



ISSN (E): 2277- 7695

ISSN (P): 2349-8242

NAAS Rating: 5.03

TPI 2021; 10(2): 06-14

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[www.thepharmajournal.com](http://www.thepharmajournal.com)

Received: 10-01-2021

Accepted: 05-02-2021

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## Research Article

# Comparative analysis of evolution of regulatory environment in USA, Europe and Japan

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DOI: <https://doi.org/10.22271/tpi.2021.v10.i2a.5657>

## Abstract

The industry of healthcare products is the utmost regulated segment as patients are not equipped with expert knowledge to determine the efficacy, safety, and quality of these products. Thus, the regulations come into play to ensure effectiveness and safety of healthcare products. The regulatory environment throughout the world is transforming incessantly to make it viable and objective. United States of America (USA), Europe (EU), and Japan are the most regulated geographies in the world. USA is the largest pharmaceutical market. Europe as a collective region is the second biggest pharmaceutical market. Japan, however, is the third largest single country market of pharmaceuticals. The objectives of the present study are to gain evidence on the existing regulatory set-up, key areas of regulatory focus and relative analysis of the evolution of regulatory environment in the USA, Europe, and Japan. The methodology used is a relative study based on original research carried out based on evidence available from universal resources and analysis of the facts, statements, and projections of regulatory focus.

The findings included various areas of regulatory focus in three geographies including user fee, paediatric research, clinical trials, drug safety, anti-counterfeit/falsified medicines, price reimbursement policies, regulatory compliance, medical devices and biologicals regulations, ICH Q12 guideline, veterinary product reforms, review and approval pathways/timelines, breakthrough therapies, endocrine disruptors, and collaborative approaches etc. As internationally leading regulators, USFDA, EMA, and PMDA are working on specific areas of local and global interest in regulating healthcare products segment. The comparative analysis reflects discrete and overlapping goals to being reforms in regulating healthcare products.

**Keywords:** Regulatory environment, current focus, evolution, globalization, significance, regulations, coordination, collaboration

## Introduction

Medicinal products are characteristically distinctive and different from regular consumer goods. The patients as ultimate consumers are not well supplied with the specialized expertise essential to judge the aspects of efficacy, safety, and quality of the medicinal products. Attributes like efficacy, safety, and quality strengthen the trust in healthcare systems, healthcare practitioners, pharmaceutical industry, and distributors <sup>[1]</sup>. Hence healthcare products industry is the most regulated of all industries. Regulatory authorities are responsible to enforce the regulations under regulatory framework and issue guidelines to regulate drug development, marketing authorizations, manufacturing, labelling, and marketing of the healthcare products <sup>[2]</sup>. Healthcare products' regulations include numerous activities that mutually reinforce and aim to promote and safeguard public health through the objectives relevant to development, manufacture, storage, distribution, dispensing, awareness, and assurance of efficacy, safety, and quality of healthcare products <sup>[3, 4]</sup>.

While protecting public health is primary objective but it is also often complained about regulations leading to bottlenecks to therapeutic advancements and accessibility of life-savior medications to deprived patients because of the time consumed. The mechanisms designed to meet these objectives vary between countries <sup>[1, 3]</sup>.

## Evolution of regulatory environment

The regulatory environment across the globe is changing incessantly. The sustainability of the regulatory framework is only possible through its evolution at local, regional, and global level with time. The operational environment in healthcare sector is considerably different to other industries and it can be attributed to the distinct relationship between the regulators, industry

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(businesses/producers), healthcare providers and patients as consumers. The pharmaceutical sector has witnessed significant changes in past two decades. Global standards for pharmaceutical regulations have been adopted by certain countries while others have established hybrid versions of regulations. The main fundamental tool in public health is to have access to medication [5]. It is tricky to forecast the international regulatory environment in the upcoming years as globalization has driven greater harmonization like inclusivity in the International Conference on Harmonization of standards (ICH). Local initiatives are vital in transmitting information from specific countries to the global stage [6].

United States of America (USA), Europe (EU), and Japan are the most regulated geographies. USA is the leading pharmaceuticals market in the world and accounts for more than 40% global pharmaceutical sales [7, 8]. On the other hand, the pharmaceutical market in EU positions it as the next largest pharmaceutical market place globally with approximately 24% of the market share. Europe has Germany, France, Italy, United Kingdom and Spain as topmost five pharmaceutical markets in ranking orders [7, 9]. Japan, however is, the leading single country markets, following the USA and China, with roughly 7% share of the global market [10].

