Chapter 1

Drug Regulation in Nutshell

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KEY POINTS

- The chapter compiles an overview of the purpose, applicability, relevance, history, and services of the regulatory authorities worldwide with major functions of the drug regulatory authorities in global perspective.
- Evolution, structure, legal frame, acts, and rules of various regulatory authorities like Indian,USA, Canada, Europe, China, Japan, Brazil and Australia, and their fundamental variability in the foundation of drug laws and scope of implementation.
- Organization and functional mechanism of Indian Drug Regulation with special focus to CDSCO, DCGI, and different committees along with an overview of the State Drug Control Organization.
- Looking into the differing level of control, astringency and complexity of the regulatory authorities worldwide, harmonization of technical requirements for medicines regulation is a need of the time. International harmonization initiatives have been adopted by different groups of countries to make uniform technical requirements for medicines regulation, viz. legislation, guidelines, procedures, quality, safety, and efficacy-related requirements.
- Regulatory Affairs is a fast developing department in pharmaceuticals with the expansion of business having broad scope. The roles and responsibilities of regulatory professionals cover not only to handle regulatory approval of drugs but also in research and development, clinical trials, manufacturing, advertising and post-marketing surveillance.

INTRODUCTION

Pharmaceuticals play a vital role in saving our lives, restoring health, preventing diseases and epidemics. In the period between 1930–50s, many pharmaceutical companies have flourished, and trade in the pharmaceutical industry has taken international dimensions. At the same time, circulation of toxic, substandard and counterfeit drugs on the national and international market has increased due to ineffective regulation of production and trade in pharmaceutical products. These substandard drugs have taken the lives of many as sulfanilamide incident in the United States of America in the mid-1930s led to deaths of 107 children and thalidomide disaster of the 1960s which caused congenital disabilities in children. Diethylene glycol contamination in paracetamol has led to multiple tragedies in Haiti and India. Safety and quality issues arise with the use of drugs containing toxic substances, impurities, unverified efficacy, substandard, outright fake and counterfeit drugs with the potential to cause unknown and severe adverse reactions. The problems of drug safety and efficacy related severe adverse reactions can effectively be tackled by establishing robust drug regulatory system.

The therapeutically used drugs and other devices are strictly regulated by the jurisdiction in most of the countries worldwide to protect the public from harmful and dubious medicines. The primary aim of therapeutic goods regulation is to protect the health and safety of the population. Regulation ensures the safety, quality, and efficacy of the therapeutic products covered under the scope of the regulation. Drug regulation provides legal guidelines for manufacturing and marketing and trade-related activities of all types of products made available with medicinal claims by the public and private sectors. Development, production, importation, exportation, and distribution of therapeutic products are astringently regulated to ensure compliance with the prescribed standards. Therapeutic products are registered before they are allowed for distribution and marketing. The critical functions of drug regulatory bodies are the inspection of manufacturing facilities, product safety assessment and registration (marketing

authorization), control of quality, adverse drug reaction monitoring, and control of drug promotion and advertising. Though each of these functions targets a different aspect of pharmaceutical activities, all of them are under taken simultaneously to ensure adequate consumer protection. Highly developed drug regulation framework is currently implemented in countries like the United Kingdom, the United States of America, Australia, Canada, Japan, and China. Well-formulated and strictly implemented drug regulation in these countries was possible with overwhelmed participation of consumers, and other stakeholders with enhanced political support that promoted transparency, accountability and protection from external influence.

STRUCTURE OF DRUG REGULATORY ORGANIZATIONS

Medicines regulation requires collective input of medical, scientific and technical knowledge and operates within a legal framework. Regulatory functions involve interactions with stakeholders, e.g. manufacturers, traders, consumers, health professionals, researchers and governments making implementation a real challenging job. Drug regulation is generously needed to be updated to match up with changes and new challenges in the scientific knowledge. The current scenario of drug regulation has evolved to its present status over a long time evolution. Along with this, the scope of legislative and regulatory powers has gradually expanded, to keep pace with the ever-increasing complexity of the sophisticated pharmaceutical sector. In most of the instances, the enactment of comprehensive drug laws was a result of public demand that led to the adoption of more restrictive legislation to provide stronger safeguards for the public following some significant public hazards due to adverse effects.

Worldwide legal structures of the regulatory authorities are considerably variable from the foundation of drug laws to their scope of implementation resulting in a regulatory gap between countries. For instance, in some countries, registration of herbal and homeopathic drugs are not required while, in others, legal mandates are not imposed on the exportation of drugs. Drug laws should be comprehensive enough to cover all areas of pharmaceutical activity in the respective country itself along with covering aspects of drugs which are exported to other countries. Regulatory guidelines describing the procedures and standards provide practical means to the regulatory authorities to implement laws. Whereas most of the drug regulatory organizations in developed countries have very well-defined and well-documented guidelines, but some drug regulatory authorities in underdeveloped countries do not have documented standard procedures for registration and inspection. WHO and other international agencies are providing support to countries in developing drug regulation structure, despite that less than 20% of WHO Member States have a well-developed system. Nowadays export and import of drugs and pharmaceuticals are flourishing as a growing market. The discrepancy in regulatory tools leads to variations in the implementation of the law and transparency of law enforcement.

In India, drug regulation is enforced both at state and national levels by various bodies. Some countries, such as the United States, drugs are regulated at the national level by a single agency, but in some other jurisdictions as in Australia, it is regulated at the state level only. In some countries, a single agency controls all functions related to drug regulation and jurisdiction having full command authority. In some other countries, like India, drug regulatory functions are assigned to more than one agency, at different levels of government control making the exercise of drug regulation fragmented. Under this type of organizational structure, command, coordination, and control of multitude

regulatory functions to ensure adequate drug regulation is an enormous task. India, with a federal system of government, some drug regulatory activities are delegated to the State. Implementing public health policy through multiple levels of regulation concerning independent authorities requires a concerted effort between the agencies, and on the other side this type of system decentralize the activities and increases the effectiveness of the policy, but in a divided system, there can be a problem with the unity of command over drug regulatory functions. Indian drug regulatory structure is designed in a way that there is a central coordinating body (i.e. Drug Controller General of India) with overall responsibility and accountability for all aspects of drug regulation. The DCGI has an established official route for coordination and information flow at the national level covering entire country to support decision-making in all aspects of drug regulation. Drug regulation is not the sole mission of all the drug regulatory authorities, regulatory agencies in some countries are given non-regulatory functions due to political considerations or shortage of resources. This may lead to shift of focus from one function to another compromising performance and ineffective drug regulation.

Safety and quality issues are the main reasons that the authorities assess the medicines before they are placed on the market. Before placing a new Medicinal Product in the market, the applicant must perform extensive quality, toxicology, and clinical studies. The results of such studies are submitted to regulatory authorities for a review of conformance to the quality and safety standards of medicine, only then the medicines can be released in the market for consumers use. Regulatory agencies also work with custom and police department for inspecting medicinal products at ports and other points of entry, and distribution outlets. The regulatory authority helps in the detection and investigation of crimes involved in the illegal trade of medicines for apprehending and prosecuting criminals. The requirements made for veterinary medicines also same as that are intended for human consumption. Currently, the drug regulatory organizations, clinical evaluation boards, quality control laboratories, and pharmacovigilance information center have developed gradually to a level of excellence. Still though several areas in drug regulation *viz*. post-marketing surveillance, ADR reporting, control of drug information, etc. receive relatively little attention in the implementation process. Unlicensed manufacturers, importers, wholesalers, retailers and even individual persons engaged in the pharmaceutical business pose severe challenges to drug regulation. There is a big challenge in front of the regulatory agencies to control and monitor activities in the informal pharmaceutical sector. Informal sector mainly involves counterfeit products and products of dubious quality. Faulty exaggerated claims of efficacy especially related to herbal products are widespread in the informal sector. Increased globalization of the pharmaceutical trade has lead to the proliferation of harmful substandard and counterfeit medicines circulating in national and international markets. Pre-marketing safety and efficacy testing and documentation are primarily given more importance than post-marketing activities. Post-marketing surveillance, ADR monitoring and re-evaluation of registered products should also be given equal priority in drug regulation. Drug information received from the consumers and manufacturer has a significant influence on rational drug use. Monitoring of the post marketing safety along with accuracy and appropriateness of drug information provided to the public is generally inadequate which is now actively controlled by WHO with international pharmacovigilance networking system.

Regulatory, organizational structure and the working process need to have routine monitoring to identify problems in implementation and to determine loopholes in the system. Performance review by the supervisory body and peer analysis of guidelines implementation system should be implemented strictly by the regulatory bodies for performance appraisal and identification of areas requiring improvement. Drug regulation system in every country has some strength and weaknesses. Implementation of appropriate functional structure and continuous up gradation of guidelines ensures enforcement and enactment of policies. In many third world countries, medicine legislation and regulatory guidelines are 'copied' from other countries that do not reflect national realities and are not regularly updated. Every country should have drug regulation guidelines suitable to the national legislative framework. Regular updating of the medicine legislation and regulations must address new pharmaceutical issues arising as a result of continuous scientific and technological changes occurring in the field. Competent human resource, freedom from political and commercial influence, well defined standards and procedures, outcome-oriented systematic monitoring, comprehensive and up-to-date laws will contribute to regular and effective updating of drug regulation system in a country.

MAJOR FUNCTIONS OF DRUG REGULATORY AUTHORITIES

- Controlling and monitoring the quality of marketed medicines
- Ensure adequate supply of quality medicines at affordable prices
- Control the supply and pricing of essential and life saving medicines
- Define the medicinal products categories and activities to be regulated
- Provide legislation, Acts and Rules related to all the activities of medicines trade
- Define the roles, responsibilities, rights, and functions of all individuals/agencies involved in the manufacturing and trade of medicines
- Publish medicines regulation guidelines for better understanding of regulatory aspects and facilitate their implementation
- Define the norms, standards, and specifications applied for assessing the safety, efficacy, and quality of medicines
- Set the qualifications and standards required for all those handling medicines
- Licensing for the manufacturing, distribution, and sale of medicines
- Define the terms and conditions for suspending, revoking or canceling activity and product licenses related to manufacturing and sale of medicines
- Define prohibitions, offenses, penalties, and legal actions
- Marketing authorization for import and export of medicines
- Inspecting manufacture premises, wholesale and retail outlet of medicines
- Controlling promotion and advertisement of medicines
- Work with Pharmacopoeial commission that sets standards for all drugs manufactured, sold and consumed in India
- Work with Central Drug Testing Laboratory which is the appellate laboratory for testing of drugs
- Inspection and controlling of blood banks
- Inspecting and controlling clinical trials centers in respective states
- Monitoring adverse reactions of medicines
- Providing appropriate information on medicines to professionals and the public
- Train staff to carry out regulatory related functions
- Create mechanisms to ensure transparency and accountability in regulatory function

- Establish mechanisms to deal with public/consumer complaints
- Participate in state and central schemes, harmonization of regulatory processes and standards, mutual recognition of regulatory decisions with an aim to prevent duplication of effort to reduce workloads and save resources.
- Networking and exchange of information with other regulatory authorities

Many developing and underdeveloped countries are unable to ensure the safety, efficacy, and quality of medicines available on their markets because of limitations in standard regulatory systems. Countries with limited resources for regulatory implementation should primarily focus on encouraging the development of the pharmaceutical industry by controlling the sale and distribution of drugs. Drug regulation is perceived as an obstacle to the availability of low cost medicines in the markets of such countries. Drug regulation though in many instances may delay and prolongs the availability of new and potent molecules in the market for diseases of high lethality rate like cancer and AIDS.

On the other hand, the political environment in some countries favors the demand for new medicines for local patients without fully understanding the importance of effective guideline implementation that ensures the availability of effective and safe medicines. Balancing these two sides of the swift availability of new molecule and comprehensive assessment of safety is indeed a difficult task and can only be possible with a strict time line based regulatory system. Drug regulatory bodies must ensure both the viability of pharmaceutical industries as well as the availability of high standard medicines at a low cost. Harmonized or centralized regulation system in particular speeds up the reviews and evaluations in a fixed timeline so that new medicines can be approved in the shortest possible time.

DRUG REGULATION WORLDWIDE

UNITED STATES

In the United States, the US Food and Drug Administration (USFDA) regulates therapeutic goods. Under the joint jurisdiction of the FDA and the Drug Enforcement Administration (DEA) possession of some substances are prohibited as per schedule of the Controlled Substances Act. *Tea Importation Act* came into force on 1897 was possibly first consumer protection law in the USA. At that time, there were no Federal laws governing use or distribution of any drug. Heroin, morphine, and cocaine-like substances were readily available and sold as part of "patent" medicines to cure wide categories of pain from menstrual cramps to toothaches in children. In *1906, the Pure Food and Drug Act* was enacted strictly implementing a 'labeling law' for foods and drugs. The first comprehensive federal consumer protection law was implemented in 1906. *The Pure Food and Drug Act*, which prohibited misbranded and adulterated food and drugs in interstate commerce.The passage of the 1906 Act was due in large part to the untiring scientific and political efforts of Harvey Washington Wiley, who at that time was a chief chemist of the Bureau of Chemistry of the U.S. Department of Agriculture, FDA's predecessor. Previous to 1914, restrictions were on the State or local level only, and those restrictions were few and far between and commonly targeted to use by certain *groups*.

Up till the early 1930s, some egregious examples of consumer products that poisoned, maimed and killed many people spurred national outrage. The requirement of toxicity testing before marketing drugs or cosmetics was enacted in 1938 following a lethal toxic effect of sulfanilamide dissolved in diethylene glycol which unfortunately caused kidney poisoning and killed 107 people. This amendment also implemented directions needed to be used on the package and made the first

mention of "use by an instruction from a physician only" in other words, prescription vs. non-prescription medicines. The enactment of the *1938 Federal Food, Drug, and Cosmetic Act* (FFDCA), replaced the earlier *Pure Food and Drug Act of* 1906. This has given authority to USFDA, to tighten controls over drugs and food. It includes protection of consumer from unlawful cosmetics and medical devices, and enhanced the government's ability to enforce the law. The amendment states that a drug had to be effective for what it was intended and approval had to be obtained before conduction human trial, which was introduced in 1962. Comprehensive *Drug Abuse Prevention and Control Act* (*Controlled Substance Act of 1970*) bought the drugs under the act and also under Federal jurisdiction that dealt with both narcotics and other "dangerous" drugs. The *Comprehensive Methamphetamine Control Act, 1996* restricted access to chemicals and equipment used in the manufacture of methamphetamine and increased penalties for possession of these plus the manufacture and sale of the drug. The act has been amended many times, till most recently to add requirements about preparations that can be used in bioterrorism. In the year 2009, President Obama signed the Family Smoking Prevention and Tobacco Control Act along with the formation of the FDA center for tobacco products.

The USFDA is an agency within the U.S. Department of Health and Human Services consisting of the Office of the Commissioner and four directorates overseeing the core functions of the agency. USFDA is responsible for protecting the public health by assuring the safety, effectiveness, and quality of human and veterinary drugs, vaccines and other biological products, medical devices, food, cosmetics, dietary supplements, tobacco products and products that give off radiation.

Some of the USFDA's specific responsibilities include control of:

- Product and manufacturing establishment licensing
- Establishing safety standards for blood transfusions
- Conduct research to establish product related standards and to develop improved testing methods
- Product approvals
- Drug manufacturing standards
- Quality and safety of biologics
- Quality and safety of drugs
- Quality and safety of cosmetics
- OTC and prescription drug labeling
- Quality and safety of all food products (except meat and poultry)
- Quality and safety of bottled water
- Quality and safety of medical devices
- Premarket approval of new devices
- Tracking reports of device malfunctioning and serious adverse reaction
- Quality and safety of radiation emitting electronic products
- Quality and safety of veterinary drugs and devices
- Quality and safety of livestock feeds
- Quality and safety of pet foods

Federal Register and Code of Federal Regulations

As required by law, the Food and Drug Administration publishes regulations in the *Federal Register* before issuing a final rule, in the federal government's official publication for notifying the public. All approved rules, proposed rules, notices, executive orders and other presidential documents of Federal agencies and organizations are officially published daily in the Federal Register that is published by the Office of the Federal Register, National Archives and Records Administration (NARA). The Federal Register is updated daily and is published on Monday through Friday, except Federal holidays.

The final rules promulgated by a federal agency are published in the Federal Register and ultimately reorganized by topic or subject matter as 'codified' in the Code of Federal

Regulations (CFR). The CFR is annually published in the Federal Register and in addition to this CFR is also published in an unofficial format online on the Electronic CFR website, which is updated daily. The CFR is divided into 50 titles that represent broad subject areas of federal regulation. The rule explaining the regulatory requirements of drugs are published under *Title 21 of Code of Federal Regulations*. The 21 CFR governs USFDA, the Drug Enforcement Administration (DEA) and the Office of National Drug Control Policy (ONDCP). The 21 CFR is divided into three chapters:

- Chapter I: Food and Drug Administration (The Federal Food, Drug, and Cosmetic Act.)
- Chapter II: Drug Enforcement Administration (for controlled substances)
- Chapter III: Office of National Drug Control Policy

Chapter I is divided into 12 subchapters that are concerned with drugs, cosmetics, biologicals, medical devices, tobacco products controlled by the Food and Drug Administration under the Department of Health and Human Services.

Orange Book (Approved Drug Products with Therapeutic Equivalence Evaluations)

The USFDA publishes a list of prescription drugs in 'Approved Drug Products with Therapeutic Equivalence Evaluations' that is commonly known as the Orange Book, identifying the drug products approved on the basis of safety and efficacy under the Federal Food, Drug, and Cosmetic Act. The Drug Price and Competition Act (Hatch-Waxman Act) requires FDA to publish the Orange Book.

