Review Article

Recent Advancement in Regulatory Affairs

Gangu Sreelatha*, A. Bhavana Reddy, B. Keerthi Reddy, C. Pranathi Sena Reddy, T. Rama Rao
Department of Pharmaceutical Analysis, CMR College of Pharmacy, Hyderabad, Telangana, India -501401.
***Corresponding author's E-mail:** sreelatha1801@gmail.com

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ABSTRACT

Regulatory affairs also called Government affairs is comparatively a new profession gained popularity due to government's desire to protect public health. By controlling the safety and efficacy of products in many areas which includes Veterinary medicines, medical devices, Pharmaceuticals, Pesticides, Agrochemicals, Cosmetics and Complimentary medicines. Regulatory affairs in pharma industry mainly works as a link between the pharmaceutical company and the regulatory agencies across the world. It is widespread in all the departments including R&D, Clinical trials and Product development. The regulations will be usually maintained in a CTD (Common Technical Document) which provides Quality, Safety and Efficacy for a new drug. Each country has their own regulatory bodies who works in co-ordination with international bodies like WHO, ICH, WTO, PAHO, WIPO, FDA. This article describes the role of regulatory affairs in different departments including clinical trials, the need for regulation has been discussed along with responsibilities of regulatory affairs professionals, recent advancements and current issues in drug regulation.

Keywords: Regulatory affairs, Pharmaceuticals, R&D, CTD, FDA, Clinical trials, Drug regulations.

INTRODUCTION

Regulatory affairs are combination of field of science and management. It is also a profession which deals with regulations in pharmaceutical industries, medicines, medical gadgets and in development of medicines. Regulatory affairs professionals are the people who work in small or multinational cooperative pharmaceutical industries as an advisory committee. Regulatory affairs consist of laws and regulations which should be implemented while developing, testing and marketing the drug and drug products. The regulatory affairs act as a connection between pharmaceutical company and health authority of the country. The regulatory frame work is constantly improved and harmonized to achieve the goals of patient safety. Regulatory affairs are used to collect, analyse, interpret and communicate the risk vs benefit of health care products all over the world. Fig 1 represents the various phases in Regulatory Affairs. It is a science which helps in developing new tools, standards and approaches which gives assurance for the safety, efficacy and performance of drugs. Pharma regulatory professionals make sure the product tally all the regulations and laws governing the regulatory affairs. Drug regulatory affairs also involves in the clinical trials of the drugs which are done under the set of rules of Drug and Cosmetic act of India. It deals with the manufacturing, sale, distribution of drugs fulfilling the criteria and concerns of state and central authorities, for the approval of new drug products.[1,2]

Figure 1: Regulatory Affairs

1. HISTORY

A. India

In India the 1st patent law was introduced in 1856, over the years many regulations have been developed and evolved.

Here is the Table 1 representing the various list of regulations in India.

Table 1: List of regulations in India[3]

Year	Regulation
1856	First Indian Patent Law.
1859	First major revision of Indian patent law.
1872	Indian Contract Act.
1878	Opium Act.
1888	Indian Inventions and Design Act.
1911	Indian patent and Design Act.
1919	Poison Act.
1926	The India Trade Unions Act.
1930	Dangerous Drug Act.
1940	Drug and Cosmetic Act.
1945	Drug and Cosmetic Rule.
1947	The Industrial Disputes Act.
1948	The Pharmacy Act.

1951	The industries Act.
1954	Drugs and Magic Remedies Rule.
1955	Drug Price Control Order.
1956	The Medicinal and Toilet Preparation Act.
1958	The Trade and Merchandise Marks Act.
1968	The Insecticide Act.
1970	Indian Patent Act.
1985	Narcotics and Psychotropic Substance Act.
1986	The Bureau of Indian Standards Act.
1999	The Trade Mark Act.
2000	The Design Act.
2002	Competition Act.
2005	Indian Patent Act.
2011	Drugs and Cosmetic Act.
2013	Parliamentary Committee Report.