USA is major and most regulated pharmaceutical market in the world. There were hardly any regulations in USA in the 18<sup>th</sup> century and now it is the highly regulated market worldwide. Generally, the world looks up to USA for taking initiative either independently or through collaborative ventures like ICH to come up with understanding and eventually regulation on a new topic or area of concern. The USA usually has the world's most stringent standards for approving new drugs. These standards are most demanding over the globe [11].

One of the highly viewed regulatory system globally exists in EU. This mechanism includes of parliament of EU, "European Commission (EC)", and the council of ministers. A present there are 27 countries as part of EU. On 31 January 2020, the United Kingdom has withdrawn from the union. Iceland, Liechtenstein, and Norway, members of "European Free Trade Agreement (EFTA)" are related to EU through "European Economic Area (EEA)" to establish an internal market [11-14].

Japan is the third largest pharmaceutical market and one of the leading regulated geographies globally. Conventionally, the pharmaceutical industry faced trust issues from Japanese public as the medicines from west were deemed to be dangerous. The emphasis had been on safety and quality concerns, instead of efficacy. This had led to decrease in the development of drugs and clinical trial research in Japan. The concept of ethnic bridging in ICH guidelines has been very influential with an aim to reduce the duplication of clinical studies by inferring clinical information from one to another section. Large pharmaceutical corporations have now been conducting multinational trials involving western and Japanese sites. This is facilitating the global simultaneous submission to the major regulatory authorities of the world including Japan [15].

The main aims of this research were to:

- a. Access the essential information to understand the current set-up of regulatory environment in USA, Europe, and Japan
- b. Identify the key areas of current and future regulatory focus for the regulatory authorities of these regulated geographies

- c. Perform a comparative analysis of the evolution of regulatory environment of USA, Europe, and Japan based on these regulatory focus areas.

## Methods

This manuscript discusses the comparative analysis of evolution of regulatory environment in USA, Europe, and Japan.

## Selection of geographies

USA, Europe, and Japan were considered as geographies of interest for this research. The selection was based on the fact that these are among the most regulated countries/region and known as regulatory stewards as ICH tripartite region. These are considered to be trend setters of global regulatory landscape.

## Product types in scope

The research based study was carried out on all product types including conventional medicinal products, biologicals, medical devices, new chemical entities (NCEs), generics, drug substances, traditional medicines etc.

## Data and information collection process

The methodology used is based on original empirical research. Explicitly, the elements of analysis of facts, statements, and projections of regulatory focus are performed through the empirical research on the current universal resource pertaining to the subject matter. The resources used are from the published guidelines, legislations, official statements, official communications and notices, official gazettes and reports from the healthcare product regulators or their cooperation ventures like World Health Organization (WHO). Furthermore, the published reviews or research articles, opinions of regulatory experts, books, published reports or white papers by the industry sponsors or organizations in the healthcare sector relevant to the subject were studied.

## Results

### Current set-up of regulatory environment

#### Regulatory environment in USA

The Food and Drugs Act of 1906 constitutes extremely comprehensive and efficient system of public health and consumer safety. The public health system was totally revamped with the enforcement of The Federal Food, Drug, and Cosmetic Act of 1938. The rules for drug safety were bolstered by Kefauver-Harris Amendments of 1962 and manufacturers were needed to demonstrate efficacy of their drugs. The safety and efficacy of new medical devices were secured through the Medical Device Amendments of 1976. The regulator in USA is "Food and Drug Administration (FDA)" and safeguards the efficacy and safety of all drugs, biologicals, medical devices, and veterinary drugs. Additionally, as regulator for Food products FDA ensures safety of most of food products for human consumption and animal feed [16].

Effective from March 31, 2019, USFDA commenced operational implementation of its restructuring to fulfil its objective to protect and promote public health. USFDA comprises of seven different functional centers and nine functional offices as subdivisions, each focused on a major area of regulatory responsibility [17, 18].

