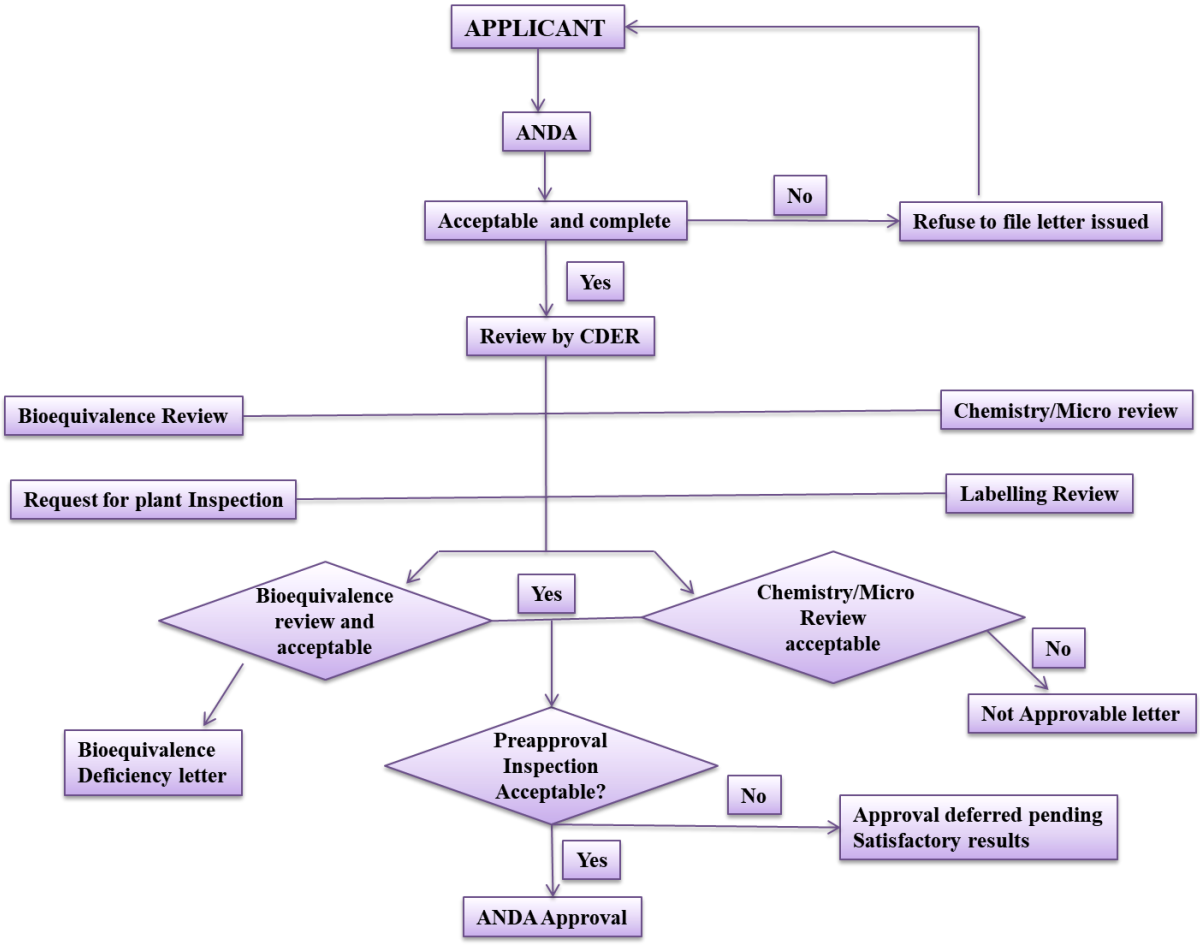

Figure 4. ANDA review process flowchart

CONCLUSION

- ♣ Applicable for generic drug
- ♣ Compare to NAD less time taken (1-2 years)
- ♣ Costs of drugs are less
- ♣ Nonclinical studies and clinical investigations are nonessential except bioavailability and bioequivalence

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FOOD AND DRUG ADMINISTRATION (FDA)

INTRODUCTION

- The Food and Drug Administration (FDA or USFDA) is an agency of the United States Department of Health and Human Services
- It is responsible for regulating and supervising the safety of foods, dietary supplements, drugs, vaccines, biological medical products, blood products, medical devices, radiation-emitting devices, veterinary products, and cosmetics
- The FDA has its headquarters at White Oak, Maryland. The agency also has 223 field offices and 13 laboratories located throughout the 50 states, the United States Virgin Islands, and Puerto Rico.
- In 2008, the FDA started opening offices in foreign countries, including China, India, Costa Rica, Chile, Belgium, and the United Kingdom.

FDA-ORGANISATIONS

- ✓ The Office of the Commissioner (OC)
- ✓ The Center for Drug Evaluation and Research (CDER)
- ✓ The Center for Biologics Evaluation and Research (CBER)
- ✓ The Center for Food Safety and Applied Nutrition (CFSAN)
- ✓ The Center for Devices and Radiological Health (CDRH)
- ✓ The Center for Veterinary Medicine (CVM)
- ✓ The National Center for Toxicological Research (NCTR)
- ✓ The Office of Regulatory Affairs (ORA)

FDA-LEGAL AUTHORITY

- 1902 – Biologics Control Act.
- 1906 – Pure Food and Drug Act.