B. United states of America:

In US the 1st pharmacopoeia committee was established in 1820 and over the years many regulations have been developed and evolved.

Table 2 represents the various list of regulations in US.

Table 2: List of regulations in US

Year	Regulation
1820	United States Pharmacopoeia Committee Established.
1848	Import Drug Act.
1901	Vaccines Tragedy was happened.
1902	Biologics Control Act.
1906	Food and Drug Act.
1907	First certified colour Regulation.
1912	Sherley Amendment.
1927	Reorganised into Bureau of chemistry, soils, food, drug &insecticide.
1930	Current Food and Drug Administration.
1938	Food and Drug Cosmetic Act.
1951	Durham Humphrey Amendment Act.
1962	Kefauver-Harris Drug Amendment Act.
1976	Medical Device Amendment.
1983	Orphan Drug Act.
1984	Drug Price Competition and Patent Terms Restoration Act.
1990	Safe Medical Device Act.
1994	Uruguay Round Agreement Act.
1998	Paediatric Rule.
1999	Clinical Trails.Gov foundation.

C. European union (EU):

In EU the 1st regulation started in 1950 over the years many regulations have been developed and evolved.

Table 3 represents the various list of regulations in EU.

Table 3: List of regulations in EU [4,5]

Year	Regulation
1950	Promoting New Sedative Drugs.
1957	Formation of European Economic Commission.
1964	Helsinki declaration was established to prevent unethical and risky clinical trials.

2. WORLDWIDE REGULATORY AGENCIES

In Worldwide Regulatory Agency there are many regions involved for regulations like Australia, New Zealand, North America, Europe, Middle East, Africa, South America.

In table 4 various list of Worldwide Regulatory Agencies are being showed.

Table 4: List of worldwide Regulatory Agencies[6]

Region	Country name	Regulation agencies/body.
Australia / New Zealand	Australia	Therapeutic goods Administration (TGA).
	New Zealand	MEDSAFE.
North America	Canada	Health Canada.
	USA	Food and Drug Administration (FDA).
Europe	America	Scientific Centre for Drug and Medicinal Technology Expertise.
	Austria	Agency for Health and Food Safety (AGES).
	Bulgaria	Bulgarian Drug Agency.
	Belgium	Federal Agency for Medicines and Health Products.
	Cyprus	Ministry of Health.
	Croatia	Agency for Medical Products and Medical Devices of Croatia.
	Czech Republic	State Institute for Drug Control.
	Denmark	Danish Medicines Agency.
	Estonia	State agency of Medicines.
	Finland	Finish Medicines Agency.

	Germany	Federal Institute for Drugs and Medical Devices.
	Georgia	Regulation agency for Medical and Pharmaceutical Activities.
	Greece	National Organization for Medicines.
	Hungary	National institute of pharmacy.
	Ireland	Irish Medicines Board.
	Iceland	Icelandic Medicines Agency.
	Italy	National institute of Health.
	Lithuania	State Medicines Control Agency.
	Luxembourg	Ministry of health.
	Malta	Maltese Medicines Authority. And Moldova Medicines Agency.
	Netherlands	Medicines evaluation Board.
	Norway	Norwegian Medicines Agency.
	Portugal	National Authority of Medicines and Health Products.
	Romania	National Medicines Agency.
	Poland	The Office for Registration of Medicinal Products, Medical Devices and Biocidal product.
	Russia	Ministry of Health of the Russian federation.
	Serbia	Medicines and Medical Devices Agency of Serbia.
	Slovakia	State Institute for drug Control.
	Slovenia	Ministry of Health.
	Spain	Spanish Medicines Agency.
	Sweden	Medical Products Agency.
	Switzerland	Swiss Agency for Therapeutic Products.
	Ukraine	Ministry of Health.
	United Kingdom	Medicines and Healthcare regulatory Agency (MHRA).
Middle East	Egypt	Ministry of Health.
	Iran	Ministry of Health.
	Israel	Ministry of Health.
	Jordan	Jordan Food and Drug Administration.
	Saudi Arabia	Saudi Food and Drug authority.
Central / south America	Argentina	ANMAT.
	Brazil	Agencia National de Vigilancia Sanitaria.
	Columbia	Instituto Nacional de Vigilancia Medicaments y Alimentos. (INVIMA).
	Jamaica	Ministry of Health.
Asia- Pacific	India	Central drug Standards Control Organization (CDSCO).
	Bangladesh	Bangladesh Indonesia – POM (pengawas Obat Dan Makanan).
	Japan	Ministry of Health, Labour and Welfare. (MHLW).
	South Korea	Korean Food and Drug Administration. (KFDA).
	Laos	Food and drug Department.
	Malaysia	Ministry of Health. (MOH).
	Nepal	Department of Health Administration.
	Philippines	Department of Health. (DOH).
	Singapore	Health Sciences Authority (HAS).
	Sri-Lanka	Ministry of Health.
	Taiwan (Republic of China)	Taiwan food and Drug Administration.
	Thailand	Food and Drug Administration of Thailand.
	Vietnam	Drug Administration of Vietnam.
Africa	Algeria	Ministry of Health and Population.
	Botswana	Ministry of Health.