The criterion for inclusion of any product in Orange Book is that the product has an effective approval and has not been withdrawn for safety or efficacy reasons. The publication does not include drugs on the market approved only on the basis of safety. The Orange Book contains therapeutic equivalence evaluations of approved multisource prescription generic drug products approved under Section 505 of the Federal Food, Drug, and Cosmetic Act to provide public information for state health agencies, prescribers and pharmacists. The Orange Book also lists patents and use codes provided by the drug application owner. The generic drug manufacturer can get the approval of a drug under the Hatch-Waxman Act only after expiration of the Orange Book listed patent or in case the patent is invalid or unenforceable. Orange Book was first published in 1980, and each subsequent edition has included new approvals and made appropriate changes in data. Orange Book is composed of four sections:

- Approved prescription drug products with therapeutic equivalence evaluations.
- Approved over-the-counter (OTC) drug products not covered under existing OTC monographs.
- Drug products approved under Section 505 of the Federal Food, Drug, and Cosmetic Act administered by the Center for Biologics Evaluation and Research.
- A cumulative list of approved products that have never been marketed, for exportation, for military use, have been discontinued from marketing or approvals other than safety or efficacy reasons after being discontinued.

This book index the prescription and OTC drug products by trade name (proprietary name) or established name (if no trade name exists) and by applicant name (holder of the approved application, who may not necessarily be the manufacturer of the product). Established names for active ingredients usually conform to official compendia names or the United States Adopted Names (USAN) as described in 21 CFR 2994e. The Addendum contains patent and exclusivity information of the prescription, OTC, approved drug products and the discontinued drug product. The Orange Book does not include drug

products with tentative approvals, but it lists the drug product and the date of approval in the appropriate approved drug product list when the tentative approval becomes a final approval.

The multisource drug products are assigned a therapeutic equivalence code. The user can determine the approval status of the product following the coding system for therapeutic equivalence evaluations (e.g. a particular strength of an approved drug) as therapeutically equivalent to other pharmaceutically equivalent products (first letter) and to provide additional information on the basis of FDA's evaluations (second letter).

Multisource drugs are placed into two basic categories, indicated by the first letter of the relevant therapeutic equivalence code as follows:

a. Drug products that FDA considers to be therapeutically equivalent to other pharmaceutically equivalent products, i.e. drug products for which there is no known or suspected bioequivalence problems. These products are designated AA, AN, AO, AP, or AT, depending on the dosage form. The products are designated as AB, in case the actual or potential bioequivalence problems have been resolved with adequate *in vivo* and/or *in vitro* evidence supporting bioequivalence.
b. Drug products that FDA considers not to be therapeutically equivalent to other pharmaceutically equivalent products, i.e. drug products are designated as BC, BD, BE, BN, BP, BR, BS, BT, BX when the actual or potential bioequivalence problems have not been resolved by adequate evidence of bioequivalence.

Every product in the Orange Book is a subject to regulatory action at all times. Thus the approved products may be found in violation of one or more provisions of the Act. FDA believes that the retention of a violative product in the Orange Book will not have any significant adverse health consequences, as other legal mechanisms are available to prevent the product from marketing. FDA may, however, change a product's therapeutic equivalence rating or call for assessment as of whether the product meets the criteria for therapeutic equivalence. Efforts are made to ensure that the annual edition of the current Orange Book is accurate. Applicants are requested to inform the FDA about any changes or corrections, related to the product's marketing status that can result in the product being moved to the discontinued drug product list in writing within 180 days.

Purple Book (Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations)

The Patient Protection and Affordable Care Act (Affordable Care Act), 2010 authorize amendment of the PHS Act to include an abbreviated licensure pathway for biological products demonstrated to be biosimilar to or interchangeable with an FDA licensed biological product. A single biological product licensed by FDA under Section 351(a) of the Public Health Service Act (PHS Act) against which a proposed biological product is evaluated in an application submitted under Section 351(k) is considered as a reference product. Healthcare providers are allowed to prescribe biosimilar and interchangeable biological products similarly as they prescribe other medications. The Biologics Price Competition and Innovation (BPCI) Act of 2009 permits that an interchangeable product can be substituted for the reference product without the intervention of the healthcare provider who prescribed the reference product. In contrast, a biosimilar product should be specifically prescribed by the healthcare provider and cannot be substituted for a reference product at the pharmacy level.

The Purple Book lists biological products like biosimilar and interchangeable biological

products licensed by FDA under the PHS Act. The Purple Book includes FDA evaluation status of a biological product licensed under Section 351(k) of the PHS Act as to be biosimilar to or interchangeable with a reference biological product already licensed as FDA biological product. Along with the evaluation status of the biological product for reference product exclusivity, the Purple Book also includes the date for licensing approval of the biological products under Section 351(a) of the PHS Act. Biosimilar and interchangeable biological products licensed under Section 351(k) of the PHS Act are listed under the reference product to which similarity or interchangeability was demonstrated. The resource lists all reference biological products licensed under Section 351(a), side-by-side with all corresponding biosimilars and interchangeable products licensed under Section 351(k) that is the primary purpose of Purple Book along with providing information on any existing reference product exclusivity protecting a reference biological product.

This book is designed to enable the user to verify whether a particular biological product has been determined by the Food and Drug Administration (FDA) to be a biosimilar or interchangeable with a reference biological product. The lists cross-reference the names of biological products licensed under Section 351(a) with the names of biosimilar or interchangeable biological products licensed under Section 351(k). A separate list is provided for the biological products regulated by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER). The list will identify the date of the first licensure if a biological product is protected by a period of reference product exclusivity and will also mention the date for exclusivity expiry. The list does not identify periods of orphan exclusivity and their expiration dates for biological products. The Purple book lists are updated periodically to include the biological products licensed under Section 351(a) or Section 351(k) and/or it determines the date of the first licensure for a biological product licensed under Section 351(a) of the PHS Act.

CANADA

In Canada, Food and Drugs Regulations are governed by the "*Food and Drug Act*" and associated regulations. The Therapeutic Products Directorate (TPD) implements the Food and Drug Regulations and the Medical Devices Regulations as per the authority of the *Food and Drugs Act,* to ensure safety, efficacy, and quality of pharmaceutical drugs and medical devices offered for sale in Canada. Under the authority of the Financial Administration Act, the TPD also administers fee regulations for drugs and medical devices. Food and drugs regulation have seven parts along with schedules defining different categories of drugs in list and tables:

- Part A: Administration
- Part B: Foods
- Part C: Drugs
- Part D: Vitamins, minerals, and amino acids
- Part E: Cyclamate and saccharin sweeteners
- Part G: Controlled drugs
- Part J: Restricted drugs

Part B contains regulation guiding safety and quality of alcoholic beverages, soft drinks, milk products, spice, fruits and vegetables, poultry products and food packaging details. Part C is for manufacturing licensing of drugs, GMP, radiopharmaceuticals, biologicals, clinical trials, drug categories like a new drug, non-prescription drugs, steroidal drugs, and sales regulation. Health Canada believes that disease prevention and health promotion can cut down the health care costs and improve the quality of life in the long term. Drug policy of Canada has traditionally favored punishment of even the smallest of offenders, until it was partially broken in 1996 with the passing

of the *Controlled Drugs and Substances Act. Controlled Drugs and Substances Act* defines eight different schedules of drugs and describes new penalties enforced for the possession, trafficking, exportation, and production of controlled substances. This law replaced the *Narcotic Control Act* and Parts III and IV of the *Food and Drugs Act* which deal with the advertisement of controlled substances. Canada was the first country in the world to legalize the use of cannabis for the terminally ill patients in 2001. The Canadian Food Inspection Agency (CFIA) is assigned to the mission of safeguarding food, animals, and plants to enhance the health and well being of Canada's people, environment and economy.

EUROPE

United Kingdom

A comprehensive regulatory system was introduced in the United Kingdom in 1968 though there was some regulation previously imposed since the time of King Henry VIII. The first comprehensive licensing system for medicines in the UK was the *Medicines Act of 1968*. The new *Medicines Act* brought legislation on medicines with the introduction of many other legal provisions for the control of medicines. The Act provided a system of licensing of manufacturing, sale, supply, and importation of medicinal products into the UK. Safety monitoring is achieved by ensuring that product labels, leaflets, prescribing information and advertising meets the required standards lay down by the Regulations. A three-tiered classification system is enforced in the United Kingdom:

- General Sale List (GSL)
- Pharmacy Medicines (PM)
- Prescription Only Medicines (POM)

Controlled Drugs (CD) are some commonly known substances having high abuse/addiction liability separately scheduled under the *Misuse of Drugs Act 1971* within the POM and the *Misuse of Drugs Regulations 2001*.

Following the introduction of Medicines Act, 1968, many amendments were made, and the government consolidated medicines legislation, into one set of new regulations, the *Human Medicines Regulations 2012*. A comprehensive regime for the marketing authorization, manufacture, import, distribution, sale, supply, labeling, advertising and for pharmacovigilance of products were introduced. This regulations introduced some limited policy changes related to statutory warnings for over the counter products, membership of review panels, health professionals' exemptions, provisions for Patient Group Directions, pharmacist-instigated changes to prescriptions and repeal in some sections of the *Medicines Act 1968* with 349 regulations in 17 parts, followed by 35 schedules. Some of the other vital regulations are: The Medicines (Sale or Supply) Regulations 1980 (Miscellaneous Provisions), The Medicines (Pharmacy and General Sale—Exemption) Order 1980 and The Medicines (Products Other Than Veterinary Drugs) Order 1984 (General Sale List), that was consolidated by the Human Medicines Regulations 2001. The Medicines (Advertising) Regulations 1994 was revoked and consolidated by the Human Medicine Regulations 2001. The Medicines (Responsible Pharmacist) Regulations 2008 describes the duties of responsible pharmacists for safe and effective running of a pharmacy business at the outlets. The Medicines for Human Use (Marketing Authorisations, etc.) Regulations 1994, The Prescription Only Medicines (Human Use) Order 1997, The Medicines for Human Use (Manufacturing, Wholesale Dealing, and Miscellaneous Amendments) Regulations 2005 and The Medicines for Human Use (Prescribing by EEA Practitioners) Regulations 2008 was also revoked and consolidated.

Medicines and Healthcare products Regulatory Agency (MHRA) regulates the

medicines for human use in the United Kingdom that is an executive agency of the Department of Health. The MHRA was formed in 2003 with the merger of the Medicines Control Agency (MCA) and the Medical Devices Agency (MDA). The MHRAs primary objective is to ensure that all medicines on the UK market meet appropriate standards of safety, quality, and efficacy to safeguard public health. The agency achieves its objective through a system of licensing before the marketing of medicines, and monitoring of medicines and acting on safety concerns after they have been placed on the market.

MHRA has three centers:

- The Clinical Practice Research Datalink (CPRD) aimed to improve public health by using anonymized NHS clinical data
- The National Institute for Biological Standards and Control (NIBSC) is a global leader in the standardization and control of biological medicines
- The MHRA responsible for safety, quality and effectiveness of medicines, medical devices, and blood components

The MHRA classifies drugs and regulates marketing authorization of the drug products. MHRAs prime objectives are:

- Inspection of the pharmaceutical manufacturing facility,
- Enforcement of requirements in manufacturing, sales, and distribution,
- Implementing medicines control policy,
- Representing UK pharmaceutical regulatory interests internationally and publishing quality standards for drugs,
- Promoting international standardization and harmonization to assure the efficacy and safety of biological medicines,
- Ensuring the adoption of a safe and secure supply chain for medicines, medical devices, and blood components,
- Supporting innovation and research beneficial for the development of public health,
- Educating the public and healthcare professionals about the risks and benefits of medicines, medical devices and blood components for safe and effective use.

Medicines must meet the standards of safety, quality and efficacy standards before granting marketing authorization for market release. This authorization covers all the main activities associated with the marketing of medicinal products and reviewing all the research and test results in detail. MHRA along with the expert advisory bodies set up by the Medicines Act ensures safety, quality, and efficacy as the primary criteria on which legislative control of human medicines functions. MHRA experts assess applications seeking approval for new medicines to ensure they meet the required standards. In April 2013, MHRA merged with the National Institute for Biological Standards and Controls (NIBSC). The MHRA also works closely with other health promotion bodies like National Patient Safety Agency (NPSA), Care Quality Commission (CQC), Health Protection Agency (HPA) and National Institute for Clinical Excellence (NICE) providing guidance on the promotion of good health and the prevention of ill health in national level.

Following the Brexit (British exit) pole, UK has decided in June 2016, a referendum to leave the European Union (EU) by March 2019. Following the event of the EU referendum, MHRA is analyzing for the best options and opportunities concerning effective regulation of medicines and medical devices in the UK. While negotiations continue, the UK remains a full and active member of the EU, with all the rights and obligations of EU membership firmly in place. UK Government gave a clear, public statement of its desire to retain a close working partnership in respect of medicines regulation after the UK leaves the EU in the interests of public health and safety. UK's current regulatory relationship with the European network remains unchanged until the exit negotiations are concluded. MHRA

uploaded a link to update pharmaceutical companies on exit preparations in January 2018.

Norway

Norwegian Medicines Agency (NoMA) established in 2001 has united different branches of public administration of pharmaceuticals in Norway in one single agency. NoMA is subordinate to the *Ministry of Health and Care Services Act* as the legislative authority. NoMA supervises production, clinical trials, and marketing of pharmaceuticals. The Mission of the NoMA is to safeguard public and animal health by ensuring the efficacy, quality, and safety of medicines. NoMA is in charge of marketing authorization, classification, vigilance, pricing, supply chain, reimbursement and providing information on medicines to prescribers and the public.

The European Economic Area (EEA) comprises 28 EU member states, and the three EFTA (European Free Trade Association) states Iceland, Liechtenstein, and Norway. Through the EEA Agreement and the EEA Joint Committee Decisions Norway complies to implement EU regulations and directives though it is directly not a member country in EU, Norwegian regulation for pharmaceuticals is harmonized with EU regulation. These regulations and directives concern the marketing authorizations for manufacturing and distribution of pharmaceuticals, supervision of use and clinical trials. Norway, as part of the European Economic Area, adheres to EU-regulations regarding marketing authorizations. The NoMA contributes to the work of the European Medicines Agency (EMA), alongside agencies from the EU-member states. Ministry of Health and Care Services of the Norwegian government participates in binding work with the EU under The European Medicines Agency (EMEA) in various committees and working groups.

Medicines in Norway are divided into five separate groups:

- Class A: Narcotics, sedative-hypnotics and amphetamines in this class require a special prescription form
- Class B: Restricted substances which can easily lead to addiction
- Class C: All prescription-only substances
- Class F: Substances and package sizes not requiring a prescription
- Unclassified: Brands and packages not actively marketed in Norway

Iceland

Medicines in Iceland are regulated by the Icelandic Medicines Control Agency (IMA), a governmental Agency under the Ministry of Welfare. IMA's responsibilities are an assessment of quality and safety of medicinal products, medical devices, conduct inspections to confirm regulatory requirements and to guarantee consumer protection. The Agency issues permission for clinical trials, classifies natural products and food supplements, controls ads on medicines and publishes a catalog of Medicinal Products. IMA is an independent regulatory authority, functions under the Ministry of Welfare. One of its primary functions is to issue marketing authorizations for medicines in Iceland and also works in close collaboration with regulatory authorities in the European Economic Area (EEA). IMA controls surveillance of the pharmaceutical industry in Iceland and contribute to the availability of unbiased information on medicines to the health professionals and consumers.

Medicinal product is defined as 'Any substance or compound claimed to have properties which can be used for treating diseases in humans or animals or preventing diseases or any substance or compound which can be used by humans or in animals or given to them either for the purpose of restoring, rectifying or amending a physiological

function through pharmaceutical or immunological action or influencing the metabolism or for confirming a diagnosis of a disease' as per the amended *Medicines Act No 93/1994. IMA* issues list with the classification of substances and compounds concerning the pharmaceutical activity and/or harmfulness, including substances/compounds banned/permitted as consumer products, i.e. any substance independent of origin:

- Humans, e.g. blood or blood products
- Animals, e.g. microorganisms, animals, tissues, serum, toxic chemicals, extracts, substances processed from the blood.
- Herbs, e.g. plants or plants parts and extracts.
- Other substances, e.g. elements, substances from natural resources, substances formed by chemical reactions or combinations.

The IMA build up a formal quality management system in 2001 about other regulatory agencies in the field of medicinal products as well as guidelines from international agencies were foreseen at that time, and constant regulatory changes were also taken into account. Strengthening of quality management has been done at IMA by increasing the number of active procedures, establishing specific Procedures Teams to oversees implementation of quality related issues and the progress there off. Under the auspice of the Heads of Medicines Agencies (HMA), self-assessments helped in assessing the status of the quality management system in the agency. Benchmarking of European Medicines Agencies (BEMA) and internal audits initiated has benefited the management for reviewing essential functions of the agency. The advisory committee of the Agency, named Pharmaceutical Committee comprises five members with broad expertise in medicine. The Chairman is appointed by Minister and other members are appointed in consultation with the Chairman for a four-year term. For dealing veterinary medicinal products the Chief Veterinary Officer and a veterinarian appointed by the Ministry controls the regulation procedure. The IMA is responsible for regulatory surveillance of medical devices as per the *Act on Medical Devices, No. 16/2001*. Manufacturers should ensure that their devices are safe and fit for intended purpose before they are CE marked. In concern to pharmacovigilance, all adverse reactions should be reported to IMA by the healthcare professionals, veterinarians and members of the public. IMA is a Web trader in the EMA database, Eudra Vigilance, and reports all adverse reactions received to that database.

Switzerland

Swiss Agency for Therapeutic Products called SwissMedic is the central Swiss supervisory authority for therapeutic products. Medicines in Switzerland are regulated by Swissmedic public service organization of the federal government with headquarters in Bern. The country is not a member of the European Union and thus regarded as one of the easiest places to conduct clinical trials of new drug compounds. Swissmedic is linked to the Federal Department of Home Affairs (FDHA) which connects Swissmedic to the Federal Council (the Swiss government).