The Federal Register, an official publication of US

government is used by USFDA to publish the regulations. The practice of “notice and comment rulemaking (NPRM)” is consistently applied to issue rules to ask for public comments. Where there is limited information to decipher and make decision on the specifics of a regulatory pathway, agency issues an advance notice of proposed rulemaking (ANPRM) [19].

**Regulatory environment in Europe (EU)**

The regulatory framework in EU is based on the principle of marketing authorization issued by competent regulators to protect public health. A therapeutic product for human use may be centrally authorized through the European Commission or *via* national or community procedures by national regulators. These requirements and the laws for examining approved products, are covered in the Directive 2001/83/EC for human, 2001/82/EC for veterinary and in Regulation (EC) 2004/726. These directives and legislations cover harmonized aspects of manufacturing, wholesale and marketing of healthcare products, performing clinical trials, and promotion of research in specific subjects like rare diseases, advanced therapy healthcare products, and therapeutic products for children. All the legislations relevant to medicinal products for human use are scheduled in volume 1 of "The Rules Governing Medicinal Products in the European Union". A comprehensive description of the marketing authorisation practices, and additional regulatory guidance are covered in volume 2 “Notice to Applicants” [20].

The national authorities work together with the ‘European Medicines Agency (EMA)’ and further with the EC to form a regulatory network and system to regulate medicines [21].

EMA employed amendments to its organizational formation to operate efficiently. EMA is administered by an autonomous Management Board consisting of 36 members. The day to day activities are performed by

thousands of experts from all over Europe as part of EMA's seven scientific committees those are overseen by an Executive Director [22].