	Ghana	Food and Drug Authority.
	Kenya	Pharmacy and Poison Board.
	Morocco	Ministry of Health.
	Rwanda	Ministry of Health.
	South Africa	Medicines Control Council. (MCC)
	Swaziland	Ministry of Health.
	Tanzania	Tanzania Food and Drug Authority. (TFDA)
	Uganda	National Drug Authority.

3. INTERNATIONAL ORGANIZATION

- World Health Organization [WHO]
- International Conference on Harmonization [ICH][7]

4. WHY NEED TO REGULATE?

To ensure the quality safety and effectiveness of pharmaceutical products in order to maintain and protect the public health there is a moral and legal expectation that the necessary precautions to be taken to ensure the highest possible standards of quality, safety, efficacy and benefit relative to risk even if no pharmacological product is totally safe and effective in every situation.

1. All substances are poisons, there is none which is not a poison. The right dose differentiates a poison and a remedy.
2. To ensure quality, safety and efficacy of drug products in order to assure the continued protection of Public Health.
3. No drug product is completely safe or efficacious in all circumstances, but there is a moral, as well as legal, expectation that appropriate steps are taken to assure optimal quality, safety and efficacy by the producers concerned. Benefit versus Risk.

A. Regulatory affairs relating to pharmaceutical drugs:

To protect public health by monitoring the efficacy and safety of products in a different type of industries, including pharmaceuticals, veterinary medicines and complementary medicines led to the development of regulatory affairs, and the company's manufacturing and marketing these products must make sure that they deliver high quality goods now a days. The majority of companies have specialized departments with regulatory affairs specialists.[8]

5. ROLE OF REGULATORY BODIES IN DRUG DEVELOPMENT PROCESS

In order to get new items licenced, the department must be knowledgeable of the applicable regulations and they should be aware of the agreements that business has with the authorities and they further provide the authorities with yearly reports. An area of regulatory affairs is a governmental effort to safe guard the public's health as well as the safety and effectiveness of the gadgets, pesticides, agrochemicals, cosmetics and alternatives. The medical treatment and the development testing production and marketing of these products like wise wish to guarantee that they are supplying goods that are reliable and beneficial to the health and welfare of the general population.

A. The primary duties of regulatory agencies are:

- To create proper legalisation covering all products with a therapeutic claim and all pertinent pharmaceutical activities, whether carried out by the public or the private sector.
- To improve public health and safeguard the public from harmful and questionable pharmaceuticals.
- The early nonclinical investigations, product development, manufacturing and post marketing surveillances are all handed by regulatory organisations.
- The regulatory affairs department also manages the special control prescribing and pricing of medications.
- Data is gathered by regulatory affairs from all organisations involved in medication development.[9]

B. Regulatory affairs in R & D

In order to shorten the time to marketing, the regulatory affairs personnel collaborate with R&D and F R&D to produce cutting edge goods and projected to improve the organizations revenue losses resulting from postponed marketing which will eventually get cancelled out by the substantial material.[10]

C. Regulatory affairs in clinical trials:

Regulatory affairs professionals serve as the company's main point of contact with international regulatory organisation including governmental bodies (US FDA, CDSCO, MCCA, TGA etc) these professionals help with the approval process for new products by providing timely reports of fresh data gathered in trails to the state regulatory agencies.