Five categories to cover different types of Delivery as per Swissmedic are:

a. Single delivery on medical prescription
b. Repeated delivery on medical prescription
c. Prescription free delivery after consultation of a specialist, restricted to pharmacy/chemist
d. Prescription free delivery after consultation of a specialist restricted to pharmacy, chemist, and drug store
e. Prescription free delivery without consultation in all shops/stores

Switzerland's Federal Drug Policy aims at harmonization of the various drug strategies of the cantons (states) and the 1951 *Narcotics Act*. The history of Switzerland's drug policy

began towards the end of the 1960s when there was an increase in psychoactive drug use. Like many other countries, at the beginning of the 1980s, HIV-AIDS epidemic hit Switzerland as a consequence of the miserable state of drug addicts. In the 1990s, Switzerland introduced new measures to reduce the problems associated with drug use and adopted a new national drug strategy. Currently known as "ProMeDro,"the Swiss government adopted a federal program to reduce the problems related to drug use on February 20, 1991, which was based on the concept of 'harm reduction.' These measures mark the beginning of Switzerland's drug policy, based on a fourfold approach: Prevention, law enforcement, treatment, and harm reduction. The Federal Council passed the *Ordinance Governing the Medical Prescription of Heroin* authorizing heroin-assisted treatment, setting objectives, eligibility criteria and administrative measures for providing such treatment on 1999.

The *Federal Act on Medicinal Products and Medical Devices (Therapeutic Products Act, TPA) 2000*, issued by the Federal Assembly of the Swiss Confederation, is to protect human and animal health and to guarantee that high quality, safe and effective therapeutic products are placed on the market.

The Medical devices ordinance along with the TPA forms the legal basis of regulation of medical devices in Switzerland which classify the medical device as

·Classical medical devices: corresponding to European directive 93/42/EEC

- *In vitro* diagnostic medical devices: Corresponding to European Directive 98/79/EC.
- Active implantable medical devices: Corresponding to European Directive 90/385/EEC.
- Devices produced using devitalized human tissue: Within Switzerland, these devices are counted as classical or active implantable medical devices.

In September 2003, USFDA and SwissMedic signed a memorandum of understanding (MOU) to enhance and strengthen communication and public health promotion, cooperative activities related to the regulation of human or animal pharmaceutical products and human medical devices in Switzerland and the United States. Information exchanged under the MOU also includes non-public information exempt from public disclosure under the laws and regulations of Switzerland or the United States. As per the mandate of the Federal Council in 2013, Swissmedic implements Marketing Authorisation for Global Health Products (MAGHP) procedure with the National Medicines Regulatory Authorities (NMRAs) of the East African Community (EAC) to accelerate and increase access to high-quality, essential medicines for populations living in low-income countries. This was aimed to increase the efficiency of the regulatory registration and review process focusing on stakeholders value-added activities and strengthening the regulatory authorities ability to protect citizens health. The WHO Pre-Qualification Team (WHO PQT) can also be involved in this marketing authorization procedure with Swissmedic.

In 2017 Swissmedic authorizes electronic application format for submission of documents (eDok) for authorization and variation requests regarding both human medicinal products. It does not replace the electronic Common Technical Document (eCTD) and is more straightforward, in technical respects, as the eCTD format. The electronic data replaces the necessary paper copies required with a paper submission. Swissmedic carries out the review based on the documentation submitted electronically and archives the paper original as a legally binding document. When submitted via the portal, the eDok format is considered to be a purely electronic format without the need for any paper documents. When submitted by post, the eDok format is considered to be a paper format requiring the

submission of a complete paper copy as the original paper version. When eDok application is submitted via the Swissmedic eGov Portal, the uploads completely replace paper documents submission and data carriers. Even documents with signatures are no longer necessary since authentication takes place via the Portal log-in corresponding to a fully electronic application format.

JAPAN

The pharmaceutical regulatory authority of Japan is the Pharmaceutical and Food Safety Bureau (PFSB) of the Ministry of Health, Labor, and Welfare (MHLW), government organization similar in function to the FDA of other countries. The MHLW was originally established in 1938 aimed at improvement and promotion of social welfare, social security, and public health. The MHLW was merged with the Ministry of Health and Welfare (MHW) and the Ministry of Labour in 2001 as part of the government program. Japanese MHLW is a complex organization as its ancestor, the MHW which has implemented many current regulations and decisions. Consolidation of the services of the Pharmaceuticals and Medical Devices Evaluation Center of the National Institute of Health Sciences (PMDEC), formed the Pharmaceuticals and Medical Devices Agency (PMDA), established in 2004. In conjunction with the MHLW, the PMDA is responsible for reviewing drug and medical device applications. The PMDA works with the MHLW to assess new product safety, develop comprehensive regulations and monitor post-market safety. The PMDEC, usually known as 'The Center', is the actual decision maker for approval of new drug applications (NDAs).

The PMDA reviews new drugs, generic drugs, OTC drugs/behind-the-counter (BTC) drugs, and quasi-drugs, and conducts re-evaluations of previously approved drugs. Orphan drugs and other priority drugs are given priority reviews following their clinical significance. The Pharmaceutical Safety and Environmental Health Bureau (PSEHB) is one of the 11 bureaus of the MHLW. In addition to policies to assure the efficacy and safety of drugs, quasi-drugs, cosmetics, and medical devices, and safety in medical institutions, the PFSB also ensures the health of the general public including policies related to blood supplies and blood products, and narcotics and stimulant drugs. The PMDA evaluates new drugs for approval based on the reliability of the studies conducted, efficacy outcome based on properly designed clinical studies, the clinical significance of the results, any unacceptable risks overwhelming the benefits and ensures continuity in efficacy and safety of the drug from quality assurance standpoint. The essential tasks of the agency are:

- Scientific review of market authorization applications for drug and medical device as per Japanese pharmaceutical law.
- Review and approval of NDAs for drug and medical device.
- Advice on clinical trials and dossiers for the registration procedure.
- Inspection and conformity assessment as per Good Clinical Practice (GCP), Good Laboratory Practice (GLP), and Good Practice Systems and Programs (GPSP).
- Auditing and inspection of marketing authorization holder manufacturers ensuring conformance with GMP, and Quality Management System (QMS) as per product family.
- Collection, analysis, and distribution of data on post-marketing quality, efficacy, and safety of medicines and medical devices.
- Regulation of medical software
- Advising consumers on the safety issues of approved drug products.
- Research on the development of standards for post-marketing drug safety.
- Payment towards compensation for medical costs and lost wages for the

sufferers of injury or disability resulting from the use of medical products.
- Disbursement of compensation funds to the HIV infection victims due to blood transfusions.

Modern pharmaceutical legislation in Japan was originated with the enactment of the Regulations on Handling and Sales of Medicines in 1889. The Pharmaceutical Affairs Law (PAL) was enacted in 1943 and revised several times. The current PAL is the result of complete revisions in 1948 and 1960. In 2002, the PAL was revised for safety assurance of biotechnology, genomics and post-marketing surveillance policies. After that, the provisions on the enhancement of safety measures for biological products came into effect in 2003 and control on medical devices and regenerative medicine products in 2013. The current Japanese regulations laid out in the *Pharmaceuticals and Medical Devices Act* (PMD Act), came into force on 2014 replacing the Pharmaceutical Affairs Law (PAL) that consists of 17 chapters and 91 articles. The PMD Act secures the quality, efficacy, and safety of pharmaceuticals, medical devices, regenerative and cellular therapy products, gene therapy products and cosmetics. This act affects all aspects of Japanese medical product registration, including in-country representation, certification processes, licensing, and quality assurance systems. The PMDA defines cellular and tissue-based (regenerative medicine) products that are intended to be used for reconstruction, repair, or formation of structures or functions of the human body, treatment or prevention of diseases and gene therapy. To ensure early access to regenerative medical products, the PMD Act significantly shortens clinical trial phase period to approve on a conditional authorization basis.

PMDA classifies medical devices depending on the risk level:
- The general medical device (Class I)
- Controlled medical device (Class II)
- Specially controlled device (Class III and Class IV)

General medical devices do not need to undergo the approval process of MHLW and PMDA but only require notification/self-declaration on the product. Controlled medical devices can be certified by an authorized third-party or reviewed by the PMDA. Specially controlled medical devices must be reviewed and approved by the PMDA and MHLW.

CHINA

The pharmaceutical industry in the People's Republic of China covers synthetic chemicals and drugs, prepared traditional Chinese medicines, medical devices, apparatus and instruments, hygiene materials, packing materials and machinery. Impending growth of Chinese pharmaceutical market has persuaded the government to realize the importance of strict supervision of pharmaceutical market. The government has put forward several regulations and reform measures over the past couple of years. The Department of Drug Administration under the Ministry of Health, merged with the "State Pharmaceutical Administration of China" (SPAC) in March 1998, to become the State Drug Administration (SDA) to oversee all drug manufacturing, trade, and registration.

The current *Drug Administration Law* of the People's Republic of China came into effect on 2001 after several revisions. All institutions and individuals associated with research, production, distribution, use or administration of the drug in the People's Republic of China has to abide this Law. This Law was enacted to strengthen drug administration to ensure drug quality and safety for human subjects, protect the public health interest and legitimate rights of the drug users. It contains ten chapters covering drug manufacturing, distribution, quality and efficacy, packaging, pricing, advertising, hospitals, and legal liabilities.

Chapter I: General Provisions
Chapter II: Control over Drug Manufacturers
Chapter III: Control over Drug Distributors
Chapter IV: Control over Pharmaceuticals in Medical Institutions
Chapter V: Control over Drugs
Chapter VI: Control over Drug Packaging
Chapter VII: Control over Drug Pricing and Advertising
Chapter VIII: Inspection of Drugs
Chapter IX: Legal Liabilities
Chapter X: Supplementary Provisions

The SDA was restructured and become the State Food and Drug Administration (SFDA) in 2003. Formation of SFDA was an important step as with this the Chinese government established a single drug regulatory authority eliminating the diverge standards that prevailed among provincial government agencies centralizing the Chinese healthcare regulatory system. The current drug regulation law controls all the aspects of pharmaceutical manufacturing, drug distribution and sell, drug registration, requirements for manufacturing of Traditional Chinese Medicines (TCM), medicine packaging and medical device manufacturing. SFDA also overlooked advertising of all medications of both Western and TCM originated. SFDA implemented mandatory compliance with new GMP certification by all pharmaceutical companies in China in 2004 to sell drug products in China. In 2005, SFDA enforced GLP to investigative drugs, TCM injections and biotechnology products.

In March 2013, the SFDA was rebranded and restructured as the China Food and Drug Administration (CFDA), elevating to a ministerial-level agency directly under the State Council of the People's Republic of China. The CFDA has replaced the overlapping regulators with an entity similar to the FDA of the United States, streamlining regulation processes for food and drug safety. The CFDA comprehensively supervises the safety of food, health food, and cosmetics also with authority of drug regulation in mainland China. CFDA is charged with the registration, testing, and administration of pharmaceuticals, over-the-counter drugs, traditional Chinese medicine, and medical devices.

CFDA categories for drug registration:

- Category I: New drugs not yet approved in any country.
- Category II: Drugs seeking approval for a new route of administration that is not approved in any country.
- Category III: Drugs approved in other countries but not in China.
- Category IV: Drugs made by changing the acidic or alkaline radicals or metallic elements of the salt of a drug approved in China without changing the original pharmacological effects.
- Category V: Changed dosage form of a drug approved in China without changing the route of administration.
- Category VI: Generic form of a drug with existing national standards in China.

The CFDA considers drugs approved and marketed in other countries as new drugs in China, and previously approved therapies are designated as category III import drugs that require clinical data from trials conducted in China to support an application. Full clinical development in China is required for drugs that have not been approved anywhere yet to submit a category I new drug application for market approval. Regulations for the Supervision and Administration of Medical Devices come into force in 2000. 'Medical devices' as defined by these regulations refer to any instrument, apparatus, appliance, material, or other articles that are being used alone or in combination, including the software necessary for its proper application. Rules for classification of medical devices were adopted at the executive meeting of CFDA in 2015, that became effective as on 2016.

According to the factors which may influence the degree of risk of medical devices, medical devices are divided as:

- Non-active and active medical devices, according to structural characteristics.
- Body-contacting and non-body-contacting devices, according to whether they are in contact with the human body.

According to the use pattern, structural characteristics are divided as:

- Non-active body-contacting devices
- Non-active non-body-contacting devices
- Active body-contacting devices
- Active non-body-contacting devices

According to the degree of risk (from low to high), the medical devices are divided into class I, class II and class III.

BRAZIL

The National Health Surveillance Agency, named the "Agência Nacional de Vigilância Sanitária" (ANVISA) enforced in 1999 regulates therapeutic goods in Brazil under the Brazilian Health Ministry. The autarchy is connected to the Ministry of Health and functions by a Board of Directors made up of five members under a special regime, with administrative independence, stability, and financial autonomy. ANVISA open spaces for society to give its opinion on critical health-related issues and to ensure transparency in regulatory actions. The basic regulation structure and the medical device classification schemes in Brazil are similar to those found in the European Medical Devices Directives (MDD) 93/42/EEC. For registration process of a medical device in Brazil the first step is to determine the device classification. This is critical for ensuring a smooth registration process. There are five main categories:

1. **Normal Medicines:** Cough, cold and fever medicines, antiseptics, vitamins and others which are sold freely in pharmacies and some supermarkets.
2. **Red Stripe Medicines:** These medicines are to be sold only with a medical prescription like antibiotic, antiallergenic, anti-inflammatory, etc. medicines. In Brazil, it is not uncommon to get this type of prescription medicine over the counter without a prescription, as governmental control is loose.
3. **Red Stripe Psychoactive Medicines:** These medicines are sold only with a "Special Control" white medical prescription with carbon copy, which is valid for 30 days. The pharmacist must retain the original after the sale, and the patient keeps the carbon copy. Drugs include anti-depressants, anti-convulsants, some sleep aids, antipsychotics, anabolic steroids, and other non-habit-inducing controlled medicines.
4. **Black Stripe Medicines:** These medicines are to be sold only with the "Blue B Form" medical prescription, which is valid for 30 days and must be retained by the pharmacist after the sale. This category includes sedatives (benzodiazepines), anorexia inducers and other habit inducing controlled medicines.
5. **"Yellow A Form" prescription medicines:** These medicines are sold only with the "Yellow A Form" medical prescription that is the most tightly controlled, which is valid for 30 days and must be retained by the pharmacist after the sale. This includes amphetamines and other stimulants (such as methylphenidate), opioids (such as morphine and oxycodone) and other strong habit-forming controlled medicines.

ANVISA is empowered to establish technical regulations, control and inspection procedures for drugs, medical devices, food, cosmetics, sanitizing products, pesticides, tobacco products, blood and blood products. The agency is also responsible for coordinating the National Health Surveillance System (SNVS), the National Program of Blood and

Blood Products and the National Program of Prevention and Control of Hospital Infections, monitoring of drug prices and performing pharmacovigilance activities.

The USFDA and the ANVISA have come under Statement of Cooperation (SOC) recognizing the importance of timely and effective communication and collaboration to enhance the activities of mutual interest in scientific and regulatory areas. This SOC is intended to strengthen existing structures and develop new opportunities for cooperative engagement in regulatory and scientific matters, and public health protection that is related to the products that both agencies regulate. This collaboration is intended to facilitate the effective exchange of information, develop new or strengthen existing cooperative efforts/initiatives, and coordinate with other countries and with stakeholder groups relevant to product regulation within their respective countries or a broader global context.

AUSTRALIA

The Therapeutic Goods Administration (TGA) regulates therapeutic goods in Australia. Drugs and poisons are regulated through scheduling under individual state legislation under the guidance of the national Standard with Uniform Scheduling of Drugs and Poisons (SUSDP). Under the SUSDP, medicinal agents generally belong to one of the five categories:

- Unscheduled/exempt
- Schedule 2 (S2): Pharmacy Medicines
- Schedule 3 (S3): Pharmacist Only Medicines
- Schedule 4 (S4): Prescription Only Medicines
- Schedule 8 (S8): Controlled Drugs

The legislation governing medicines in Australia is the *Therapeutic Goods Act 1989* which establishes a national system of controls for medicines. The Therapeutic Goods Advertising Code and the Australian Code of Manufacturing Practice for Therapeutic Goods are the two main codes that govern the advertising and manufacturing of medicines in Australia. The *Therapeutic Goods Act 1989*, that came into effect on 15 February 1991, provides a national framework for the regulation of therapeutic goods in Australia and ensure their quality, safety, and efficacy. The TGA regulates therapeutic goods via pre-market assessment, enforcement of standards, licensing of Australian manufacturers, post-market monitoring and verifying overseas manufacturer's compliance with the same standards as their Australian counterparts. TGA regulates medicines, medical devices, chemicals, gene technology, blood, blood and tissues products. Medicines are classified as registered medicines or listed medicines, depending on their ingredients and claims made. Registered medicines are further classified as non-prescription (low risk) registered medicines and as prescription (high risk) registered medicines. The degree of control imposed on registered medicines is higher than that of listed medicines as they are evaluated for safety, quality, and efficacy while listed medicines are evaluated for safety and quality only. The regulatory framework is based on a risk management approach designed to ensure public health and safety, but at the same time also endeavor to relax the industries from the unnecessary regulatory burden.

Necessarily, any product for which therapeutic claims are made must be entered in the Australian Register of Therapeutic Goods (ARTG) before the product can be supplied in Australia. The ARTG is a computerized database of information about therapeutic goods for human use approved for supply in/or exported from Australia. *The Therapeutic Goods Act* (1989), regulations and orders set out the requirements for inclusion of therapeutic goods in the ARTG including advertising, labeling, product appearance and appeal guidelines. The relevant state or territory legislation covers some provision

such as the scheduling of substances and the safe storage of therapeutic goods.