- 1938 – Federal Food, Drug, and Cosmetic Act.
- 1944 – Public Health Service Act
- 1951 – Food, Drug, and Cosmetics Act Amendments
- 1962 – Food, Drug, and Cosmetics Act Amendments
- 1966 – Fair Packaging and Labelling Act
- 1976 – Medical Device Regulation Act
- 1987 – Prescription Drug Marketing Act
- 1988 – Anti-drug Abuse Act
- 1990 – Nutrition Labelling and Education Act
- 1992 – Prescription Drug User Fee Act
- 1994 – Dietary Supplement Health and Education Act
- 1997 – Food and Drug Modernization Act
- 2002 – Bioterrorism Act
- 2002 – Medical Device User Fee and Modernization Act (MDUFMA)
- 2003 – Animal Drug User Fee Act
- 2007 – Food and Drug Administration Amendments Act of 2007.

FDA- MISSION

- ❖ The FDA consists of employees drawn from a wealth of science and public health professions. Biologists, physicians, chemists, biomedical engineers, toxicologists, pharmacologists, veterinarians, and specialists in public health education and communication.
- ❖ FDA employs approximately 11,516 people who work in locations around the United States.

FDA REGULATE

- ✓ Foods, except for most meat and poultry products, are regulated by the U.S. Department of Agriculture.
- ✓ Food additives
- ✓ Infant formulas, Dietary supplements
- ✓ Human drugs
- ✓ Vaccines, blood products, and other biologics
- ✓ Medical devices, from simple items like tongue depressors to complex technologies such as heart pacemakers.
- ✓ Electronic products that give off radiation, such as microwave ovens and X-ray equipment.
- ✓ Cosmetics.
- ✓ Feed, drugs, and devices used in pets, farm animals, and other animals.
- ✓ Tobacco products.

FDA INSPECTION

FDA inspects manufacturers or processors of FDA-regulated products to verify that they comply with relevant regulations.

Inspection includes:

- ✓ Vaccine and drug manufacturers
- ✓ Blood banks
- ✓ Food processing facilities dairy farms animal feed processors
- ✓ Facilities that conduct studies in people (clinical trials).
- ✓ Laboratories that conduct studies in animals or microorganisms when these studies are used to apply for FDA approval of a medical product.
- ✓ Foreign manufacturing and processing sites for FDA- regulated products that are sold in the United States. Imported products at the border

CFR TITLE 21

C.F. R – Code of Federal Regulation is a codification of general rules and regulations also known as administrative law published in the federal register by the executive department and agencies of the federal government of the United States.

- ✓ Title 21 of the CFR is reserved for rules of the Food and Drug Administration.
- ✓ CFR 21 was received from the Government Printing Office (GPO) and contains the most recently received revision.
- ✓ Food and Drugs: Parts 1 to 1499 different types of parts to food, drug, cosmetic and medical devices, *etc*

21 CFR PART 11- ELECTRONIC SUBMISSION AND ELECTRONIC SIGNATURE

- ★ 21 CFR part 50- Protection of human subjects
- ★ 21 CFR part 54- Financial Disclosure by Clinical Investigators
- ★ 21 CFR part 56- Institutional Review Board
- ★ 21 CFR part 101-Food Labelling.
- ★ 21 CFR part 104-Nutritional quality guidelines for foods
- ★ 21 CFR part 106- Infant Formula Quality Control Procedures
- ★ 21 CFR part 110- Cgmp Practices in manufacturing packing or holding human food.
- ★ 21 CFR part 210- Cgmp Practices in manufacturing, packing or holding of Drugs: General
- ★ 21 CFR part 211- Cgmp Practices for finished pharmaceuticals
- ★ 21 CFR parts 225- Cgmp Practices for medicated feeds.
- ★ 21 CFR part 312- Investigational new drug application
- ★ 21 CFR part 314- Application for FDA Approval to Market a New Drug
- ★ 21 CFR parts 600 to 680- For biological products.

CONCLUSION

- ♣ The Subcommittee is pleased to note that FDA has made significant strides in strengthening its scientific capabilities in response to the 2007 Mission at Risk report. Its drug review program is a global leader in both speed and quality of review, the focus on improving its science infrastructure is to be applauded, and the new food safety legislation promises to bring a new scientific focus on food protection that will greatly reduce foodborne illness.
- ♣ Nevertheless, medical and technological advances continue to occur at a steady and relentless pace, and FDA must stay abreast if it is to remain the preeminent public health agency that the public expects. To do that, the Subcommittee urges FDA leadership to embrace the findings and recommendations embodied in this report, which are targeted not on changing the organization but on strengthening it for the challenges ahead.

REFERENCES

1. FDA, 21 CFR Part 11, "Electronic Records; Electronic Signatures; Final Rule." Federal Register, **1997,** 62, 13429.
2. FDA, Compliance Program Guidance Manual, "Compliance Program 7348.810 – Bioresearch Monitoring - Sponsors, Contract Research Organizations and Monitors," February 21, **2001**.

QUESTION BANK

1. If you were to leave Food and Drug Administration, what would be the reason?
2. What benefits does Food and Drug Administration offer?
3. What questions did they ask during your interview at Food and Drug Administration?
4. What is Food and Drug Administration sick leave policy? How many sick days do you get per year?
5. What advice would you give the CEO of Food and Drug Administration about how to improve it?
6. How do you feel about going to work each day at Food and Drug Administration?