D. Role of regulatory affairs in product development:

The regulatory agencies are in charge of managing and handling the product and they typically provide advice. Once the approval procedure is over, these bodies can begin development under IND/NDA rules which often emphasise the drug pharmacovigilance features and post market

properties, additionally it serves as a reminder of the medicine renewal term.

The general function of regulatory affairs goes beyond the registration of products, they provide the highest level of strategic and technical advice to businesses, their involvement starts with product creation, marketing and post marketing plans at all times, they provide legal and technical advice and criteria enable businesses to build new goods more quickly and more affordably.[11]

6. REGULATORY AFFAIRS IN PHARMACEUTICAL INDUSTRY

Regulatory affairs are developed by the government to protect the health of the public by ensuring the efficacy and safety of the products including pharmaceutical products, fertilizers, pesticides, medical gadgets, veterinary medicines, agrochemicals and cosmetics. The manufactured product should satisfy the need of public and ensure their health. The finished products are tested and evaluated according to the guidelines or legislation. It is the company's responsibility to discover, manufacture, test and market the products and should contribute for the welfare of people. Fig 2 represents the Drug Development Process. The regulatory affairs department should know the legislation requirement in all the company's export markets.[12,13]

Drug development process involves -

A. Development Phase:

- Abide to legislative regulation.
- Acquiring scientific advices from authorities.
- Involvement in project discussion and participation.
- Submission of application of clinical trials.
- Project strategy/management.
- Electronic submission.

B. Approval Phase:

- Evaluation procedure.
- Project management/strategies.
- Project meeting.
- Testing.

C. Post Approval:

- Compliance/management.
- Product review
- Post approval.
- Renewals.
- Report. [7,14,15]