TGA exercise overall control on the supply of therapeutic goods by three main processes:

Pre-market assessment: Prescription medicines, some non-prescription medicines and medical devices assessed to have a higher level of risk are evaluated for quality, safety, and efficacy. Once approved for marketing in Australia these products are included as 'registered' products and are identified by a number. Products assessed having a lower risk like many non-prescription medicines including most complementary medicines and low risk medical devices are also evaluated for quality and safety. Once approved for marketing in Australia, these products are included as 'listed' products and are identified by a number. Product strength, side effects, potential harm caused after prolonged use, toxicity and the seriousness of the medical condition for which the product is intended to be used are the factors taken into account while assessing the level of risk.

Licensing of pharmaceutical manufacturers: All Australian manufactures of therapeutic goods should be licensed with TGA. The manufacturing processes must comply with the principle of good manufacturing practice (GMP). The aim is to protect public health by ensuring that medicines and medical devices meet pre-defined standards of quality assurance and are manufactured in a clean and free of contaminants condition.

Postmarketing vigilance: Postmarketing activities include investigating reports of ADR related problems. Laboratory testing of products available in the market and monitoring of products is done to ensure compliance with the legislation.

The TGA is the leading government agency responsible for enforcing the regulations of medicines in Australia, as part of the Health Products Regulation Group (HPRG) in the Australian Government Department of Health. The TGA is responsible for administering the provisions of the legislation. The TGA carries out assessment and monitoring activities to ensure that the therapeutic goods available in Australia are of an acceptable standard. The TGA ensures that the Australian community has access to therapeutic advances within a reasonable time. TGA has three major divisions:

- Medicines Regulation Division: This division evaluates applications to approve new medicines for supply in Australia and monitoring of medicines approved for supply in Australia.
- Medical Devices and Product Quality Division: This division monitors medical devices approved for supply in Australia and works to ensure Australian and international therapeutic goods manufacturers meet specified standards.
- Regulatory Practice and Support Division: This division provides operational, regulatory, policy advice and specific support services that ensure efficient, best practice administrative operations in the Health Products Regulation Group.

The TGA has seven statutory expert committees it may call upon to obtain independent advice on scientific and technical matters. The TGA is focusing on implementing changes to ensure greater emphasis on transparency of regulatory decision-making processes, business process reform and a more strategic approach to the use of information technology to support regulatory operations. In 2009, the TGA commenced a significant program of business process reforms (BPR program) for the regulation of prescription medicines in Australia. An advertising regulatory framework was released in 2011, for therapeutic goods other than prescription medicines. In concern to medicines and medical devices regulation, some changes have now been implemented under the Government's Response to the Review of Medicines and Medical Devices Regulation in 2016, with

further reforms in progress or upcoming. The first set of legislative changes were passed in 2017 focusing on new assessment pathways for medicines and medical devices. The second tranche of legislative review is underway.

DRUG REGULATION IN INDIA

The Indian pharmaceutical industry sector is one of the largest, most advanced and rapidly growing among the developing countries with a wide range of products. Keeping in pace with this fast growth, the Indian pharmaceutical industry, the regulatory bodies are also coming out with major inclusions, amendments and revisions in guidelines to be in equivalence with international regulatory perspective. Indian pharmaceutical industry is having an advanced infrastructure, technological capability and qualified work force. India regulatory system is implementing and adopting the changes in guidelines, i.e. Good Manufacturing Practices (GMP), Good Clinical Practices (GCP) and Good Laboratory Practices (GLP) to be at peer with global standards to ensure supply of quality drugs at affordable prices to the Indian population.

Manufacturing, sale and distribution of medicines in India are regulated by Central Drugs Standard Control Organization (CDSCO) under Ministry of Health and Family Welfare and respective states licensing authorities headed by Directorate General of Health Services. CDSCO regulate the pharmaceutical products through Drug Controller General of India (DCGI) of India. CDSCO is India's prime regulatory body for pharmaceuticals and medical devices.

CENTRAL DRUGS STANDARD CONTROL ORGANIZATION (CDSCO)

The CDSCO is the Central Drug Authority for discharging functions assigned to the Central Government under the Drugs and Cosmetics Act. CDSCO regulates the manufacturing of large volume parenteral (LVPs), blood bank, new drugs, clinical trials, class III, and IV diagnostic kits. Under the *Drug and Cosmetics Act*, manufacture, sale, and distribution of drugs is the primary concern of the State authorities while the Central Authorities are responsible for approval of new drugs, clinical trials, developing standards for drugs, control the quality of imported drugs, coordination of the activities of State Drug Control Organisations. CDSCO provides expert advice encouraging uniformity in the enforcement of the Drugs and Cosmetics Act. CDSCO headquarter is located at FDA Bhawan, New Delhi. CDSCO has six zonal offices (Mumbai, Kolkata, Chennai, Ghaziabad, Hyderabad, and Ahmedabad), five sub-zonal offices, 13 port offices and seven central laboratories under its control. The Zonal Offices work in close collaboration with the State Drug Control Administration and assist them in securing uniform enforcement of the Drug Act and other related legislation. The zonal offices do pre-licensing and post-licensing inspections, post-market surveillance and recall when necessary.

The CDSCO establishes safety, efficacy and quality standards for pharmaceuticals and medical devices. The primary functions of CDSCO are:

- Laying down standard and approval of new drugs
- Approval and licensing to manufacture LVPs, vaccines, sera and biotechnological products as Central Licence Approving Authority
- Licensing of blood banks and setting standards for blood products
- Licensing of medical devices and class III and IV diagnostic agents
- Grant of test license and NOCs for export of drugs
- Grant of license for the export of drugs for personal use
- Import registration and licensing and regulation of standards of imported drugs

- Regulation and approval of clinical trials and clinical research
- Amendment of Drug and Cosmetics Act and Rules
- Participation in WHO GMP certification scheme
- Publishing and updating the Indian Pharmacopeia
- Publishing and updating the list of drugs approved for marketing
- Publishing and updating the list of regulated pharmaceuticals and devices
- Publishing and updating the list of banned drugs and cosmetics
- Publishing and updating the list of drugs prohibited for manufacture and sale
- Publishing and updating the list of banned medical devices and diagnostics
- Laying down standard and publication of guidance documents registration requirements of LPVs, vaccines, sera, biological, medical devices and diagnostics
- Testing of drugs by central laboratories
- Monitoring adverse drug reactions
- Conducting training programmes for regulatory officials and government analysts
- Quota distribution of narcotic drugs for use in medicinal formulations.
- Developing regulatory measures, amendments to Acts and Rules and guidance on all technical matters concerned to drug regulation.
- Coordinating the State Drugs Control Organizations to achieve uniform administration of the Act and policies.

For all drug and device licensing applications CDSCO appoints notified bodies to perform conformity assessment and testing to ensure compliance with their standards. CDSCO safeguards public health by ensuring the quality, safety, and efficacy of drugs, cosmetics and medical devices as the Central Drug Authority. For fulfilling functions allocated by the Central Government under the Drugs and Cosmetics Act, CDSCO formatted different committees with eligible members to review clinical trials of new drugs, and medical devices. CDSCO endorses experts of 25 panels from various therapeutic areas. Experts are selected and approved by the government from various therapeutic fields of medicine all over the country. The names of experts from various Govt. Medical Colleges and hospitals are added as deemed necessary by the government.

In addition to its regulatory functions, the CDSCO also offers technical guidance, training to the regulatory officials and analysts, and monitors adverse events. The CDSCO works with the WHO to promote Good Manufacturing Practice (GMP) and international regulatory harmony in India. CDSCO has adopted the Common Technical Document (CTD) format for technical requirements for registration of pharmaceutical products for human use since 2008. The adoption of Drug Master File (DMF) and drug product dossier concepts as in CTD format in tune with the global requirements are helping the Indian pharmaceutical industry for quick entry to the global markets, and simultaneously patients are assured to receive good quality and safe medicines.

The Drug Controller General of India (DCGI)

DCGI is responsible for licensing of specified categories of drugs such as blood and blood products, IV Fluids, vaccine and sera. Within the working structure of CDSCO, the Drug Controller General of India (DCGI) is responsible for approval of new drugs, medical devices and clinical trials in India. DCGI is appointed by central Govt., Directorate General of Health Services, all the state drug control organization named Food and Drug Administration (FDA) function under this umbrella. The Drug Technical Advisory Board (DTAB) and the Drug Consultative Committee (DCC) advise the DCGI on related issues. Central Licensing Approval Authority (CLAA) handles the

licensing and classification of medical devices. DCGI headquarter deals with new drugs, import of drugs and medical devices, whereas the six zonal offices (Mumbai, Kolkata, Chennai, Ghaziabad, Ahmedabad, and Hyderabad) perform GMP audit, inspection of manufacturing units of LVPs, sera, vaccines, and blood products, and maintain coordination with state authorities. Six Central Drug Testing Laboratories (Mumbai, Kolkata, Chennai, Kasauli, Guwahati, Chandigarh) function under the DCGI overseeing quality control of drugs and cosmetics, and validation of test protocols.

Drug Technical Advisory Board (DTAB)

DTAB is a statutory body under the provision of *Drugs and Cosmetics Act* to advise the Central Govt. on the technical matter related to implementation of *Drugs and Cosmetics Act* and Rules and to carry out other assigned duties by this Act. DTAB counsels Central and State government on drug control related technical issues. The DTAB consists of the following members as per the current Drugs and Cosmetics Act, 1940 and Rules, 1945 amended up to the 31st Dec 2016:

1. The Director General of Health Services *ex officio, as* Chairman
2. The Drugs Controller, India, *ex officio*
3. The Director of the Central Drugs Laboratory, Calcutta, *ex officio*
4. The Director of the Central Research Institute, Kasauli, *ex officio*
5. The Director of the Indian Veterinary Research Institute, Izatnagar, *ex officio*
6. The President of the Medical Council of India, *ex officio*
7. The President of the Pharmacy Council of India, *ex officio*
8. The Director of the Central Drug Research Institute, Lucknow, *ex officio*
9. Two persons nominated by the Central Government from states drugs control office
10. One person elected by the Executive Committee of the Pharmacy Council of India (teaching faculty of Pharmacy from an Indian university or an affiliated college)
11. One person elected by the Executive Committee of the Medical Council of India (teaching faculty in medicine from an Indian university or an affiliated college)
12. One person nominated by the Central Government from the pharmaceutical industry
13. One pharmacologist elected by the Governing Body of the Indian Council of Medical Research
14. One person elected by the Central Council of the Indian Medical Association
15. One person elected by the Council of the Indian Pharmaceutical Association
16. Two persons appointed as Government Analyst nominated by the Central Government

All the nominated and elected members of the Board hold office for three years but also eligible for re-nomination and re-election. The Board subject to the previous approval of the Central Government, make bye-laws fixing a quorum and regulating its procedure to conduct all functions. The Board can constitute sub-committees for a period not exceeding three years or in a case as decided temporarily for the consideration of particular matters with persons who are not members of the Board. The Central Government appoints a person to act as Secretary of the Board and also provide clerical and other staff as considered necessary as per the Drugs and Cosmetics Act 1940 and Rules 1945 (amended up to 31st Dec 2016).

Medical Devices Advisory Committee (MDAC)

MDAC is to advise the CDSCO in making decisions on approval of new medical devices, import registration and marketing authori-

zation of devices. The importer/manufacturer of the new medical device is required to furnish clinical data to satisfy the MDAC. The Committee members review and assess the safety and efficacy data submitted with the application, where industry representatives require to present the data about concerned projects. Based on the recommendations of MDAC decision on the product approval is taken by CDSCO. Seven MDAC is now functioning under CDSCO, namely:

1. MDAC: Cardiovascular
2. MDAC: Dental
3. MDAC: Reproductive and Urology
4. MDAC: Orthopedics
5. MDAC: Ophthalmic
6. MDAC: General
7. MDAC: Miscellaneous

Medical Devices Technical Advisory Board (MDTAB)

The Drugs and Cosmetics (Amendment) Bill, 2013, recommends insertion of new Section 5A. As per this section, the Central Government shall, by notification, constitute a Board to be called the Medical Devices Technical Advisory Board. This board is deemed to advise the Central Government and State Governments on technical matters pertaining to medical devices, arising out of the administration of this Act and other functions as assigned by or under this Act. The Board shall consist of the following members, namely:

1. The Director-General, Indian Council of Medical Research, who shall be the Chairperson, *ex officio*;
2. The Drugs Controller General of India, *ex officio*;
3. One expert each with qualifications and experience in the field of medical devices, to be nominated:
    a. The Department of Science and Technology;
    b. The Department of Atomic Energy;
    c. The Department of Electronic and Information Technology;
    d. The Central Government from the Government testing laboratories connected with the testing of medical devices;
    e. The Indian Council of Medical Research;
    f. The Bureau of Indian Standard;
    g. The Defence Research and Development Organisation;
4. One expert from the field of biomedical technology from recognized technical educational institutions, to be nominated by the Central Government;
5. One expert from the field of biomaterial or polymer technology from recognized technical educational institutions, to be nominated by the Central Government;
6. One person representing recognized consumer associations to be nominated by the Ministry of Consumer Affairs;
7. One pharmacologist to be nominated by the Central Government from recognized medical or research institute in the field of medical devices;
8. One expert to be nominated by the Central Government from recognized medical or research institute from amongst persons involved in the conduct of clinical trials;
9. One person to be nominated by the Central Government from the medical device industry.

The nominated members of the Board shall hold office for three years, and shall be eligible for re-nomination for not more than two consecutive terms. The Board may, in consultation with the Central Drugs Authority, and subject to previous Central Government approval can make bye-laws fixing quorum and regulating the procedure for the conduct of all business transacted to it. The Board may constitute sub-committees and may appoint to such sub-committees, the

persons who are not a member of the Board for a period not exceeding three years, as it may decide, for the consideration of particular matters. The Central Drugs Authority shall appoint a person to be the Secretary of the Board and shall provide the Board with such staff as the Central Drugs Authority considers necessary.

Subject Expert Committee (SEC)

SEC is formed by CDSCO comprising of 8 experts from medical specialties out of which one has to be a pharmacologist. In case of absence of an expert in a meeting, another member from the approved panel, having requisite specialization and experience, can be invited to attend the meeting. The experts comprehensively review and assess the non-clinical data, toxicology data, preclinical data, clinical trial phase I, II, III data and make essential statements advising Drug Controller General of India (DCGI) on the approval recommendations. The panel held high standards and follow the national regulations and specific rules that need to adhere for approval and licensing of drugs. Each member evaluates individually and gives written expert comments within a time frame of 6 weeks of receiving the proposal. SEC give its final opinion after the evaluation of the proposal within the regulatory framework and practical utility of the products. In case of a suggestion or revision is required in the initial proposal, the committee can deliberate meeting considering the initial decision. The experts are required to be nondiscriminatory in the recommendations and maintain utmost discretion of the documents submitted by the applicants. SEC works on approval of the following categories:

- To evaluate applications of potential new substances or new drugs of chemical and biological origin
- To evaluate applications of biological product vaccines and r-DNA derived products
- To evaluate applications of fixed dose combinations of two or more drugs that are to be presented for the first time in the country
- To assess the status of global clinical trials happening all across the world for the new drug applied for approval in the country
- To evaluate the applications of global clinical trials filled by manufacturer outside India
- Procedural matters like safety or root cause analysis when needed or asked by the Ministry or Government requiring expert opinion
- To counsel and assist in the planning and preparation of guidelines for clinical research industry and for developing the acceptance/rejection criteria for marketing of new drugs belonging to different therapeutic categories.
- To recommend a road map of research to the pharmaceutical companies to manufacture new medications that cater to the Indian population
- To examine the utility and anticipated nature of new drugs that include assessment of risk versus benefits for patients for the innovated new drug compared to existing drugs and the unmet need in the country.
- To assist in any other matters that CDSCO needs advice.

SEC currently in function are:

1. Ophthalmology
2. Oncology and hematology
3. Nephrology
4. Pulmonary
5. Antimicrobial, antiparasitic, antifungal and antiviral
6. Cardiology and renal
7. Metabolism and endocrinology
8. Neurology and psychiatry
9. Analgesics, anesthetics and rheumatology
10. Gastroenterology and hepatology

11. Reproductive and urology
12. Dermatology and allergy
13. Orthopedics
14. Vaccine section
15. Endocrinology
16. Radio-diagnostic
17. Dentistry

New Drugs Advisory Committee (NDAC)

NDAC was formally assigned by CDSCO to take decisions on approval of new drugs, new formulations, fixed dosage combination(s), modified dosage forms, a formulation with additional indication/formulation with additional strength. Twelve New Drug Advisory Committee's (NDAC) were in function previously before DCGI renames new drug advisory committee as subject expert committee in 2014.

Drug Consultative Committee (DCC)

It is a statutory body under Section 7, Chapter II of the Drugs and Cosmetics Act with all State Drugs Controllers as its members to advise the central government, the state government and the DTAB on matters relating to the uniform administrative implementation of the Drugs and Cosmetics Act and Rules throughout the country. DCC consists of two representatives of the central government and one nominated representative from each state government. DCC enforces drug control measures in all the states and forms rules for national level implementation. DCC issues license for import of biological, biotechnological and other related unique products. The Drugs Consultative Committee consists of two nominated representatives of the Central Government and one nominated representative from each state government. The Drug and Cosmetics Amendment Bill 2013 and 2015, recommends substitution of Section 7 to constitute a consultative committee to be called the "Drugs, Cosmetics and Medical Devices Consultative Committee." This committee will advise the central government, the state governments, the Drugs Technical Advisory Board and the Medical Device Technical Advisory Board on any matter tending to secure uniformity throughout India regarding administration of this Act. The Drugs, Cosmetics and Medical Devices Consultative Committee shall consist of the following members, namely:

a. The Drugs Controller General of India, who shall be the chairperson, *ex officio*;
b. Two representatives of the Central Drugs Authority nominated by it;
c. The Secretary-cum-Scientific Director of the Indian Pharmacopoeia Commission;
d. One representative of the Pharmaceuticals Export Promotion Council nominated by it;
e. One representative of the Department of Revenue, Ministry of Finance, Government of India dealing with the administration of the Narcotic Drugs and Psychotropic Substances Act, 1985; and
f. One representative of each state government who is incharge of the matters relating to the regulation of drugs, cosmetics and medical devices in that state.