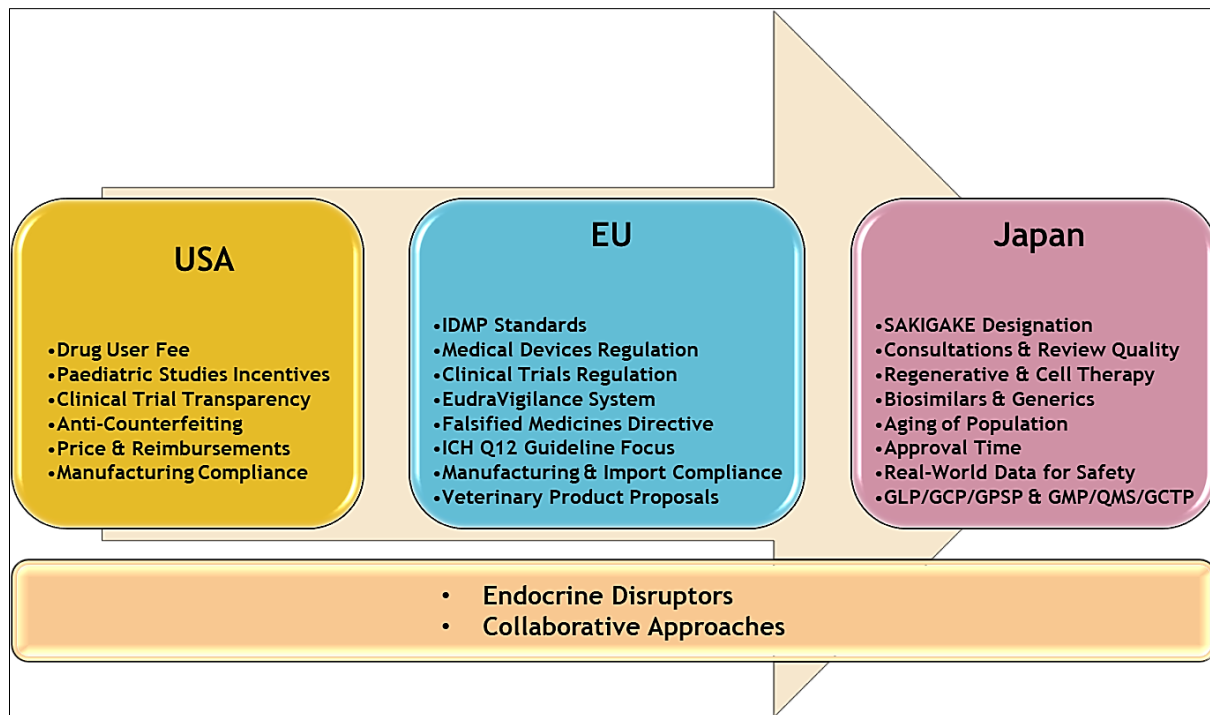
**Regulatory environment in Japan**

‘Pharmaceutical and Medical Device Act’ and other laws associated to establishments, control of poisonous, narcotics and psychotropic substances etc. form the basis of pharmaceutical administration. The application and administration of these laws and comprehensive rules are issued by the administration in the legislative ordinances and notifications. Pharmaceutical Affairs Law was retitled to be the ‘Pharmaceutical and Medical Device Act’ in November 2014. The aims of this act are to get better public health. This is fulfilled through regulations necessary to ensure safety, efficacy and quality of medicines and other healthcare products. Furthermore, this act promotes research & development of drugs, devices and regenerative therapy products that are specifically crucial for health care.

In 2004, various centers performing the activities related to pharmaceutical regulatory under the “Ministry of Health, Labour and Welfare (MHLW)” were integrated to form the “Pharmaceutical and Medical Devices Agency (PMDA)”. The PMDA handles the complete advisory and review work from the preclinical phase to authorization and post-authorization surveillance of new drugs and medical devices. The PMDA comprises of 28 offices, 4 groups, and the Kansai and Hokuriku branches [23].

**Key areas of current and future regulatory focus**

The research found that three major geographies have been working with focus in some of the specific areas of significance. These key regulatory focus areas are depicted in Fig 1.



**Fig 1:** Key regulatory focus areas

## Regulatory focus in USA

### Drug user fee

USFDA's mission of safeguarding the public health and promoting innovation is facilitated by the user fee programs. "Generic Drug User Fee Act (GDUFA)" and "Medical Device User Fee Amendments (MDUFA)" were initiated as well as amended in recent years. These laws are intended to pace the access to effective and safe generic medicines and devices to the society and reduction in expenditures to industry. Until 2012, the user fee requirements existed only for new drug applications and devices. GDUFA and amended MDUFA provisions have increased the capacity of the authority to carry out essential program functions and save on costs with the reduction in review timelines [24-56].

### Paediatric drug studies

The paediatric exclusivity incentive allows FDA to award six months of exclusivity to market for the sponsors that carry out voluntary paediatric investigations in accord with a written invitation released by the Agency. Despite being effective in adults all the drugs cannot be expected to exhibit similar efficacy in children. Establishment of safety in paediatric patients must be investigated as children may respond more sensitively to adverse drug reactions than adults. Additionally, children are in phase of development and growth and this needs to be taken into consideration [27].

### Clinical trial transparency

As part of regulation, USA mandates the inclusion of some redacted information on the ongoing clinical trials at the clinical trial registry (ClinicalTrials.gov). This provision offers access to information relevant to clinical studies being conducted on a wide-ranging disease and/or conditions to various groups including patients, family of patients, practitioners of health care, investigators, and the society [28]. As part of clinical trials transparency quest to make more information available, new provisions of Plain Language Summaries (PLS) or Lay Language Summaries (LLS) of clinical trials are being worked upon by regulators. PLS need to explain the key elements of the clinical trial in non-technical language that can be understood by layperson. US regulators do not yet require a PLS until it is determined whether the summaries can be produced without being promotional or misleading [29].

### Anti-counterfeiting

USA has put a lot of focus recently on implementing regulations to barricade the counterfeit healthcare products from the market and supply chains. The manufacturers of healthcare products shall be required to provide batch-level traceability through product serialization at unit level to ensure compliance to the "Drug Supply Chain Security Act (DSCSA)" [30].

### Price and reimbursements

The drug price and reimbursement regime in USA are complicated due to the multi-payer mechanism and overlaying requirements for market entry. The product coverage and price are established by the coverage of payer and other factors including cost containment measures. Market entry necessitates pass through this complicated structure to ensure access of medications to patients, reimbursement and appropriately valued for coverage. Efforts

to ensure compliance to overlaying regulatory needs and minimizing risk associated to enforcement action are crucial [31].

### Manufacturing compliance and GMP

The regulatory norm for healthcare products is the current Good Manufacturing Practice regulations enforced by the USFDA. Globally, the manufacturers are inspected by the FDA for conformity with cGMP. FDA has recently been very stringent in compliance to cGMP standards due to increased observations of substandard drugs or manufacturing practices. The guidance for manufacturers on cGMP provides a path forward but are not a compulsory if adequate alternate approaches are undertaken to comply with the regulations [32].