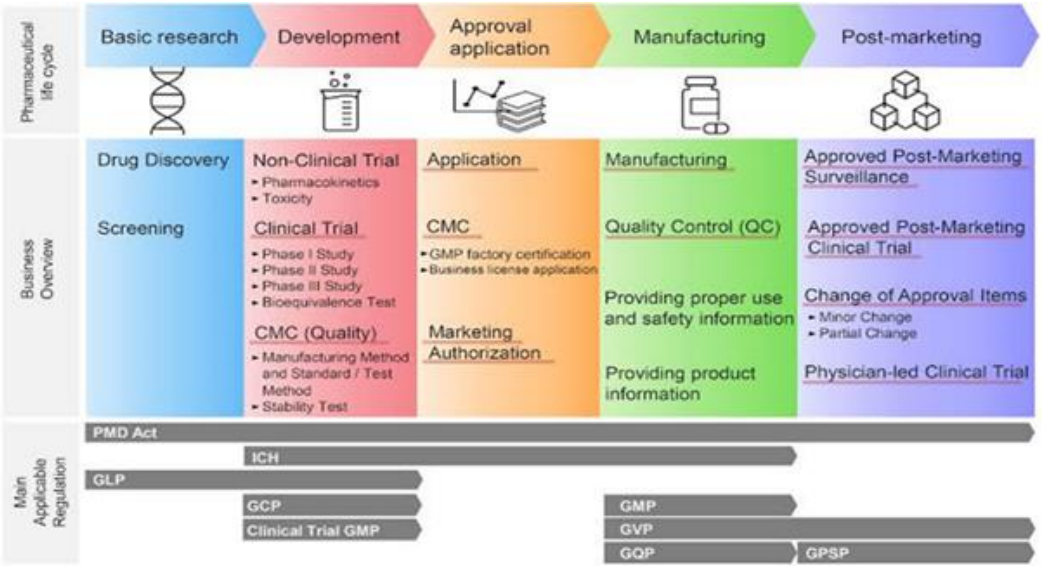

Figure 2: Drug Development process

7. RELATION BETWEEN RA AND CTD (WHAT IS CTD AND eCTD)

CTD (Common Technical Documents), the document that provides quality, safety and efficacy data for a new drug that is to be submitted to several regulatory authorities for approval is known as the common technical document. It aids in the structured presentation of the information and to standardise the structure of the application to be submitted to different health authorities for the approval of a new drug. ICH had suggested the creation of a common technical document and this format helps in saving the time that was required for preparing NDAs in different format for submission to different authorities, as result. As European medicines agencies, the food and drug administration and the ministry of health, labour and welfare of Japan collaborated to create the CTD, which is applicable in all three of these countries. Europe the United States and Japan is maintained by ICH. Fig 3 represents the Common Technical Document.

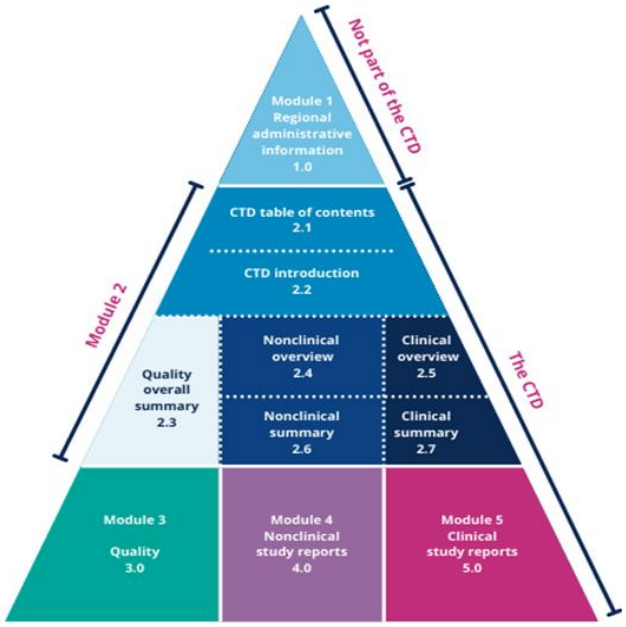

Figure 3: CTD (Common Technical Document)

A. Organisation of the common technical document:

CTD is prepared by using A4 size paper 8.5x11″ the text, the text could be printed learning a left handed margin large enough to prevent the printing text from being distort due to binding and the font size could be 12, the format for placing the references should be in accordance with the most recent edition of the uniform requirement for manuscripts submitted to biomedical journals, new roman pages of the documents should be numbered alphabetically and any abbreviations used in the document should be defined at the very first instance.

A digital version of the CTD is known as the eCTD. The regulatory viewpoint states that "The eCTD is described as an interface for industry to agency transfer of regulatory information while at the same time taking into mind that the facilitation of the creation, review, lifecycle management, and archival of the electronic submission." According to technical perspective, the eCTD is a CD/DVD holding a structured collection of common folders that contain PDF and SAS (Statistical Analysis Software) files (Can also be submitted through agency web portals). An XML file (Extensible Markup Language) that represents the submission's basic structure serves as the eCTD backbone. Common technical documents are available electronically, it is format in which data and documents are transmitted electronically to the appropriate regulatory authority by utilising a programme. It is a digital document created by a pharmaceutical business or a government organisation. The largest challenge is applying correctly in the application, even though the eCTD format is clear. When a document does not follow the necessary format, the application should be rejected, which could cause problems for the promoter and the application. The eCTD need to be simple to distribute and review, more resource-efficient, and cost and stress free for the organisation. The electronic table of contents for the eCTD should be very well organised, searchable and self-validating. Beginning on January 1, 2008, the FDA will begin implementing eCTD. At that point, eCTD will become the standard for electronic submission. From 2007 to 2008, the FDA mandated that all electronic submission be made in eCTD formal. However, paper copies continue to be accepted from 72 in 2006, the number of and a filling to the FDA has grown compared to 1550 in 2009. To maintain the massive data of the complete submission, such as submission details and receiving company, maker, identification etc and paper work.[16]