The DCMDCC must meet at least twice in a year or when required by the central government or, as the case may be. The Central Drugs Authority have the power to regulate its procedure. Though proposed, this has not been implemented in The Drugs And Cosmetics Act, 1940 and Rules, 1945 amended up to 31st Dec 2016.

Central Licences Approving Authority (CLAA)

CLAA issues license for blood banks, blood components, manufacturing of LVPs, medical devices manufacturing and approval for the commercial laboratory. The CLAA is responsible for classification of medical devices, publishing and updating guideline, enforcing safety standards, appointing

notified bodies to oversee conformity assessment, conducting post-market surveillance, and issuing warnings and recalls for adverse events of the related products. The CLAA acts as the chief regulatory authority for medical devices. The Third Schedule proposed for inclusion after the Second Schedule in the Drugs and Cosmetics (Amendment Bill) 2013 was to empower the CLAA to issue the license for the following categories of drugs, though not been implemented in The Drugs and Cosmetics Act, 1940 and Rules, 1945 amended up to the 31st Dec 2016:

1. RNA interference based products
2. Monoclonal antibodies
3. Cellular products and stem cells
4. Gene therapeutic products
5. Xenografts
6. Modified living organisms

National Pharmaceutical Pricing Authority (NPPA)

NPPA was formed by the Government of India under the *Drugs (Prices Control) Order, 1995*, to fix/revise the prices of controlled bulk drugs and formulations towards enforcing price regulation and availability of the medicines in the country. The organization is also entrusted with the task of recovering any overcharged amounts to the consumer by the manufacturers for the controlled drugs. It also monitors the prices of decontrolled drugs as an effort to keep them at reasonable levels. The functions of NPPA are:

1. To implement and enforce the provisions of the Drugs (Prices Control) Order.
2. To advice the central government on changes/revisions required in the pharmaceutical policy.
3. Monitor the availability of drugs, identify shortages and take remedial steps
4. Collect and maintain data of production, exports, and imports, the market share of individual companies, and the profitability of companies for bulk drugs and formulations.
5. Undertake, sponsor studies relevant to the pricing of drugs and pharmaceuticals.
6. Recruit the officers and other staff members of the Authority.
7. Deals with all legal matters arising out of the decisions of the Authority.
8. Assist the Central Government in the parliamentary matters relating to the drug pricing.

One of the major responsibilities of NPPA is to formulate, revise and implement national 'Pharmaceutical Policy' to ensure abundant availability of good quality essential pharmaceuticals at reasonable prices within the country. The 'Pharmaceutical Policy' formulates Government approach relating to drugs and pharmaceutical sector, covering all aspects of pharmaceutical business, i.e. quality control over drug and pharmaceutical production, distribution, encouraging research and development in the pharmaceutical sector, cost effectiveness, exports promotion of pharmaceuticals by reducing barriers to trade, promoting rational use of pharmaceuticals, import promotion and encouraging pharmacy education. This policy reflects the approach of the government for the overall growth of the pharmaceutical sector compatible with the country's needs and with a particular focus on endemic diseases relevant to India by creating an environment conducive to channelizing a higher level of investment into research and development and education in pharmaceuticals in India. The objective of this policy is to create an incentive framework for the pharmaceutical industry which can promote new investment in the pharmaceutical industry and encourages the introduction of new technologies and new drugs.

Indian Pharmacopoeial Commission (IPC)

IPC is an autonomous institution that acts under the Ministry of Health and Family Welfare, Government of India dedicated for the setting of standards for drugs, pharma-

ceuticals and healthcare devices. It also provides Reference Standard substances and training for the professionals. The IPC is a registered Society since 9th December 2004, under the provisions of the Societies Registration Act, 1860, under Act No. 21 (1860) related to registration of Literary, Scientific and Charitable Societies. The primary functions and working areas are:

- Develop comprehensive monographs for drugs, active pharmaceutical ingredients, excipients, dosage forms and medical devices for inclusion in the Indian Pharmacopoeia. IPC also revise and update Indian Pharmacopoeia on a regular basis.
- Prepare monographs of drugs like national essential drugs list and their dosage forms.
- Prepare monographs for products in the market for not less than two years except for particular categories of new drugs like antiretrovirals, antitubercular and anticancer drugs and their formulations introduced recently requiring priority attention.
- Develop Pharmacopoeial tests methods with special attention to the manufacturing methods used by the indigenous industry for monitoring the toxic impurities of the concerned drugs.
- Upgrade the levels of testing methods as per the sophistication in analytical testing/instrumentation available while framing the monographs.
- Preparation, certification, and distribution of Indian Pharmacopoeial Reference Substances including the impurities and degradation related products.
- Collaborate to at peer with the standards of international pharmacopoeias like the European Pharmacopoeia, British Pharmacopoeia, United States Pharmacopoeia, Japanese Pharmacopoeia, harmonizing with global standards.
- Organize educational programs and research activities for spreading and establishing awareness on the need and scope of quality standards for drugs and related materials.

NEW INITIATIVES

The Indian pharmaceutical regulatory bodies are coming out with significant changes to keep pace with the international regulatory scenario. In pursuance of the same, the Amendment Bill of Drugs and Cosmetics Act 2013 have proposed new implementations to bring about revolutionary changes in the Indian pharmaceutical industry. Some of the initiatives are the revision of DTAB and DCC constitution along with the revision of CLAA powers.

Drugs defined as New Drugs under the Drugs and Cosmetics Act are subjected to bioavailability/bioequivalence (BA/BE) evaluations through clinical trials, which are reviewed by the DCGI. A drug has a New Drug status for four years from the date of first permission. After four years, the State Licensing Authority grants the license, but they do not insist for BA/BE and clinical trial studies which are essential to establish the efficacy of the drugs. Central Drugs Standard Control Organisation (CDSCO) has come out with new draft guidelines on the approval of clinical trials and new drugs.

Central Drug Authority (CDA)

The CDA is an initiative to centralize the drug licensing in respect of 17 categories of very critical drugs. The central licensing authority is empowered to issue licenses for categories of drugs as of sera, serum proteins intended for injection, vaccines (including DNA vaccines and vaccines containing living genetically engineered organisms), toxins, antigens, and anti-toxins, antibiotics (beta-lactams and cephalosporins), preparations meant for parenteral administration, hormones and preparations containing hormones. The other drugs like r-DNA

derived drugs, RNA interference based products, monoclonal antibodies, cellular products, and stem cells, therapeutic gene-products, xenografts, cytotoxic substances (anti-cancer drugs), blood products and modified living organisms are included in the list as per the bill. The bill introduced in the Rajya Sabha on 29th August, 2013 for Drugs and Cosmetics (Amendment) Act, 2013 proposed insertion of new chapter, namely Chapter IA after the Chapter I of the Principal Act proposing formation of a new body called CDA though not been Implemented in The Drugs And Cosmetics Act, 1940 and Rules, 1945 amended up to 31st Dec 2016.

Proposed Constitution of CDA

The Central Government shall constitute an Authority to be known as the CDA to exercise the powers conferred on, and perform the functions assigned to it by or under this Act by notification in the Official Gazette.

The CDA shall be a body corporate by the name aforesaid, having perpetual succession and a common seal, with the power to acquire, hold and dispose of property, movable and immovable both and to contract by the said name, sue or be sued. The head office of the CDA shall be in the National Capital Region. The CDA may, with the prior approval of the Central Government, by notification in the Official Gazette, can establish its offices at places considers necessary in India.

Proposed Composition of CDA

The CDA shall consist of the following:

a. Secretary to the Government of India, Ministry of Health and Family Welfare, Department of Health and Family Welfare—*Chairperson, ex officio*
b. Secretary to the Government of India, Ministry of Health and Family Welfare, Department of Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homoeopathy—*Member, ex officio*
c. Secretary, Department of AIDS Control and Director General, National AIDS Control Organisation, Ministry of Health and Family Welfare—*Member, ex officio*
d. Secretary to the Government of India, Ministry of Commerce and Industry, Department of Commerce—*Member, ex officio*
e. Secretary to the Government of India, Ministry of Chemicals and Fertilisers, Department of Pharmaceuticals—*Member, ex officio*
f. Secretary, Department of Health Research and Director General, Indian Council of Medical Research, Ministry of Health and Family Welfare—*Member, ex officio*
g. Secretary to the Government of India, Ministry of Science and Technology, Department of Biotechnology—*Member, ex officio*
h. Director General Health Services, Directorate General of Health Services, New Delhi—*Member, ex officio*
i. Additional Secretary or Joint Secretary and Legislative Counsel in the Legislative Department, Ministry of Law and Justice, incharge of the Group dealing with the work relating to the Ministry of Health and Family Welfare—*Member, ex officio*
j. Additional Secretary or Joint Secretary in charge of the Drugs Quality Control Division in the Ministry of Health and Family Welfare—*Member, ex officio*
k. Four experts having such qualifications and experience to be nominated by the Central Government in such manner as may be prescribed—Member (shall hold office for three years from the date of their nomination, and shall be eligible for re-nomination)
l. Four State Licensing Authorities to be nominated by the Central Government in such manner as may be prescribed—Member
m. Drugs Controller General of India—Member-Secretary, *ex officio*

Proposed Powers and Functions of CDA

a. As specified by regulations, the guidelines, norms, structures, and requirements for the effective functioning of the Central and State Licensing Authorities
b. Assess the functioning of the Central and State Licensing Authority periodically
c. Issue directions to the Central Licensing Authority and the State Licensing Authorities to ensure compliance with the guidelines, norms, structures, and requirements specified
d. Review, suspend or cancel a permission, license or certificate issued by the Central Licensing Authority or the State Licensing Authorities
e. As specified by regulations, collect the fees or charges for issue or renewal of licenses, certificates, approvals and permissions by the Central Licensing Authority and the State Licensing authorities
f. Coordinate, mediate and decide upon the disputes arising out of the implementation of the provisions of the Act and rules and regulations made thereunder between two or more States Licensing Authorities
g. Constitute such committees or sub-committees as it considers necessary for the efficient discharge of functions and exercise of powers under this Act
h. Recommend to the Central Government the measures as regard to the standards of drugs, cosmetics and medical devices for effective implementation of the provisions of this Act
i. Perform such other functions as may be prescribed by the Central Government.

The powers of the CDA is going to be with the Central Drugs Standard Control Organisation (CDSCO), as per specifications by regulations, the guidelines, norms, structures, and requirements for the effective functioning of the Central and State Licensing Authority. The DCGI shall act as the Central Licensing Authority and shall have powers to:

a. Issue, renew, suspend or cancel licenses or certificates or permission, as the case may be, for import, export or manufacture of drugs, cosmetics or medical devices or permission for conducting clinical trials;
b. Recall or direct to recall any drug, cosmetic or medical device;
c. Collect the fees or charges for issue or renewal of licenses, certificates, approvals and permissions issued by the Central Licensing Authority under this Act.

Formation and implementation of CDA have not been materialized in The Drugs And Cosmetics Act, 1940 and Rules, 1945 amended up to 31st Dec 2016.

STATE DRUG CONTROL ORGANIZATION

Every State and Union territory in India has its individual setup of food and drug control administration headed by Drugs Controller/Commissioner under the State Health Ministry. Deputy Drugs Controller, State Licensing Authorities and Drugs Inspectors work under the administrative powers of Drugs Controller. The state drug testing laboratory functioning under the FDA is involved in testing the quality of drugs sampled by the regulatory personnel. Functions of the state FDAs are:

- Administrative regulation of medicinal product retailers, wholesalers, and manufacturers
- Inspection and licensing of pharmaceutical manufacturing units in the respective state
- Licensing of commercial drug testing laboratories
- Approval of drug formulation for manufacturing
- Monitoring quality of drugs and cosmetics manufactured in the respective state
- Monitoring quality of drugs marketed in the respective state
- Pre and Post licensing inspections
- Recall of substandard drugs

- Investigation and prosecution in respect of the contravention of legal provisions
- Inspection and licensing of wholesale and retail medical shops

INTERNATIONAL HARMONIZATION INITIATIVE BY REGULATORY BODIES

The term "regulatory harmonization" has different definitions depending on the context of its usage. The virtual interpretation can be "the process by which the interpretation and/or application of technical guidelines can be made to be uniform or mutually compatible between the participating agencies". Harmonization of drug regulation signifies harmonization of technical requirements for medicines regulation, viz. legislation, guidelines, procedures and all quality, safety, and related efficacy requirements of the medicinal products. Worldwide from country to country these requirements differ in the level of control, astringency, and complexity in different types of marketing authorization applications. Harmonization of technical requirements for medicines regulation is a need of the time looking into the fast growing and expanding business scenario of multinational companies. Globalization of medicinal product related activities, i.e. research and development, manufacturing and distribution increasingly demand regulatory cooperation across borders, which inevitably affects the initiatives driven by a group of countries having a similar economic interest. Identification of the particular "harmonization" requirements that each harmonization initiative aims is indispensable in determining future directions. The driven benefits of any harmonization initiative are:

- Companies can apply for marketing authorization to all the collaborating countries of a particular harmonization umbrella with only one data set for all regions, and consequently, the amount of human and animal experimentation is reduced as the scientific study parameters applicable are same.
- Fast regulatory communication and information sharing are possible due to common regulatory standards for scientific evaluation and inspection of premises which facilitate quick processing.
- Local products are likely to be easily acceptable for export to other countries under universal harmonization treaty as quality related aspects will be trustable to the general public.
- The cost of regulatory documentation development for both new and multi-source/generic medicines are reduced due to exemption from multiple regulatory licensing application submission with saving of the application fee and working hour requirements, which can lead to lower prices.
- Faster access and availability of medicines with high public health value (pediatric medicines, medicines for commonly occurring diseases or emergencies in public settings) and for rare diseases (orphan drugs) are assured.
- Harmonization, in turn, increases competitiveness not only between the pharmaceuticals of national level but also international level between the member countries resulting from the availability of shared markets.
- The most important benefit of drug regulation harmonization is the equality in quality of medicines available to the population of underdeveloped, developing and developed countries assuring the equal right of everybody to have quality medicine irrespective of the physical and economic barrier.

Harmonization policy works on the successful collaboration of the regulatory organization of all the member countries' under the treaty. It could not be effective if all significant aspects of regulation are not addressed. All these benefits of drug regulatory harmonization can

be achieved when harmonization policy development aims at the real goal of:

- True harmonization is not just development of common standard documentation, it requires continuous communication, effective collaboration, information sharing, mutual recognition and shared working cultures aimed at building capacity and trust between member countries.
- Harmonization can be adopted for similar or collaborative approaches in drug registration paving the way for mutual recognition and/or centralized registration in the longer-term future.
- Harmonization does not require the loss of national sovereignty/autonomy, but the similarity in policy adoption and execution is expected.
- Common documentation should be developed stipulating the requirements for registration and marketing authorization. Joint scheduling and drug product classification can be adopted between member countries with specific legislation applicable to a particular country.
- Regular effective and meaningful communication enables member countries to choose what information they will use and why.
- Collaborative mechanisms, such as joint assessments of applications or inspections of facilities, does not always imply collaborative decision-making, which will help safeguard the individual legal interest of the member countries.
- Harmonization of technical requirements can create a "common technical language" for collaborating regulators. Continuous training, effective communication, and collaboration are needed to build mutual trust and avoidance of duplication.
- Political will and support by member country governments are required for defining and achieving clear long-term objectives like creating a common market and faster market access.
- Strong commitment from major concerned stakeholders (regulators), effective governance structure, well-resourced secretariat, support of authorities, adequate human and financial resources, clearly defined processes and procedures, continuous updating and follow-up, transparent and effective communication between stakeholders is mandatory to brought forward a highly effective harmonization program resulting implementation of all objective driven guidelines.
- The primary factors responsible for futile harmonization effort are: Lack of political support and transparency with poor communication, ambiguously defined objectives with no 'reality check' for implementation, ineffective governance, inefficient functioning secretariat, absence of mechanisms to ensure timely update implementation, lack of experience, human resource and financial allocation.

The Nordic Council on Medicines (NLN) was formed in 1975 with the five European Nordic Countries (Denmark, Norway, Sweden, Finland, and Iceland) as members. NLN was a successful cooperation and supported in the development of modern medicines regulations in these countries. The Nordic Council was closed down in 2002, as all member countries inclined for participation in the EU procedures coordinated by the European Medicines Agency in London. The European Community (EC now the European Union) started harmonization of regulatory requirements of healthcare products in the member states in the 1980s.

World Health Organization (WHO) initiated its harmonization process in 1980 with the organization of International Conference of Drug Regulatory Authorities (ICDRA), which is now biennially convened by the WHO. In the same period of 1980s bilateral discussions between Europe, Japan, and the US started on possibilities for harmonization. Specific action plans began to materialize in 1989 at WHO

International Conference of Drug Regulatory Authorities (ICDRA) in Paris. Soon afterward, the authorities of Europe, Japan and US approached the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) to discuss a joint regulatory international harmonization initiative. The International Conference on Harmonization (ICH) came into existence in a meeting in April 1990, hosted by the European Federation of Pharmaceutical Industries and Associations (EFPIA) in Brussels conceptualizing a unique harmonization initiative involving the regulators and research-based industries of US, EU, and Japan.