### Regulatory focus in Europe (EU)

#### Standards on identification of medicinal products (IDMP)

IDMP standards specify the use of standardized definitions for the identification and description of healthcare products for human use. EMA is employing the criteria in a phased manner based on the domains of substance, product, organization and referential (SPOR) master data. This shall facilitate the global dictionaries on drugs, consistent product submissions, clinical trials, linkage of the safety information of product globally, GMP and inspections through accessible information, enhancement of the signal detection proficiencies, rapid detection of product risks to coordinate product recalls and rapid detection of falsified medicines [33, 34].

#### Medical devices regulation

The European Union in April 2017 adopted "EU Medical Devices Regulation (EC) 2017/745 on Medical Devices (MDR)" and "Regulation (EC) 2017/746 on In-Vitro Diagnostic Devices (IVDR)". These regulations intend to uphold safe and timely access to inventive devices, increase harmonization among member states, and re-gain confidence of public. The noteworthy amendments introduced through the regulations increased scrutiny in the review approvals for CE marking, review, audit of notified bodies, audit of manufacturers by notified bodies, common technical specifications, identification and traceability of devices, reclassification of devices, clinical assessment and investigations, post-authorization surveillance (PMS), vigilance and market surveillance, and change in format of technical files. On 23 April 2020, the transitional period was extended up to 26 May 2021 due to COVID-19 pandemic to prevent shortages of essential medical devices [33, 35].

#### Clinical trials regulation

The provisions of clinical trials shall undergo a significant change with implementation of "Clinical Trial Regulation (Regulation (EC) No 536/2014)" upon roll out of EU portal and database "Clinical Trials Information System (CTIS)". The harmonized assessment and supervision processes through CTIS are being achieved for clinical trials across EU. The set up and maintenance of CTIS shall be carried out by EMA in partnership with the member states and the EC. The new regulation enables the harmonization with the enhanced EudraVigilance legislation and simplifies Adverse Safety Reporting. This shall form an environment beneficial to performing clinical trials in EU observing supreme criteria of safety for participants and improved transparency of information [33, 36].

The regulation also incorporates provisions for the submission of Plain Language Summaries (PLS). Clinical trial transparency is a critical element of patient centricity and PLS help bridge the gap between the research and the patient communities [37, 38].

### Enhanced eudra vigilance system

EudraVigilance is a system for supervising the drug safety through electronic reporting to facilitate quick detection of likely safety concerns [39]. Updated EU pharmacovigilance legislation, effective in 2012 instituted substantial amendments to electronic recording conditions for believed adverse reactions. This brings better support for safety supervision through efficient mechanism for agencies, sponsors, and practitioners in health care. The legislation mandates the enhancement of EudraVigilance to achieve simplified recording, improved quality of data, searches, analysis, and tracking mechanisms along with implementation of the ISO and ICH standard on individual case safety report (ICSR) [33].

### Falsified medicines directive

EU embraced Directive 2011/62/EC or Falsified Medicines Directive (FMD) in January 2013 because of the significant health hazard presented by falsified medications. A delegated act (EC) 2016/161 was also worked by EC in parallel to safe guard consistency and crucial safety features necessitated by the legislation. A task force on IDMP is at work to determine the IDMP data to the FMD like Global Trade Item Number (GTIN) of product and integrate the European Medicine Verification System (EMVS). The prevention of entrance of falsified medicines into legal supply chain is aimed by this directive. Serialization of commercial pack or secondary level is necessitated by FMD [33, 40].

### International council for harmonisation Q12 (ICH Q12) guideline

ICH Q12 guideline offers a basis to simplify the process of managing the post-authorization Chemistry, Manufacturing and Controls (CMC) variations in unpredictable and effectiveway. This further promotes incessant improvement, bolstering quality, and enabling dependable product supply. ICH Q12 adoption will affect regulatory dossier by improving on the handling of post approval changes through efficiencies; Pharmaceutical Quality System (PQS) through improved familiarity and change management mechanisms; and application of post-approval change management protocols and plans. ICH Q12 implementation is likely to aid patients, biotech and pharmaceutical industry, and regulatory agencies by incessant betterment of post approval practices [33, 41].