8. List of responsibilities of regulatory affairs department:

- Keep in touch with international legislation, guidelines and customer practices.
- Keep up to the date with a company's product range.
- Ensure that company's products comply with the current regulations.
- The regulatory affairs professional's job to keep track of the ever-changing legislation in all the region in which the company wishes to distribute its products. They also advice on the legal and scientific rest vaints and requirements and collects collate and evaluate the scientific data that their research and development colleagues are generating.
- Manage review adult report and compliance regulatory and customer inspection.
- Have adult to provide physician and other health care professionals with accurate and complete information about the quality, safety and effectiveness of the product.[17]

9. REGULATORY AFFAIRS PROFESSION

The development of new drug and its marketing requires many years but it is essential to meet the regulatory requirements from beginning to end of product development. It upholds to permit evaluation of drug in the shortest possible time.

The drug regulatory affairs professional plays a key in every phase of development and advises regulatory strategies following the new chemical entity discovery to post marketing events. DRA professional should have minimum eligibility of degrees like B.SC, M.SC, Ph. D, M.D, B. pharmacy, M. pharmacy or PharmD and also should have adequate knowledge on local, national, and global regulatory affairs.

DRA professional should have organizational communication and interpersonal skills He/she should coordinate with the different teams and involve in team discussions to get necessary document for completeness and accuracy.[8,17,18]

10. PHARMAREGULATORY AFFAIRS JOBS

Professionals in pharmaceutical regulatory affairs positions will be expected to undertake a variety of duties, from

staying current on market developments to creating product labels and patent information. In addition to gathering and assembling a lot of data and preparing employment in pharmaceutical regulatory affairs, as well as licencing submissions and involve speaking with medical professionals and researchers, performing clinical trials and discussions with regulatory authorities workers and regulatory inspections adjusting procedures as necessary to meet with new or update laws and regulations and the professionals have the opportunity to work with affairs consultants in a variety of field that need for high degrees of knowledge in different pharma regulatory affairs positions

11. Responsibility of regulatory affairs professionals:

The duty of the regulatory affairs specialist is to stay abreast of the constantly altering legal frame works in all the area where the business intends to sell its goods. Additionally, they recommend regarding the limitations and requirements of law and science, and the gathering assembling the evaluation of the scientific information of employees. The person who conducts research and development they must present the registration and their responsibility submission of paper work to governing bodies for execution all to complete.

The responsibility of the regulatory affairs specialist is to stay abreast of the constantly evolving legal framework in every area where the company plans to sell its goods. They also offer advice on the limitations and obligations imposed by law and science and gather, compile and assess the scientific information that their colleagues in research and development are producing. They are in charge of presenting the registration. Fig 4 represents Responsibilities of Regulatory Affairs.

Figure 4: Responsibilities of Regulatory Affairs

12. RECENT ADVANCEMENT IN DRUG REGULATORY AFFAIRS

Government of India appointed certain bodies to grade the colleges, parents, employers, student and funding agencies have reliable and valid rating on pharmacy college in country.

They are:

A. National board of Accreditation (NBA) under the aegis of all India council for technical education.

B. National Assessment and Accreditation Council (NAAC) by the university grants commission[19]

13. WHAT IS THE POTENTIAL OF AI IN PHARMACEUTICAL PRODUCT DEVELOPMENT?

This is a vast field which will fundamentally change the way we currently work in drug development. High Throughput screening of drug candidates on cell arrays was a start, nowadays, we are more thinking around how to design artificial study arms to leverage real-world evidence in clinical studies. This could – given the fact that the artificial study arms represent the current standard of care (SOC) – reduce the number of patients that are randomised to SOC arms and therefore increase the number of patients that can receive the innovative drug that potentially is superior to SOC. The regulatory environment has to change with these possibilities so that results generated this way can be acceptable to regulators.