WORLD HEALTH ORGANIZATION (WHO)

The "United Nations," was conceptualized by the United States President Franklin D. Roosevelt in the Declaration by League of Nations in 1942, during the Second World War with representatives of 26 nations. The UN emerged as an international organization in Allied conferences of 1943. In 1944, representatives of the Republic of China, the United Kingdom, the United States, and the USSR represented proposal outlining the purposes of the United Nations organization, its membership, and organs, as well as initiatives to maintain international peace and security encouraging international economic and social cooperation. Brazil, Syria and some other countries qualified for membership by declarations of war of 1945.

In 1945, representatives of 50 countries met in United Nations Conference held in San Francisco to draw up the United Nations Charter and decided to set up a global health organization concerned with international public health. WHO headquarters in Geneva, Switzerland came into force on 7 April 1948, with (celebrated every year as World Health Day) constitution signed by all 61 countries of the UN in the first meeting of the World Health Assembly.

Constitution of WHO

The World Health Organization, objective is to attain the highest possible level of health by all people. As per WHO, health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity. The enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction of race, religion, political belief, economic or social condition. Healthy development of the child is of fundamental importance for the ability to live harmoniously in a coherent environment. Unequal development concerning to promotion of health and control of disease, especially communicable disease, is a common danger in different countries.

Governance of WHO

The World Health Assembly is the supreme decision making body for WHO. The WHO is headed by the director-general, appointed by the health assembly based on the nomination of the executive board. The general meeting of delegates of all the member state is held in Geneva every year in May. Its primary function is to determine the policies of the organization. The health assembly appoints the Director General, supervises the financial policies of the organization, reviews and approves the proposed programme budget.

Health assembly works considering the reports of the executive board, composed of 32 members technically qualified in the field of health. Executive board members are elected for the term of three years. The central board meeting decides the agreed agenda and resolutions for forwarding to the health assembly that adopts the administrative matters. The primary function of the board is to make the decisions and policies of the health assembly and to facilitate its work. The WHO secretariat has approximately 3500 health and other experts and support staff on fixed-term

appointments, working at the headquarters of the six regional offices and countries all over the world.

Functions of WHO

Thriving to achieve its objectives, the WHO functions on:

- Act as the directing and coordinating authority of international health work.
- Establish and maintain effective collaboration with the United Nations, specialized health care agencies, governmental health administrations, professional groups, and other such organizations.
- Assist governments in strengthening health services.
- Furnish appropriate technical assistance in emergencies with necessary aids upon the request or acceptance of governments.
- Provide and also assist in providing health services and facilities to special groups, such as the peoples of trust territories.
- Establish and maintain administrative and technical services as may be required, including epidemiological and statistical services.
- Stimulate advance work for the eradication of epidemic and endemic diseases.
- Promote cooperative working with specialized agencies towards the prevention of accidental injuries, improvement of nutrition status, housing, sanitation, recreation, economic development, betterment of working conditions and other aspects of environmental hygiene.
- Promote cooperation among scientific and professional groups contributing to the advancement of health.
- Propose conventions, agreements, regulations, and make recommendations concerning international health matters.
- Promote maternal health and child welfare.
- Foster activities in the field of mental health promotion, especially those affecting the harmony of human relations.
- Promote and conduct research activities in the field of health services.
- Improve standards of teaching and training in the health, medical and related professions.
- Study and report on administrative and social techniques affecting public health and medical care from the point of view of preventive and curative care including hospital services and social security.
- Provide information, counsel, and assistance in the field of health.
- Assist in developing a system of informed public opinion among all people on matters of health.
- Establish and revise as necessary international nomenclatures of diseases, causes of death and public health practices.
- Standardize diagnostic procedures as necessary.
- Develop, establish and promote international standards for food, biological, pharmaceutical, and similar products.

WHO had played a leading role in the eradication of smallpox. WHO's priorities are:

- Control of communicable diseases particularly HIV/AIDS, malaria and tuberculosis
- The mitigation of non-communicable lifestyle related diseases
- Eradication of epidemic, endemic and other diseases
- Safeguard of sexual and reproductive health, development and aging
- Promotion of nutrition, food security, and healthy eating
- Promotion of environmental hygiene like housing, sanitation, recreation, economic, working conditions, and other aspects
- Awareness related to occupational health issues
- Prevention of drug abuse
- Development of networking reporting, health status related data collection, handling, and publication.

As of 2013, the WHO has 194 member states, two associate members, Puerto Rico, and Tokelau and several other countries with observer status. WHO fulfills its objectives of strengthening international health services acting as the directing and coordinating authority. The WHO maintains an active collaboration of the UN with the specialized agencies, governmental health administrations, professional groups and such other organizations working on promotion of health. WHO also furnish appropriate technical assistance to promote co-operation between specialized agencies, scientific and professional groups to establish and maintain administrative and technical services. WHO's significant contributions are the promotion of conventions, agreements, and regulations, and to make recommendations on harmonization of international drug regulatory organizations.

Harmonization Initiative

Currently, only about 20% of countries have a well-developed system for medicines regulation, about 50% have regulation of varying capacity and level and rest 30% have minimal drug regulation. The problems of weak drug regulation are not bound to the national borders but have global implications. Illegal manufacturing, distribution, sales and smuggling of medicines are widespread in some countries. Many lower-income countries are unable to ensure the safety, efficacy, and quality of medicines circulating on their markets and these medicines can get access to other surrounding countries also as often controls on exported medicines are less stringent than for those used domestically. Medicines are traded as several intermediaries in free-trade zones, repackaged and relabelled which can hide their true source or identity, leading to the circulation of counterfeit medicines.

The drug regulation guidelines worldwide are different, and assessment procedures in many countries are not up to international standards and are often of administrative rather than technical nature. Medicines regulation deals with the products, processes, and practices that involve rapid scientific and technological changes. The government department responsible for drug regulation must be empowered to formulate new regulations and to propose modifications in the existing ones as and when required. In some countries, drug regulation functions come under the jurisdiction of a single agency with full authority. While in some countries, the functions are distributed between different authorities, either horizontally (e.g. the ministry of health and family welfare, the ministry of chemical and fertilizer) or vertically (central, state and union territory governments) and to function effectively coherent coordination at the national level is required which is difficult to achieve. The countries like Australia (TGA) and the United Kingdom (MHRA) recover 100% of all regulation costs from fees levied for services, whereas in Canada and the United States recover around 50–70% of their costs. In the developing and underdeveloped countries, regulatory fees are less compared to the other counterparts where the government finds it exceptionally difficult to finance the regulatory functions adequately. The fees should somehow reflect the actual cost of services as in most instances the government resources alone are insufficient to ensure effective and sustainable medicine regulation in the developing countries. Inadequate resources in the third world countries severely limit the technical assessment of dossiers. Wide-ranging exemption clauses exist between country to country which should be compromised upon while justifying risk assessment and safety evaluation of drugs. Weak political will and commitment, lack of adequate human and financial resources, inappropriate facilities and absence of substantial enforcement power make the drug regulation inadequate.

Effective enforcement of drug legislation requires coherent work between regulatory agency, customs, police, and prosecutors, but in many countries cooperation is non-existent. In many developing countries, no written policy and guidance exist for staffs on the principles, practices, and methods to be followed. Monitoring and evaluation of guideline implementation are difficult because of the lack of information and weak data management.

Despite resource constraints, only a few countries rely on regulatory decisions made by other competent authorities (such as stringent MHRAs or by the WHO Prequalification Programme). Looking into the widespread conflicts and dissimilarities, WHO is promoting regulatory collaboration and harmonization worldwide. WHO provides technical assistance for developing evidence-based regulatory systems worldwide. Direct technical support (capacity building tools, and guidance) is provided to the collaborative agencies of various regions and countries to facilitate communication among national/regional regulatory systems facilitating relevant network meetings (e.g. WHO Annual Pharmacovigilance Centres meetings, and International Regulatory Cooperation for Herbal Medicines (IRCH). WHO also helps in forming global Regulators Networks like Blood Regulators Network and Paediatric Regulators Network.

The WHO has a dual role in medicines regulation and guideline development. The first aspect is to develop internationally recognized norms, standards, and guidelines. The second aspect is to provide guidance, technical assistance, and training in order to enable countries to implement global guidelines to meet their specific medicines regulatory environment and needs.

Regulatory Support Activities

The medicines regulatory support activities of WHO focus on supporting the work of national regulatory authorities by working on:

- Assessing national medicines regulatory systems
- Preparing regulatory information and practical manuals
- Providing training opportunities
- Preparing model website for medicines regulatory authorities
- Developing a model system for computer assisted medicines registration
- Quality certification of pharmaceutical products moving in international commerce
- Organizing international conferences of drug regulatory authorities
- Promoting international cooperation and harmonization

  Successful harmonization initiative of technical requirements for medicines regulation is based on collaboration in the field of legislation, technical guidelines, and procedures. Implementation of the medicines regulation could not be effective without addressing all significant regulation aspects.

Harmonization of technical requirements for medicines regulation is advantageous for future development goals:

- Companies have to generate only one data set for all regions, and consequently, the amount of human and animal experimentation is reduced.
- The cost of development of regulatory documentation both for new drugs and multisource/generic medicines is reduced, which can lead to lower prices.
- Common regulatory standards for scientific evaluation and inspection facilitate regulatory communication and information sharing.
- Local products are more likely to be acceptable for export to other countries.
- Faster access to medicines of higher public health value (pediatric medicines, medi-

cines for common diseases or emergencies in national settings).
- Increase in competitiveness resulting from newly developed common markets.

Challenges for WHO

WHO is a highly recognized institution with its well-organized infrastructure reaching out to all countries through its regional and country offices, and has competitive advantages over other organizations. The future of quality pharmaceuticals depends on worldwide adoption of regulatory harmonization. Due to the sophistication of science, new amount of information and data is always to appraise as there is no alternative to efficient scientific communication and collaboration. The patients will always pay the price for the failure of regulators to act. WHO has promoted regulatory collaboration and harmonization since long time and bringing upon new ideas and changes. WHO is one of the most critical organizations giving help to less resourced regulators. WHO is still going through the reform process and this brought upon both opportunity and challenge.

EUROPEAN UNION

In order to ensure health protection and free movements of medicines across the European Economic Community (EEC), the European Union (EU) has harmonized requirements for research and testing among the Member States. Medicines control was an early activity area of the EEC. The first and primary EEC directive for control of medicines was introduced in 1965 (Directive 65/65/EEC) as requirement for the control of medicinal products by the *Medicines Act 1968*, matching with existing European Directives. European Community legislation then has taken precedence over the Medicines Act, its Instruments and Orders, which were amended from time to time to align with new EC requirements. The European Medicines Agency (EMA) located in London plays a central role in the network of close collaboration among the medicines authorities, concerning marketing authorizations and surveillance of medicines. EMA began operations in 1995 with the responsibility of scientific evaluation, supervision and safety monitoring of medicines in the EU. EMA is responsible for the centrally authorized medicines, but the individual Member States perform the assessments of application for National and Mutual recognition aspects. The most current relevant legislation of medicinal products for human use, given in Directive 2001/83/EC was amended by Directives 2002/98/EC, 2003/63/EC, 2004/24/EC, and 2004/27/EC. The regulations implemented in EU Directive 2010/84/EU, introduced a strengthened, clarified and more proportionate regime for pharmacovigilance in the EU market.

In the EU the two main routes for authorizing medicines are the centralized route and the national decentralized (route). For consideration under centralized authorization procedure pharmaceutical companies submit a single marketing authorization application to EMA. EMA's Committee for Medicinal Products for Human Use (CHMP) or Committee for Medicinal Products for Veterinary Use (CVMP) carry out scientific assessment of the application and give recommendation. Once approved, the centralized marketing authorization issued is valid in all EU Member States as well as in the European Economic Area (EEA) and countries like Iceland, Liechtenstein and Norway. After approval by a single marketing authorization, the license holder can market the medicine throughout the EU. The national route is based on the regulatory framework of each country of EU. The decentralized marketing authorization is valid for the respective country only.

The EU has mutual recognition agreements (MRAs) with third country authorities concerning the conformity assessment of

regulated products, GMP inspections and batch certification of medicines. MRAs allow EU authorities and their counterparts to facilitate mutual market access and greater harmonization in the implementation of standards and compliance protecting consumer safety. These agreements benefit authorities by reducing duplication of inspections, facilitate trade by reducing costs for manufacturers and waiving re-testing of products upon importation.

The regulatory guideline of the European Community document with its explicit legal basis is referred to as legislative framework intended to provide advice to applicants or marketing authorization holders, competent authorities and/or other interested parties on the best and most appropriate ways to fulfil the legal obligations laid down by the pharmaceutical legislation of the EU. The basic EU legislation is thus supported by a series of guidelines published by the Commission, grouped broadly as regulatory or scientific. The concept of regulating medical device is well established in EU, whereas many countries did not have any significant medical device regulation. The EU has implemented the New Approach Directive for medical devices, making the first significant conceptual advance in healthcare regulation in last nearly 100 years. The New Approach Directive provides broad concepts on the law, and the bulk of the technological detail delegated to comply with recognized updateable standards. The Global Harmonization Task Force has mostly adopted the European Model of medical device regulation as a general template.

THE INTERNATIONAL COUNCIL FOR HARMONISATION (ICH)

The ICH, formerly known as the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use, was launched in 1990. ICH has brought together the drug regulatory authorities of Europe, Japan, and the United States along with the pharmaceutical trade associations from these three regions, to discuss scientific and technical aspects of drug product registration. Well-defined objectives of ICH is to improve the efficiency of new drug development and registration process, promotion of public health, prevention of duplication of clinical trials in humans and to minimize the use of animal for preclinical testing without compromising safety and efficacy. ICH's mission is to reduce duplication of testing and reporting required for the research and development of new medicines. This was achieved by harmonization in the interpretation and application of technical guidelines and requirements for product registration implementing universal single application and approval system.

In the first ten years, ICH has created and developed procedures and guideline in the areas of safety, efficacy, and quality of medicinal products. In the year 2003, ICH introduced Common Technical Document (CTD) which has revolutionized the submission procedures for industry's regulatory staff. CTD has offered benefit to industry far higher than any other harmonization initiative by significantly saving time and resources. CTD greatly reduces the requirement of the huge work force and financial burdens of assembling regulatory submission to a particular drug regulatory agency and then having it reformatted for another agency. CTD replaced complex multiple submissions by a single technical dossier, which is submitted for consideration simultaneously in the three ICH regions facilitating fast approval and launch of new drugs. The CTD has also made the possible easier exchange of information among drug regulatory authorities. Earlier, USFDA and the EMA have had a confidentiality arrangement allowing the sharing of confidential information, significantly

increasing interactions between the two agencies.

In recognition to the aspiring global face of drug development, ICH updated its logo in 2010 emphasizing the benefits of harmonization for better global health. The electronic CTD (eCTD) was implemented, disseminating guideline information to non-ICH countries, yielding additional benefits to both regulators and industry. The eCTD has significantly improved the application submission efficiency and reviewer efficiency, besides delivering submission material to the reviewer in an expedited manner. In the eCTD format, it is easier to develop standardized reviewer e-templates and review tools. The CTD has rapidly become the marketing application technique of choice, and regulators are now using the principles of the CTD as a springboard to incorporate newer and better ideas in regulatory review practices.

The globalization of industry in the field of both innovative and generic medicines drove a need for common standards, which has spurred the interest of non-ICH countries also promoting earlier access to new therapies. The ICH guidelines are now recognized as reference documents due to science-based principles and defined approaches having broad utility, not limited to new drugs, giving them broader relevance. In March 1999, ICH created the Global Cooperation Group (GCG) to facilitate open communication and fluid dissemination of information with a desire to establish global linkages that extend beyond the three ICH regions. The crucial operating principal of GCG is precise that, ICH will never impose its views on any country or region and it will work closely with WHO and other international organizations to achieve its goals. The mission statement "to promote mutual understanding of regional harmonization initiatives to facilitate the harmonization process related to ICH guidelines regionally and globally and to facilitate the capacity of drug regulatory authorities and industry to utilize them" was recognized for GCG's in November 2003, to achieve the overall goal of partnership with Regional Harmonization Initiatives (RHI).

The representatives from five RHIs actively participate in GCG discussions for harmonization for better health are Asia-Pacific Economic Cooperation (APEC), the Association of the Southeast Asian Nations (ASEAN), the Gulf Cooperation Council (GCC), the Pan American Network for Drug Regulatory Harmonisation (PANDRH), and the Southern African Development Community (SADC). GCG was expanded in 2007, with the creation of a Regulators Forum including Chinese Taipei, Singapore, South Korea, Brazil, China, India and Russia. This is to authorize the representation of individual countries drug regulatory authorities (DRAs) as they were a major source of active pharmaceutical ingredients (APIs), clinical trial data, and had adopted ICH guidelines. The representatives from five RHIs and the newly established Regulators Forum promoted participation of non-ICH countries interested in implementing ICH's strategies. This initiative has created a common regulatory language promoting faster access to life-saving treatments to patients beyond ICH regions. GCG efforts have evolved from mere information sharing to active dialogue between ICH and non-ICH member countries. GCG has fostered a spirit of trust and cooperation between ICH representatives and colleagues from RHIs and DRAs perhaps the most important key to future success of ICH.

HARMONIZATION IN AFRICA

Africa is a continent of many small countries having huge diversity and complex unity, with numerous Regional Economic Communities (REC) and politically complicated environment.

Potential benefits of harmonizing medicines registration have encouraged WHO to

develop a concept paper describing the proposed approaches supporting drug registration harmonization within and across the African region (WHO Drug Information, Volume 22, Number 3, 2008). After further discussions and orientation, African Medicines Regulatory Harmonization Initiative (AMRHI) was established in 2009. AMRHI is intented to improve health in the African Region by increasing access to safe, effective and right quality medicines with strengthening of the technical and administrative capacity of participating national medicines regulatory authorities. WHO support the RECs, for necessary actions related to national implementation, strengthen national regulatory agencies and promote the inter-REC and continental exchange of information, coordination and technical consistency. WHO invited summary project proposals from committed RECs seeking financial and technical support.