### Manufacturing compliance, GMP and importation

EU Good Manufacturing Practices (GMPs) regulation is required to be complied by all the pharmaceutical manufacturers. Authorization and regular inspection of manufacturers and importers is mandated as per "The rules governing medicinal products in the European Union". Additionally, the inspections can also be carried out by the "European Directorate for the Quality of Medicines and Healthcare (EDQM) of the Council of Europe" to issue Certificates of Suitability. This certificate can substitute the majority of the information in the 'Marketing Authorisation Application (MAA)' [34]. In March 2020, provisions to manufacture and import medicinal products were published as

draft annex 21 to EU GMP guideline titled "Importation of medicinal Products" [33, 42].

### Veterinary product proposals

The new 'Veterinary Medicines Regulation (Regulation (EC) 2019/6)' is expected to be implemented in January 2022. This consist of innovative ways to enhance accessibility and safety of veterinary medicines along with stimulation of innovation and internal market. Furthermore, it shall boost the combat against antimicrobial resistance through minimizing the hazards from the usage of antibiotics in veterinary healthcare. EMA is partnering with EC and other EU partners to prepare for the application of the new Regulation. Regulation (EC) 2019/6 abolishes Directive 2001/82/EC and changes the terms of Regulation (EC) 726/2004 relevant to the authorization and monitoring veterinary medicines [33, 43].

### Regulatory focus in Japan

#### SAKIGAKE designation

In 2015, MHLW promulgated new regulations known as "SAKIGAKE" that allows for expedited regulatory consultations, review and approval provisions. These provisions are available for medicinal products nominated as breakthrough therapies required for the certain medical conditions. Such pathways have a prerequisite of early development and seek initial approval in Japan [44].

This designation system facilitates the research on ground-breaking medicines, devices, and regenerative therapies. This leads to the initial real-world application as the first approval intended in Japan, and either first in human (FIH) or proof of concept (POC) study performed in Japan [45].

#### Strategy consultations and improvement in review quality

PMDA is focused on the upgrading of quality of assessments and safety actions through enrichment of information systems [45]. The new methods to progressive evaluation through gathering and examination of electronic study data from applicants are under focus [46].

PMDA is encouraging the sponsors to have the strategic consultation throughout the drug development process. This has contributed to recent improvement seen in PMDA. The cost of this service is received from the pharmaceutical industry through "user fees" but is proving to be worthy investment [47].

#### Regenerative medicines and cell therapy

Regenerative medicine refers to therapies that replaces the diseased cells, tissue, or organs with healthy cells. Induced pluripotent stem (iPS) cells can be turned into other type of cells. Patients can be treated with their own cells without the need to be on immunosuppressant. Treatment is chiefly being used in treating only severe patients as the risk is small. However, with establishment of the safety of these procedures, these can gradually be applied to treat patients in earlier stages of diseases [48]. The promotion of regenerative medicines is additional influence in the amplified trial activities in Japan. The provisional approval up to seven years may be granted and consultations are performed through a specialized procedure. The PMDA discusses clinical pathways only after ascertaining successful manufacturing and safety aspects of these drugs [47].

#### Approval time

PMDA has shortened the time-consuming approval processes

for new products [46, 49]. Changes performed by the PMDA over the past decade resultant of improvements in the speed of new drug assessments and authorizations. As per the latest data, the average time taken to approve a standard drug in Japan (306 days) is better than USA (322 days) and EU (366 days). PMDA is authorizing orphan drugs roughly in six months after submission. PMDA is advocate of harmonization of safety and clinical studies to remove redundancy in process when data is available in other parts of the world. This is apparent by the cumulative number of international studies with Japan as a site [47].

### **Biosimilars and generics**

As numerous drug patents perish soon, Japanese industry is forced to acclimatize to a shifting market setting. Besides being a prosperous market for generic drugs, the prediction is that Japanese pharmaceutical market will transform because of the increased usage of biosimilars. This is projected to be the fastest growing segment in the future. The biosimilars are going to be vital manage costs in healthcare [50, 51].