14. WHAT ARE THE CHALLENGES OF A REGULATORY AFFAIRS PROFESSIONAL?

Nowadays, the challenges for a regulatory professional shift more and more to strategic decision-making and shaping the regulatory landscape. Pure filing, dossier compiling and publishing, submissions and other technical tasks will most likely be more and more shifted towards computers and these jobs will be lost to regulatory affairs professionals in the future. There will be more and more demand for regulatory professionals with excellent scientific, strategic and communication skills, as the regulatory work will shift to tasks that involve negotiations, shaping the field, influencing, storytelling with data – human interactions, plain and simple. Regulatory Affairs is moving away from filing and submitting, but towards strategic partnership and close cross-functional interactions within a company and with external stakeholders such as regulators and payers.[20]

15. NEW TRENDS IN REGULATORY AFFAIRS TO EXPEDITE REVIEW PROCESS

Pharmaceutical companies have a deep-rooted process for clinical development, but the outbreak of covid-19 pandemic has massively disrupted this traditional way of testing new drugs. As pandemic unravels limiting the scope of clinical studies as we know, drug manufacturing companies will need to continue to expand their search for other possibilities and devise new ways of working with accelerated digital adoption and innovation. Pharma companies can integrate the following approaches and redefine clinical development.

A. Adopting Real World Evidence (RWE)

Over the past few years, manufacturers are progressively using real-world_evidence (RWE) to support clinical trial designs and observational studies to create innovative, new treatment approaches. In 2017, the FDA relied on RWE to expand the use of Edwards Life sciences' transcatheter aortic valve replacement device for valve-in-valve procedures, the first FDA approval based on RWE without requiring new clinical trial data. COVID-19 pandemic has fast-tracked this trend towards increasing RWE as a way to test new treatments in a few weeks or months rather than the prolonged timeline typical for randomised controlled trials (RCTs).

B. Adopting Virtual First Approaches

In response to the COVID-19 emergency, many organizations are now pursuing virtual trials, especially where interventions are well understood and seen as low-risk (e.g., new indications of existing therapies for chronic diseases). The US FDA and the EMA have issued guidance in support of virtual trials. The main benefit of conducting virtual trials is that it allows to recruit specific patient segments quickly irrespective of where they reside, thus offering flexibility of location. The industry experts suggest that the virtual trials are more time-efficient, as it takes just 4 months to recruit patients unlike 7 months in the traditional process.

C. Adopting Modern Technology

The use of computers, mobile devices, and other wearable biosensors gathers and stores a large volume of health-related data. This data holds the potential to permit us to enhance the design and conduct clinical trials and studies within the health care setting. Additionally, with the advancement of sophisticated, new analytical capabilities, we are now ready to analyse these data and apply the results of our analyses to medical development and expedite the approval process.

D. Using Real-World Data (RWD)

Real-world data (RWD) captures the patient health status which can be routinely collected from a range of sources, such as:

- Electronic health records (EHRs)
- Claims and billing activities
- Product and disease registries
- Patient-generated data
- Data gathered from even mobile devices.

In 2016, the FDA focused on considering real-world evidence to alleviate the off-label drug usage in approvals. So, when the FDA reviews and approves a selected drug, it's inspecting clinical data of controlled clinical studies as the patients are in a controlled environment and can be continuously monitored and carry out direct comparisons, usually between either placebo during treatment or between different treatments.

But once we start dosing patients in the real world, there's plenty of variation in the data that gets collected, because we don't know what patients' daily life activity and resulting exposure. Thus, RWD helps in monitoring post-market safety, adverse events and to make judicious regulatory decisions.[21]

16. CURRENT ISSUES IN DRUG REGULATION

The role of drug regulatory agencies is to protect and promote public health. In everyday practice, this broad mandate translates into two distinct objectives: first, into an obligation to protect patients against ineffective or harmful drugs, and second, to protect patients against the consequences of untreated disease. The first objective results in a gatekeeper function and obliges regulators to apply stringent standards of assessment and to deny marketing authorization were deemed necessary. By contrast, the second objective requires regulators to support and enable drug development - with a view to ensuring that patients have access as early as possible to safe and effective drugs.