The collaborative mechanism was aimed at improving the regulatory approval process and operational efficiencies at the national/regional/sub-regional levels for medicines regulatory systems and processes. AMRHI focuses on medicine registration specifically of essential medicines (mostly generic pharmaceuticals) in order to maximize near-patient benefit and impact the critical disease burden that Africa is facing. The initiative works for increasing the capacity of national medicines regulatory authorities, harmonize technical requirements for the regulation of medical products, strengthening the administration, structural and technical elements of medicines regulation. AMRHI helps the member countries to enhance and facilitate decision making processes regarding the registration of medicines, establishment of a framework for joint evaluations of application dossiers and inspections of medicine manufacturing sites, information exchange as well as exercise more control over medicines circulating on the market. WHO provided technical assistance to develop harmonized approaches for medicinal product registration, GMP inspection, quality management, and information management systems development and support capacity building and training. In 2010 World Bank joined the process as a Multi-Donor Trust Fund Holder and provided advocacy for resource mobilization, fiduciary oversight, and dissemination of lessons.

REGIONAL HARMONIZATION INITIATIVES

Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S)

The PIC and PIC/S are two international conventions between countries and pharmaceutical inspection authorities providing constructive co-operation in the implementation and maintenance of harmonized GMP standards of inspectorates in the field of medicinal products. The PIC/S based in Geneva is an instrument to improve co-operation in the field of GMP implementation between regulatory authorities and the pharmaceutical industry. The PIC was founded in 1970 by the European Free Trade Association (EFTA), initially comprising Participating Authorities of 10 member countries. The inclusion of new member countries in PIC was not possible due to incompatibility between the Convention and European law. European law did not permit individual EU countries having a membership of PIC to sign agreements with other countries seeking to join PIC.

Pharmaceutical Inspection Co-operation Scheme was formed in 1995 as an informal agreement between health authorities instead of a formal treaty between countries to formalize inclusion of new members. PIC and the PIC Scheme, which operate together in parallel, are jointly referred to as PIC/S. PIC/S works on developing and promoting harmonized GMP standards and guidance

documents, training of GMP inspectors, exchange of inspectional information, continuous assessing of inspectorates and facilitating networking of competent authorities with international organizations. Currently, there are 52 Participating Authorities in PIC/S which include most EU Member States, Switzerland, South Africa, Australia, Canada, Singapore, and others. PIC/S Expert Circles facilitates discussions, and the exchange of information among Inspectors specialized in a specific area of GMP such as blood, Computerised Systems, Active Pharmaceutical Ingredients, and Quality Risk Management. Expert Circles meet regularly to develop draft guidance, recommendations, and offer training in their respective fields of specialization.

PIC/S Committee setup the Sub-Committee on Strategic Development (SCSD) in 2009 to discuss issues related to the improvement of the operation of the Scheme. Following suggestion of the Irish Medicines Boards more Sub-Committees were established, which was successfully implemented in 2014, with the mandate to define PIC/S' strategy, future policy and make proposals for improvement of structure and operation of PIC/S. PIC/S activities are now shared by 7 Sub-Committees that report back to the PIC/S Committee on the activities covered by their respective Sub-Committees in fields of:

1. Training (SCT)
2. Expert Circles (SCEC)
3. Strategic Development (SCSD)
4. Compliance (SCC)
5. GM(D)P Harmonisation (SCH)
6. Budget, Risk, and Audit (SCB)
7. Communication (SC COM)

The SCSD is also responsible for making proposals on the possible expansion of PIC/S' mandate to other areas, discuss new projects, funding options and issues related to the improvement of co-operation with PIC/S Partner Organisations. In 2010, USFDA became a member of the PIC/S network. Centre for Biologics Evaluation and Research (CBER) of USFDA has a representative on the FDA Steering Committee managing the Agency's interactions with PIC/S and actively participates in the technical group known as the PIC/S Expert Circle on Human Blood, Tissues and Cells. Australia is a member of PIC/S since 1993 while Japan got membership in 2014. Indonesia and Thailand are the only two Asian countries having a formal association with PIC/S. Mexico, Iran, and Turkey became the new member of PIC/S effective from Jan 2018.

Global Harmonization Task Force (GHTF)

The Global Harmonization Task Force (GHTF) fosters international harmonization in the regulation of medical devices. The GHTF was founded in 1992 in an endeavor to fulfil the growing needs for international harmonization in the regulation of medical devices. The GHTF was a voluntary group of representatives from regulatory, and industry authorities of Europe, Asia-Pacific, and North America collaborated to encourage the harmonization of regulatory practices to ensure the safety, effectiveness, and quality of medical devices. A Harmonization and Multilateral Relations representative serves on the GHTF Steering Committee. It has members from different national medical device regulatory authorities and members of the medical device industry whose goal was to standardize medical device regulation across the world. The representatives from five founding members, the EU, the US, Canada, Japan, and Australia actively regulates medical devices using their unique regulatory framework. The GHTF also serves as an information exchange forum for countries with underdeveloped medical device regulatory systems where thay are benefited by sharing experiences with GHTF Founding Members. The GHTF disbanded late in 2012 as the mission has been taken over by the

International Medical Device Regulatory Forum (IMDRF), a successor organization composed of officials from regulatory agencies around the world but not industry.

Asia-Pacific Economic Cooperation (APEC: 21-member economies)

The APEC forum was established in 1989 aiming to facilitate economic growth and prosperity in the 21 members of Pacific Rim countries; secretariat is based in Singapore. APEC seeks to promote free trade and economic cooperation throughout the Asia-Pacific region. APEC forum operates by non-binding commitments, open dialogue and equal respect for views of all participants. It takes decisions by consensus and commitments are undertaken on a voluntary basis. It provides coordination, technical and advisory support as well as information management, communications, and public outreach services between the member countries. APEC aims to strengthen regional economic integration by removing trade and investment impediments 'at the border', enhancing supply chain connectivity 'across the border', and improving the business environment 'behind the border'. APEC supports the multilateral trade negotiations of WTO and complements the goals of the G-20 Framework for healthy, sustainable and balanced growth in the Asia-Pacific region.

APEC leaders have recognized the importance of good regulatory performance in contributing to life sciences innovation and supported the initiative, Life Sciences Innovation Forum (LSIF) in 2002 as an 'enabler of regulatory harmonization.' APEC has adopted existing international standards and best practices for medical products and served as a vehicle to promote prospective harmonization dialogue in the area of advanced therapies. LSIF is unique as it does not work on formulating new harmonized guidelines, instead promotes the use of existing international guidelines. It encourages linkages of Asia-Pacific rim countries with the international harmonization initiatives having complementary roles in government, industry, and academia. The LSIF supports a strategic, coordinated approach to harmonization activities, and strives to complement rather than duplicate. The LSIF has endorsed the establishment of the APEC Harmonization Center and Regulatory Harmonization Steering Committee (RHSC), inaugurated in June 2009 leveraging resources and efforts towards effective medicine harmonization.

The APEC has developed and implemented a five-year plan cutting across GMPs, Good Distribution Practices (GDPs), Good Import/Export Practices, Good Pharmacy Practices and Internet sales that have a powerful influence on global regulatory harmonization scenario in the pharmaceutical supply chain realm. Besides the Pacific Rim Member countries, regulatory and standards organizations, including FDA, EMA, U.S. Pharmacopeial Convention (USP), Health Canada, European Directorate for the Quality of Medicines (EDQM), WHO and the Nigerian government are participating in the plan. FDA and Health Canada were instrumental among the other participants in convincing this multinational body about the benefits of pharmaceutical supply chain regulation harmonization as an essential component in achieving its goals. APEC has addressed eight 'chokepoints' from regulatory impediments to customs procedures and infrastructure bottlenecks with improvement in supply chain performance regarding time, cost and uncertainty. The delivery time to import goods dropped by an average 25% while the preparation period for export fell by 21% in the region. APEC economies have centralized making the export-import processes online at the border. This widely known Single Window virtual system links all government agencies involved in the export-import process, allowing companies to submit documents electronically. Fourteen APEC economies had

already adopted various stages of the Single Window system, and this also aims to link all 21 members coming on board by 2020. The member economies are committed to reducing energy intensity in the region near 45% by 2030.

Association of the Southeast Asian Nations (ASEAN: 10 economies)

The Association of Southeast Asian Nations (ASEAN) formed in 1967, is a geopolitical and economic organization of ten countries located in Southeast Asia. The members are Indonesia, Malaysia, the Philippines, Singapore, Thailand, Brunei, Myanmar, Cambodia, Laos, and Vietnam. ASEAN aims to accelerate economic growth, social progress, cultural development, protection of regional peace, stability and providing opportunities for peaceful open discussion between members. ASEAN celebrated its 40th anniversary in 2007, with an aspire to carry out free trade agreements with China, Japan, South Korea, India, Australia, and New Zealand by 2013. This Regional Comprehensive Economic Partnership (RCEP) was formed in 2018, in line with this ASEAN Economic Community (AEC) establishment in 2015 forming a more integrated group. The AEC intent to espouse industrial production capacity, encourage competitiveness, support growth and regional integration as a single market presenting for the global economy. The pharmaceutical market in South East Asia is relatively small, but the region remains attractive to the global pharmaceutical industry due to its growth potentials.

The regulatory environment in the ASEAN countries is similar in certain features but there are differences in systems and practices, and have problems of lack of consistency and transparency in the review procedure. Many of the regulatory agencies in these countries suffer from having rather weak infrastructures primarily due to limited human resources. Although a few scientific guidelines have been established in the region, the ICH guidelines are well adapted in most countries. The requirement of CPP (Certificate of Pharmaceutical Product) from the country of origin (COO) remains a crucial barrier to the registration of new drugs in the region. Among the ten ASEAN members, the five founding member countries (Singapore, Malaysia, Thailand, Philippines, and Indonesia) are more progressive with drug registration and drug development clinical trial activities. The different drug regulatory agencies in South East Asia are National Agency of Drug and Food Control in Indonesia; Drug Control Authority in Malaysia; BFAD, DoH in Philippines; ThaiFDA, Drug Control Division in Thailand; Health Sciences Authority (HSA), Centre for Pharmaceutical Administration (CPA) and Centre for Drug Evaluation (CDE) in Singapore.

Efforts toward harmonization of ASEAN pharmaceutical regulations were initiated in 1992 through the formation of ASEAN Consultative Committee for Standards and Quality (ACCSQ). ASEAN has started a harmonization initiative given many regulatory barriers and diversity in requirements hindering simultaneous regulatory submission in ASEAN countries. In this direction, a Product Working Group on Pharmaceutical (CCCSQ-PPWG) was initiated in 1998 aimed at establishing common technical requirements and quality guidelines for product registrations, and it started functioning in 1999. PPWG's objective is to develop harmonization scheme for pharmaceuticals regulations in the ASEAN member countries, to complement and facilitate elimination of technical barriers to trade posed by the regulations without compromising on quality, efficacy, and safety of drugs.

PPWG has developed and harmonized ASEAN product guidelines, i.e. ACTR (ASEAN Common Technical Requirement), ACTD (ASEAN Common Technical Dossier)

and Technical "Quality, Safety, Efficacy" guidelines. PPWG has adopted guidelines from WHO, ICH, and International pharmacopeia and developed ASEAN Quality guidelines:

- Analytical Validation guideline
- BA/BE Studies guideline
- Process Validation guideline
- Stability Study guideline

ACCSQ-PPWG in cooperation with international organizations and dialogue partners has developed projects like:

- WHO-ASEAN Harmonization project,
- ACCSQ-US Cooperation project—with three PPWG project proposals (i) Developing the Guidelines on Quality, (ii) Training on Clinical Data and (iii) Developing and Implementing the "Guideline & Implementation SOP."

ACCSQ-PPWG was also expanded for implementation of the harmonized ASEAN documents into the possible "Sectoral MRA (Mutual Recognition Agreement)." The ACCSQ-PPWG has made considerable progress, despite limitations in the existing capability and capacity of the Regulatory Authorities of ASEAN member countries. The Singapore agency HSA has progressed in the direction of harmonization by making international cooperation, signing a pact with the health authority of Australia, TGA. The cooperation is aimed at a better sharing of experiences, and this has bought an improved reviewing process to Singapore. ASEAN's drug regulatory authorities are working in very close partnership with one another and with the pharmaceutical industry to ensure the smooth functioning of implemented initiatives.

Gulf Cooperation Council (GCC: 6 Gulf states)

The Cooperation Council for the Arab States of the Gulf is a political and economic union of Arab states established in 1981, known as the Gulf Cooperation Council (GCC). The members are Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, and the United Arab Emirates. The Gulf Cooperation Council states are similar in language, geography, values, traditions, economic resources, in social and cultural factors. The pharmaceutical market in the GCC has witnessed considerable progress over the years as a result of favorable demographic and economic growth and strong government support for healthcare sector. The pharmaceutical market in these countries has reached up to 5.6 billion dollars in 2010 and predicted that sales would reach 10.8 billion dollars by 2020.

The GCC regulatory authorities have formed the Gulf Central Committee for Drug Registration (GCC-DR) including Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates, and Yemen in 1999. GCC-DR headquarter is located in the executive office for Health Ministers Riyadh, Saudi Arabia. The responsibilities of GCC-DR include:

- Registration of pharmaceutical companies.
- Registration of pharmaceutical preparations.
- Inspection of pharmaceutical companies for GMP compliance.
- Review of technical and post-marketing surveillance reports.

The company registration must be approved before the product registration, and the model used by the Gulf central registration system for all major application is an abridged assessment. GCC-DR has adopted two processes for drug registration, the Centralized registration procedure, and Decentralized registration procedure. For centralized registration, the manufacturer should fill companies registration form and pharmaceutical chemical entity/preparation registration form separately. Filled registration form and samples of chemical entity should be submitted to the executive office along with dispatching of the form and sample for the

respective countries. Every concerned country forward the file to committee after study with the recommendation. The executive office analyses the sample by a reference accredited laboratory. Following submission of prescribed fee for centralized registration GCC-DR executive office approve the registration of the company and/or chemical entity and issues a registration certificate. The remaining authentication, documentation, and fees are finalized on the country basis as per their prescribed and approved policies. Though centralization registration of drugs is not mandatory in GCC, for special classes, as follows registration through the centralized process is necessary:

- Generic drugs for which bioequivalence studies cannot be done, e.g. inhalable medicines and some nasal inhalers.
- Drugs supported by biotechnology for which bioequivalence studies cannot be done and which require clinical or pharmacodynamic studies.
- Orally administered drugs with narrow therapeutic spectrum.

In the decentralized registration process, the drug registration is regulated separately by main countries of GCC. Although there is a centralized and harmonized process for drug registration in GCC countries, the regulatory requirements for a few big countries like Saudi Arabia, UAE, Bahrain, and Kuwait are separate with well-established regulatory systems and enforcement. The GCC countries adopted the Common Technical Document (CTD) framework in 2009 and had since progressively moved towards to its implementation. Saudi Food and Drug Authority is the main regulatory body in Saudi Arabia. SFDA has a system for online application form submission followed by hard copy submission within 12 weeks. SFDA prefers drug dossier submission in eCTD format along with stability study data submission following GCC guideline for three initial batches. Ministry of Health, Bahrain, requires all necessary documents similar to other GCC countries for drug registration in the Kingdom of Bahrain but also focus on the details of company profiles and business mergers.

Medicines in Kuwait are regulated by quality, safety, efficacy standards, price control, and patent protection. Kuwait Food and Drug Authority (KuFDA) is the head regulatory agency to register pharmaceutical products. The GCC pharmaceutical market is dominated by patented drugs, whereas generics have only about 5–6% market share. Foreign drug manufacturers can only market drug products in a GCC country through local importing and distribution companies registered with the health ministry. Foreign investors are restricted to work in the pharmaceutical wholesale and distribution segment. Apart from regulating investments and drug registration, the health ministry and other government agencies also control the price of pharmaceutical products.

Pan American Network for Drug Regulatory Harmonization (PANDRH)

The Pan American Network for Drug Regulatory Harmonization (PANDRH) is a continental forum on drug regulatory harmonization established in November 1999. It is an initiative of the national regulatory authorities within the Pan American Health Organization (PAHO) region. PANDRH supports the pharmaceutical regulatory harmonization process in the America, within the framework of national and sub-regional health policies abolishing the pre-existing asymmetries.

The Components of PANDRH are:

- The Pan American Conference on Drug Regulatory Harmonization (PANDHR)
- The Steering Committee (SC)
- The Technical Working Groups (WGs)
- Secretariat

These constitute a continental forum ensuring the presence of regulatory authorities of

all PAHO member states, representatives from the regional pharmaceutical industry associations, representatives of organisms for economic integration (like Latin American Association for Integration, the Andean Community), academics, consumer groups, representatives of regional professional associations and other groups interested from all the continents sub-regions. This forum also facilitates the integration of the countries from the continent that do not belong to the sub-region blocks as Cuba, Dominican Republic and Chile. The conference disseminates the decisions of global initiatives on drug regulatory harmonization. The PANDRH is a member of the Global Cooperation Group of the ICH. Its primary objective is to support the harmonization processes through the analysis of specific regulatory aspects, the adoption of recommendations on priority subjects and harmonization of guidelines proposed by the working groups.

The PANDRH Steering Committee is the decision-making body for the strategic and operational management of the network, guiding progress on projects and activities, and making recommendations for evaluation and discussion at the Conference. The Steering Committee is composed of the Secretariat and members officially designated to represent each sub-region as North America, Central America, Cuba, the Dominican Republic, the Caribbean, the Andean Region, and the Southern Cone. Steering Committee Members are appointed for four years, ensuring rotation among the countries in each subregion. The Pan American Health Organization serves as Secretariat providing technical and administrative support to PANDRH.