### **Aging of population**

Japan's aging population is rising the quickest amongst developed countries. In 2019, there were 28% of population proportion aged more than 65 years and is expected to reach to 40% by 2050. The low-cost healthcare system will not be able to sustain as the population continue to age. This is a key focus for the Japan healthcare and patient centricity [51]. The aging population has caused high demand for the treatments and will influence the potential developments [47]. One of the trigger factors in the boom of research on regenerative medicines is expected to be this aging factor [48].

### **Real-world data (RWD) for safety assessments**

The utilization of "Real-World Data (RWD)" for safety assessments from the electronic medical records (EMRs) and patients' data in registries is promoted by PMDA. To encourage usage of RWD, the ministerial ordinance "(Good Post-Marketing Study Practice, or GPSP)" was modified and applied in 2018. The formal release of Medical Information Database Network (MID-NET®) shall support this utilization as database can be utilized by sponsors, academia, PMDA and cooperative hospitals.

There are many challenges in usage of real-world data. Incessant partnership amongst regulators and additional stakeholders will be essential to global harmonization in using RWD in the regulatory pathways [52].

### **GLP/GCP/GPSP compliance and GMP/QMS/GCTP assessments/inspections**

Manufacturing facilities and "Quality Management System (QMS)" have regulatory standards specified for them. PMDA performs compliance evaluations (document-based or physical inspections) and data integrity checks to evaluate compliance with "Good Laboratory Practice (GLP)", "Good Clinical Practice (GCP)" and "Good Post-marketing Study Practice (GPSP)", "Good Manufacturing Practice (GMP)", "Good Gene, Cellular, and Tissue-based Products (GCTP)" [46].

### **Collaboration approaches**

Both regulators and pharmaceutical industry are confronted by an assortment of challenges. The industry faces challenges that are driven by business needs and regulations. The major

challenges faced by the regulators are driven by the needs to ensure the safety, quality, and efficacy of health care products. Health authorities have been partnering amongst them and with pharmaceutical industry and continue to innovate for novel ways of working in collaborations to conquer these challenges. Such coordinated efforts have the potential to reduce the numbers of challenges that confront the healthcare sector [53].

### **Discussion**

USA, Europe, and Japan are the key geographies when it comes to effective implementation of the regulatory frameworks. The regulators of these countries/region are the drivers of regulatory environment globally and have direct or indirect influence on the regulatory policies other regulators. The current set-up of regulatory environment in these geographies has evolved tremendously over the last two centuries. The Food and Drugs Act, The Federal Food, Drug, and Cosmetics Act and various amendments in USA; Regulation (EC) 726/2004, Directives 2001/83/EC and 2001/82/EC and other associated directives in Europe; and Pharmaceutical and Medical Devices Act in Japan are foundation blocks to deliver the necessary regulatory provisions.

At various times, these regulators have been focusing on different areas of significance to ensure the regulatory advancements in their region or sometimes globally. USFDA has recently paid more attention to user fee collection for its services, which were earlier being done free of charge. This has enabled USFDA to improve on the resources and timelines of assessment. PMDA has followed similar approach to provide consultations with user fee. Further, to promote the research on paediatrics medicines FDA has considered the need for issuing incentives in the form of exclusivity to market. The need to maintain transparency in the clinical trials research is focussed by the American agency to promote the sense of openness and information to promote research and development. At the same time, EU has given a lot of focus on the clinical research too with some additional perspective. The new clinical trial regulation has paved way for a central information system and consistency of practices among member states along with transparency of trails information. Along with focus on clinical research promotion, EU is also paying attention to safety aspects through enhancements in the pharmacovigilance system through electronic reporting and harmonized practices. PMDA, Japan is fostering the use of real-world data from medical documents for drug safety evaluations.

Both clinical trial research and pharmacovigilance aspects are expected to benefit from the elements of 'Identification of Medicinal Products' standards gaining attention in EU. Such standardized descriptions will also help the initiatives against counterfeiting or falsified medicines due to the rising concerns globally. Both USA and EU have pioneered legislations in context of these challenges in supply chain of healthcare products. The 'Drug Supply Chain Security Act' of USFDA and FMD directive of EU reflects the extensive work carried out by regulators in the respective region.