This chapter summarizes the processes put in place in the European Union (EU) to ensure that regulators can meet these objectives, and briefly describes some of the challenges surrounding drug approval. The technical term in the EU for drugs is "medicinal product" and we will use that term throughout the text.[22]

17. PHARMACEUTICAL REGULATORY AFFAIRS AND IPR

A. Global regulatory challenges and current hot topics in the regulatory world

The pharmaceutical industry is a highly regulated industry. The regulatory requirements are permanently growing to ensure supply of high pharmaceutical quality, safety and efficacy of medicinal products. The factor time is now playing a more important role to allow expedited patient's access to innovative medicinal products to treat their disease and improve their life. In the EU regulatory pathway for advanced therapy medicinal products (ATMP) and further, adaptive pathway and accelerated approval

as well as conditional approval, hospital exemption, lead to an expedited access of patients to the medicines where there is an unmet medical need. Personalized medicine, individualized medicine and breakthrough designation are on the move in the US and Europe. Japan has created the priority review "sakigake" that allows expedited approval of significant innovative medicines offering priority consultations and priority reviews and assessment. Regenerative medicine such as stem cell therapy is moving forward and will revolutionize the way diseases are treated. Treatment of ageing macular degeneration (AMD) has almost

become routine with cell therapy. Others like arthritis, hepatitis, diabetes are progressing. If you can regenerate the kidney, then no need for dialysis anymore.

Currently there is a move towards multi-regional clinical trials (MRCT) following ICH guideline E 17 notably in Asia, following the initiative of Japan, China, Taiwan and Korea. This initiative will put more light on the ethnic factors to be considered in drug development for the relevant drug classes. A revision of the ICH "E 5" guideline on ethnic factors is on the radar screen as well as new ICH guideline "E17" on general principles on planning and designing MRCTS. The ICH E17 guideline reached step 2b and entered the consultation period.

Pharmacovigilance and drug safety has gained more and more focus from regulatory agencies with surveillance in Europe, risk evaluation and mitigation system (REMS) in the USA, drug safety in Japan; and more and more agencies are putting more emphasis on ICSRS, ADES and ADRS reporting. Periodic safety update reports (PSURS) are becoming periodic risk-benefit evaluation reports (PRBERS), pharmacovigilance risk assessment committee (PRAC) in the EU is (re-) evaluating safety of marketed products and is involved in safety evaluation of new drugs prior to approval. Post approval safety studies (pass) and post approval efficacy studies (PAES) are becoming part of the regulatory decision outcome. Special monitoring is adding to strengthen safety of medicines in the EU.

The falsified medicines directive in Europe has led to increased regulatory requirements. By 1st of January 2018: a 2d bar code on each pack will become mandatory, the creation of a European hub to check the packs before dispensing to the patient, identification of medicinal products (IDMP), among other requirements will add-on the challenges.

Biosimilars approvals in Europe since more than 10 years are now taking place in the USA with the first products approved as biosimilars including monoclonal antibodies. The 4-letter rule added to the inn distinguishes the biosimilar from the reference listed biologic allowing traceability. The US-FDA requests an "interchangeability" application to grant the regulatory status "interchangeable" to the approved biosimilar. Once the first interchangeable product of a reference listed biological (RLB) is approved what will be the market future of further biosimilars of the same RLB? The change in the presidency in the USA and the drug pricing discussions, revoking and replacing Obama care will have an impact on the future of medicines in the USA. New requirements are evolving for compounding pharmacies in the USA.

Europe is relaxing the biosimilars approval allowing the global reference product, introducing the 3 principles for animal studies: reduce, replace and refine, encouraging in vitro studies to replace in vivo animal studies, also allowing extrapolation of indications for the same mode of action.[23]

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