PANDRH has working groups on bioequivalence, biotechnological products, combat counterfeit medicines, good clinical practices, good laboratory practices, good manufacturing practices, medical plants, medicines classification, medicines promotion, medicines registration, pharmacopoeia, pharmacovigilance, and vaccines. PANDRH regular activities are to support the countries for implementation of approved guidelines, external quality control programs, organizing national seminars and running educational programs. The PANDRH's mission is to promote drug regulatory harmonization covering all aspects of quality, safety, and efficacy of pharmaceutical products with a pursuit for the betterment of quality of life and healthcare of the citizens of the American Member Countries. PANDRH's scope of harmonization/cooperative activities includes updating technical guidelines, standards, and regulatory processes, and strengthening of national regulatory agencies to improve drug quality assurance.

Southern African Development Community (SADC: 15 countries)

The Southern African Development Community (SADC) is an inter-governmental organization supporting socio-economic cooperation and integration along with political and security cooperation among 15 southern African states. The Southern African Development Coordination Conference (SADCC), the forerunner of SADC, was formed as a liberate alliance of nine majorities ruled states in Southern Africa with the aim of coordinating development projects to lessen economic dependence in 1980. The founding member states were Angola, Botswana, Lesotho, Malawi, Mozambique, Swaziland, United Republic of Tanzania, Zambia and Zimbabwe.

The encouraging transformation of the organization from a Coordinating Conference to a Development Community (SADC) took place on 1992 in Windhoek, Namibia when the Declaration and Treaty were signed at the Summit of Heads of State and Government giving the organization a legal status. The Member States are the Democratic Republic of Congo, Madagascar, Mauritius, Namibia, Seychelles, and South Africa. SADC

headquarters is located in Gaborone, Botswana. On 2001, the SADC treaty was amended with an overall impact on the structures, policies, and procedures.

All SADC Member States have an official or draft national medicines policy, as well as medicines legislation and regulations framework, who function under a shared regulatory network. All countries in the SADC region are members of the World Trade Organisation (WTO) and signatory in the Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS). *Medicines Registration Harmonisation Project* has been developed in the interests of regional integration of regulatory authorities in the SADC to register and control medicines using the common set of regional minimum standards. The SADC region has developed guidelines for medicines regulation and other pharmaceutical strategies focusing to improve access to medicines. SADC has strategic policy documents such as the SADC Health Policy Framework, SADC Protocol on Health, SADC Trade Protocol developed for SADC *Pharmaceutical Programme*. SADC *Pharmaceutical Programme* has these priority areas in medicine regulation:

- Strengthen capacity to review and monitor ethical clinical trials
- Strengthen the region's training centers
- Facilitate information exchange on the safety, quality, and efficacy of medicines
- Ascertain laboratories capacitation and facilitate access for testing of essential medicines and African Traditional Medicines

The SADC *Pharmaceutical Business Plan* was then developed and approved for 2007–2013 in order to operationalize the SADC Health Programme and plan. The goal of the Pharmaceutical Business Plan is to ensure availability of essential medicines along with African Traditional Medicines to reduce disease burden in the region, and to improve sustainable availability and access to essential medicines. In order to achieve the overall goal and objective the following strategies were pursued:

1. Facilitate trade of pharmaceuticals within SADC.
2. Harmonization of standard treatment guidelines and essential medicine lists
3. Developing and retaining competent human resources
4. Maximizing research and production capacity of the local and regional pharmaceutical industry
5. Strengthening regulatory capacity, supply, and distribution of pharmaceutical products
6. Promoting joint procurement of medicines of acceptable safety, proven efficacy moreover, quality at affordable prices
7. Establishing regional data bank of traditional medicine, medicinal plants, and procedures to ensure their protection following regimes and related intellectual property rights preservation
8. Developing mechanisms to respond in cases of emergency pharmaceutical needs

Development of regulatory policy and legislative framework for regulation and validation of the African Traditional medicines safety, quality, and efficacy is equally essential. Populations throughout the SADC region extensively use traditional medicines to cater their primary healthcare needs. Medicinal plants contain a vast wealth of active ingredients that can be used in the production of herbal medicines. SADC medicine registration harmonization project and business plan have actively included the African Traditional Medicines in their harmonization and quality assurance system. The SADC Free Trade Area was achieved in 2008. The SADC Secretariat was officially recognized in 2012 as having international standards in accounting, audit, internal controls and procurement.

East African Community (EAC: 6 countries)

The EAC is the regional intergovernmental organization of five countries, the Republic of Kenya, Republic of Uganda, the United Republic of Tanzania, Republic of Rwanda and Republic of Burundi. The EAC Secretariat headquarters is in Arusha, Tanzania. South Sudan is the newest member, joined the EAC in 2016. It is also referred to as the youngest nation in Africa after gaining independence in 2011. The vision of EAC is to have a stable and politically united East Africa with a deep economic, political, social and cultural integration that will improve the quality of life through value added production, trade, and investments.

The EAC has implemented a harmonized medicines regulatory system by the 1999 Treaty engaging various stakeholders in facilitating implementation of the initiative. In 2000, the Health Committee of EAC Council established working groups and medicines were placed under research, policy and health systems working group. This working group drafted a common drug policy to harmonize drug registration procedures for the partner states. EAC National Medicines Regulatory Authorities (NMRAs) has been tasked to assure the quality, efficacy, and safety of medicines by subjecting pre-marketing evaluation and authorization/registration of pharmaceutical products. Formation of EAC Customs Union in January 2005 established common external tariffs on medicines.

The main Organs of the EAC are the Summit, the Council of Ministers, the Co-ordinating Committee, the Sectoral Committees, the East African Court of Justice, the East African Legislative Assembly and the Secretariat. The Summit comprises heads of government of partner states. The Council is the central decision-making, and governing organ of the EAC constitutes with Ministers or Cabinet Secretaries from the partner states. The Co-ordinating Committee is responsible for regional co-operation and co-ordinates the activities of the Sectoral Committees. It also recommends the establishment, composition, and functions of such Sectoral Committees. The Coordinating Committee meets twice a year preceding the meetings of the Council. Sectoral Committees conceptualize programmes and monitor their implementation. The East African Court of Justice is the major judicial organ of the community which ensures adherence to the law in the interpretation and application of compliance with the EAC Treaty. The Legislative Assembly has members comprising of 45 elected members (nine from each partner state), and seven ex-officio members consisting of the minister or cabinet secretary responsible for EAC affairs from each partner state. Currently, it has 6 Standing Committees to execute the mandates:

- The accounts committee
- The committee on legal, rules, and privileges;
- The committee on agriculture, tourism, and natural resources;
- The committee on regional affairs and conflict resolution;
- The committee on communication, trade, and investment, and
- The committee on general purpose.

The Secretariat is the executive organ of the community ensuring the adoption of regulations and proper implementation of directives by the Council.

In line with the AMRHI Programme, Situation Analysis on Medicines Registration Harmonization (MRH) for the East African Community has been carried out to develop a strategy for regional medicines registration harmonization as a precursor to broader medicines regulatory harmonization initiatives on the continent in 2012. The report recommended proposal development for the EAC MRH project. The project proposal development process has been completed through collaborative consultations by stake-

holders. This includes proposal writing workshop held in Entebbe, Uganda in September 2009 and consultation and project finalization meeting held in Zanzibar, Tanzania in May 2010. The progress of the EAC Union is encouraging, with establishment of the Common Market in 2010 and the implementation of the East African Monetary Union Protocol in 2013. An appraisal of the EAC partner states before the implementation of the MRH project was held in October 2011. This appraisal aimed at sensitizing the Ministers of Health, Finance and the National Medicines Regulatory Authority on the project governance and project management structures to get their support during the implementation. Members on the appraisal team included representatives of the EAC Secretariat, The World Bank, the WHO, and the NEPAD Agency. The project proposal whose goal is to have a harmonized and efficient functioning medicines registration system within the EAC by following national and internationally recognized policies and standards, have received approval for funding. The EAC MRH project was successfully launched on 30th March 2012 in Arusha, Tanzania.

REGULATORY AFFAIRS PERSONNEL

The functions of the regulatory personnel in healthcare industries are vital in making safe and effective healthcare products. Regulatory professionals ensure compliance of guidelines in manufacturing, preparing documents for regulatory approval submissions, coordinate functions of clinical affairs and quality assurance. Regulatory professionals are employed by private sector pharma industry, government, academia, consultancy service providers involved with a wide range of products and services, including:

- Pharmaceuticals
- Medical devices
- *In vivo* and *in vitro* diagnostics
- Biologics and biotechnological products
- Nutritional products
- Cosmetics
- Veterinary products

QUALIFICATION AND EXPERIENCE REQUIRED IN REGULATORY PROFESSIONAL

In a pharmaceutical industry involvement of the regulatory professionals begin with the research and development phase of medicinal product development, moving into clinical trials and extending through premarket approvals, manufacturing, labeling, and advertising up to postmarketing surveillance.

Regulatory Affairs departments are nowadays growing in a breakneck pace with the expansion of pharmaceutical business having scope to work outside as well as within companies. As the guidelines and resources necessary to fulfil the regulatory requirements are changing and evolving, some companies also choose to outsource or outtask regulatory affairs related documentary work to external service providers. So there are many service provider entrepreneurship agencies providing free launch regulatory services for the pharmaceutical companies. Regulatory Affairs department is continually evolving and growing and is the one which is least impacted during recession, acquisition and mergers phase from 2006 to 2013. Global harmonization approaches implemented by ICH and WHO has considerably raised the standards of guidelines which has led to consistent upgradation approach in regulatory submissions and reviews, expanding the scope and work possibilities of regulatory personnel. Regulatory affairs professionals have opportunities to work in such fields which require high knowledge level involving multiple activities.

Regulatory personnel should have a proficient knowledge of the scientific background of the pharmaceutical field from

preclinical to marketing authorization and formulation development to liaising.

1. Regulatory personnel should be well aware of the latest developments within the pharmaceutical industry. Exhaustive knowledge of CFDA, GMP, cGMP, WHO and other international guidelines, *viz*. USFDA, MHRA, TGA, etc is a must have.
2. Thorough knowledge of Indian, US, Australian, Canadian, Nordic and African countries Acts, laws and legislation enforced on food, drug, cosmetics, and herbals are necessarily required.
3. Scope and aspects of current harmonization guidelines like ICH, OECD, and other mutual recognition policies, between a group of countries, export and import laws and documentary requirements related updated knowledge is must for the persons working in the regulatory field.
4. Thorough knowledge of free or reduced tariff areas with the mutual recognition treaties like WTO (World Trade Organization), ASEAN (Association of South East Asian Nations), TRIPS (Trade-Related Aspects of Intellectual Property Rights), Doha Declaration on TRIPS and Public Health, South Asian Association for Regional Cooperation (SAARC) and North Atlantic Treaty Organization (NATO) between the group of countries is required. Regulatory personnel must keep abreast with policy changes and approval process related to trade and marketing of drugs and cosmetics.
5. Thorough knowledge of national and international drug laws and legislation controlling legal aspects of drugs and medicines, *viz*. Indian Penal Code, Drugs and Cosmetics Act 1940, 21 Code of Federal regulation, Federal Food, Drug, and Cosmetics Act 1938, Australian Therapeutic Goods Act 1989, etc.
6. Jobs in pharma regulatory affairs eventually require a firm background of working in the relevant industry, business knowledge, excellent oral and written communication skill, good leadership capability and team work. To be an effective negotiator, good organizational and interpersonal communication, and coordination skill is required.
7. Strong IT skill is required along with knowledge of several computer application used for data preparation, statistical analysis, interpretation, and representation.
8. The international scope of most of the companies working in the field of pharmaceuticals essentially requires knowledge of a second/third language. It is also generally desirable to know one/two foreign languages expending the possibilities of work area helping in the proper understanding of legal and social requirement of a country.
9. In depth knowledge of different steps and stages involved in drug development, beginning from research and development to finally the new drug approval.
10. Thorough knowledge of pharmacovigilance activities.
11. Information of electronic representation and submission of data and forms, like the Common Technical Document (CTD) and Drug Master File (DMF).
12. Ability to innovatively search for solutions for complex technical and procedural problems related to drug manufacturing, marketing, and legislation.
13. Work experience with clinical or pharma organizations is desirable for working in giant multinational pharmaceuticals having diverse customer groups all over the world.
14. Regulatory personnel is involved in writing product labels and patent

information, so knowledge of all legal requirements related to copyright, trademark and patent registration is required.

The current new approach to drug regulation adopted by the regulatory bodies of developed countries will eventually become essential for all healthcare organizations of underdeveloped and developing countries as it represents the best model for delivering new healthcare advances in a reasonable time with acceptable safety. These astringent guideline implementations will, in turn, increase the job opportunities for regulatory personnel.

ROLES AND RESPONSIBILITIES OF PHARMA REGULATORY AFFAIRS PERSONNEL

Regulatory personnel has an essential role in every phase of formulation and process development. They also plan regulatory approval strategy of a new drug formulation along with planning for the post-marketing activities. Drug regulation is multidimensional profession having an international scope. Professionals working in pharmaceutical regulatory affairs handle many different tasks:

1. Active participation in discussions with Quality Assurance (QA) team and coordination of team activities.
2. Assess the completeness and accuracy of all the documentation and records maintained by the QA team.
3. Managing and collaborating regulatory inspections within the company and reviewing practices when required to meet with new or updated regulatory requirements and maintenance of regulatory approval status of all the already approved marketed drugs.
4. Collaboration between multidisciplinary team to collect and collate large amounts of information and documents required for preparing drug product licensing submissions.
5. Supervise preparation of Marketing Authorization Application for new pharmaceuticals and diagnostics including report on quality, safety, efficacy, indication, adverse reaction, and side effects and packaging specifications. Address all issues related to a product review, managing reports, and tracking post-marketing activities.
6. Ensure regulatory compliance of ND/AND application submission and tracking with FDA approval.
7. Liaising with doctors and scientists for conducting clinical trials and negotiating with regulatory authorities for ND or AND. Supervision and auditing of clinical trial sites for adherence and compliance with all regulatory guidelines and coordination between multisite clinical trials.
8. Filling application with all relevant documents for marketing authorization of drugs with new dose, new indication or a new formulation called an Investigational New Drug (IND).
9. Provisional documentation clearance from FDA for pilot scale production, manufacturing in small quantity for conduction of trials, export of drugs for testing and clinical trials, import of drug for an investigational purpose.
10. Provide advice and guidance to the international clinical research teams on drug development related issues. Supervise all steps in drug development for preparation of documentary submission required for regulatory authority approval of clinical trials from phase I to III.
11. Preparation, and monitoring of all types of documentary submissions to regulatory bodies.
12. Ensure prompt and satisfactory answers to comment or requests generated during the submission review process.

13. Facilitate data/report collection, analysis, and communication about risk and benefit of health products to regulatory agencies, medical care systems, and the general public.
14. Review of labeling, insert, information sheets and advertisement materials especially for the overseas market.
15. Negotiate most favorable labeling and product monograph insert design as per sponsors business activities while still consistent with the legal requirements of regulatory bodies. Supervise editing of labeling text in the local language, packaging leaflets, product profile and other relevant documents designed for promotion of a particular product in the market. Regulatory approval of all promotional materials and drug information leaflets before market launch.
16. Planning and monitoring of product launch activities.
17. Responsible for assuring government obligations and market driven demands.
18. Responsible for maintaining and securing approval or authorization status of the existing authorized drug products by continually fulfilling regulatory documentation requirement needed to be submitted periodically (*viz*. stability data or post-marketing safety data/pharmacovigilance data) and renewal of authorization on due time course.
19. Report state/national regulatory authorities about an adverse drug reaction or side effect.
20. Manage patent and trademark registration status of all the relevant products and procedures in the company. Maintaining and negotiating in-licensing and out-licensing agreements for most favorable conditions.
21. Keep company management up to date on the status of specific product registration, problems encountered and solutions provided there in. Inputs regarding legislation and policies changes or new guideline amendments related to scientific as well as political influences on the national and international drug regulatory scenario are also to be provided to the management.
22. For being updated with current events in drug regulation attending the seminar, conferences and meeting at the national and international platform are expected to be a part of the responsibility.
23. To serve as a representative of the company in the international platform while being a member of the global drug regulatory affairs team. Coordinate regulatory affair activities worldwide and also responsible for performing all the assigned actions required for multi-country Marketing Authorizations.

The principal objective of drug regulation for every government regulatory agency is the promotion and protection of public health. Harmonization of registration requirement initiatives supported by the international community is successfully delivering the target object as measurable public health gains. Substantial improvement in drug regulation was observed over the last several decades as the pharmaceutical manufacturers are following the business strategies required for the fulfilment of global marketplace demands. Value addition is a relatively new phrase in science and business which is equally applicable to pharmaceuticals also. The core asset of the harmonized drug regulation is its significant contribution towards public health advances that have been realized as direct benefits of harmonization, improving quality, safety, and efficacy of marketed products. These initiatives mitigate the risks of medicines related harm, greater transparency of review and approval processes, and decreased costs for the industry as a harmonized application format reduces the expense of preparing registration dossiers eliminating duplication of activities. Increased

public trust in approved medicines is the vital achievement of international harmonization apart from helping drug developers and regulatory authorities. The coming progressive future of harmonization directives will depend on:

- Strong commitment of major stakeholders, governments and pharma industries
- Allocation of necessary resources
- Information sharing to improve overall regulatory performance
- Involvement of expert knowledge base and resources
- Formation of active networks among national regulatory authorities
- Supporting cooperation, collaboration, and international understanding
- Enhancing public trust on regulatory authorities.

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