Nonetheless, PMDA, which in earlier existence (as departments under MHLW) has followed more conservative approaches historically is now focussed on its review quality, approval pathways, time lines through agency consultations and provisions of acceleration of breakthrough therapies under SAKIGAKE designation. The PMDA has been promoting the regenerative medicines and cell therapy as

evident from the increased clinical trial activities. The exclusive consultation process for such therapies has been adopted by PMDA. The focus on regenerative therapies is also linked to concern around the aging population in Japan, which is already 28% in 2019 and expected to reach 40% by 2050. In the USA, the drug price and reimbursement system are multifaceted, and focus is to ensure that essential medications are accessible and reimbursable through regulatory provisions without unnecessary risks of enforcement crackdown.

The boom of medical devices, biologicals are leading to ensure these categories of products have enhanced understanding for the development of regulatory framework. The revised medical devices regulation in EU are paving way for developed understanding and thorough control of these products. With the biological products becoming off-patent and promotion to bring guidance, the biosimilars are expected to become swiftest expanding segment in Japan.

The compliance in manufacturing has been in lot of focus for US FDA due to compliance issues and substandard practices being observed by FDA in the recent inspections. Similarly, the GMP in EU is being focused along with guidance on manufacturing and import as lot of products are manufactured

outside of EU. The provisions of import testing and quality certifications are of paramount importance. This area has also been of vital emphasis for PMDA with respect to increased level of marketing applications. Along with GMP, PMDA is taking extensive interest in Good Clinical Practice (GCP), Good Laboratory Practice (GLP), Good Post-Marketing Study Practice (GPSP), Quality Management System (QMS) and Good Gene, Cellular, and Tissue-based Products (GCTP).

To make regulatory framework nimbler to the acquired product knowledge and scientific understanding, the release of proposed guidelines on ICH Q12 are ground-breaking steps in all these geographies. These provisions to adopt flexibility by regulators and shift responsibilities towards manufacturers in the controlling mechanisms by adopting a product knowledge and quality system enhancement-based approaches.

The latest veterinary medicines regulation in EU, shall support not only the efforts in making the animal drugs accessible and safe but also minimizing the threat of anti-microbial resistance.

The results of comparative analysis of the focus areas of regulatory reforms in three countries viz. USA, Europe and Japan are listed in Table 1.

**Table 1:** Comparative analysis of focus areas of regulatory reforms in USA, Europe, and Japan

Regulatory reform areas	USA	Europe	Japan	Mechanisms
Initial drug approval process reforms	√	√	√	User fee programs, IDMP standards, accelerated and supportive review approval process like SAKIGAKE, Strategy consultations
Post-authorization changes reforms	√	√	√	ICHQ12 focus
Paediatric research	√			Paediatric studies incentives
Clinical trial research	√	√	√	Clinical trial regulations, clinical trial transparency, consultations, and promotion of regenerative medicines
Tackling counterfeiting	√	√		DSCSA and FMD, IDMP standards
Cost & reimbursement	√			Price and reimbursement focus
Quality systems, manufacturing, and other regulatory compliance	√	√	√	GMP, GLP, GCP, GPSP, QMS, GCTP, ICHQ12
Drug safety reforms	√	√	√	Paediatric research promotion, enhanced EudraVigilance, IDMP standards, use of real-world data
Regulation development on medical devices, biologicals, biosimilars	√		√	Medical devices regulation, promotion of biologicals and biosimilars
Promotion of breakthrough therapies			√	Regenerative medicines and cell therapy, SAKIGAKE designation
Reforms to tackle antimicrobial resistance		√		Veterinary products proposed regulation
Specific population or environmental concerns	√	√	√	Focus on aging population and endocrine disruptors
Harmonization and collaborative initiatives	√	√	√	Harmonization and collaborative ventures like ICH, ICH Q12, use of real-world data and adoption of IDMP standards

## Conclusion

The study demonstrates that the regulatory framework is well established over all these years through the efforts done by regulators in USA, Europe, and Japan. These provisions have created regulatory mechanisms not only in the respective geographies but also in the emerging parts of the world. However, the incessant viability of such frameworks and mechanisms is reliant on the evolution at various levels with time. All the three major regulators studied have put in emphasis on specific areas as required by the local healthcare situation. Furthermore, as global steward forces in regulating healthcare products segment, USFDA, EMA, and PMDA have taken interests in areas of global significance as well. The relative analysis of evolution in the focused areas demonstrates a lot of diverging and converging interests and local or collaborative efforts in bringing regulatory reforms in healthcare products segment.

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