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Global Trends and Updates in Regulatory Affairs

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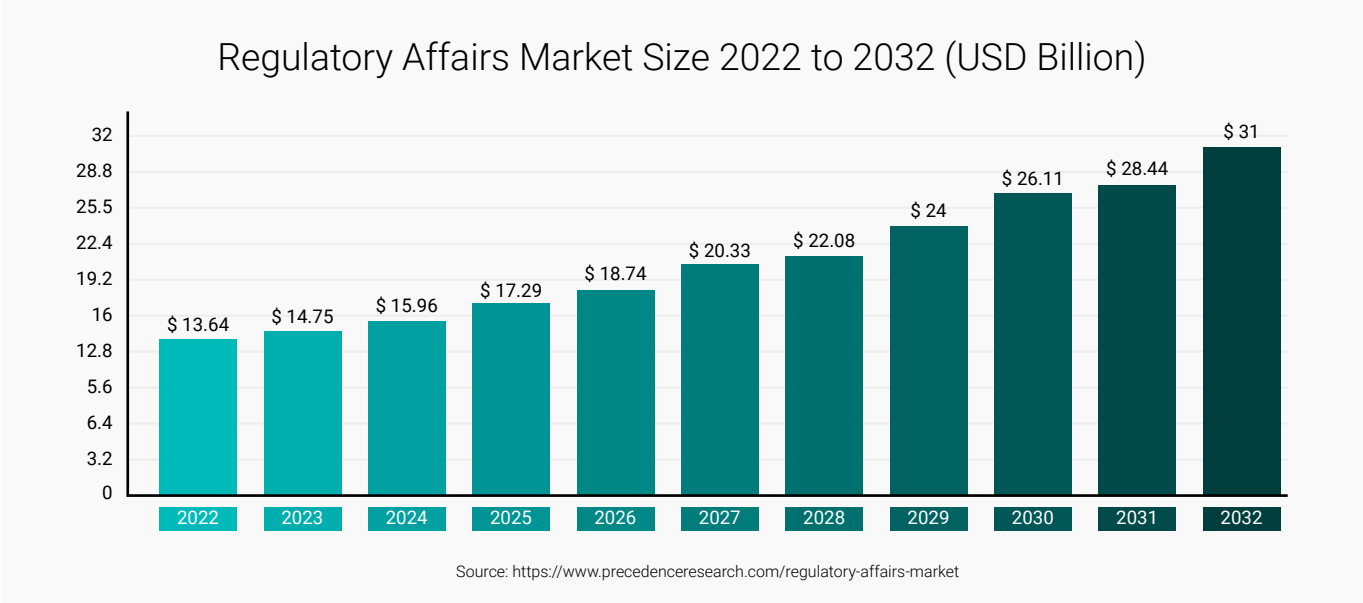
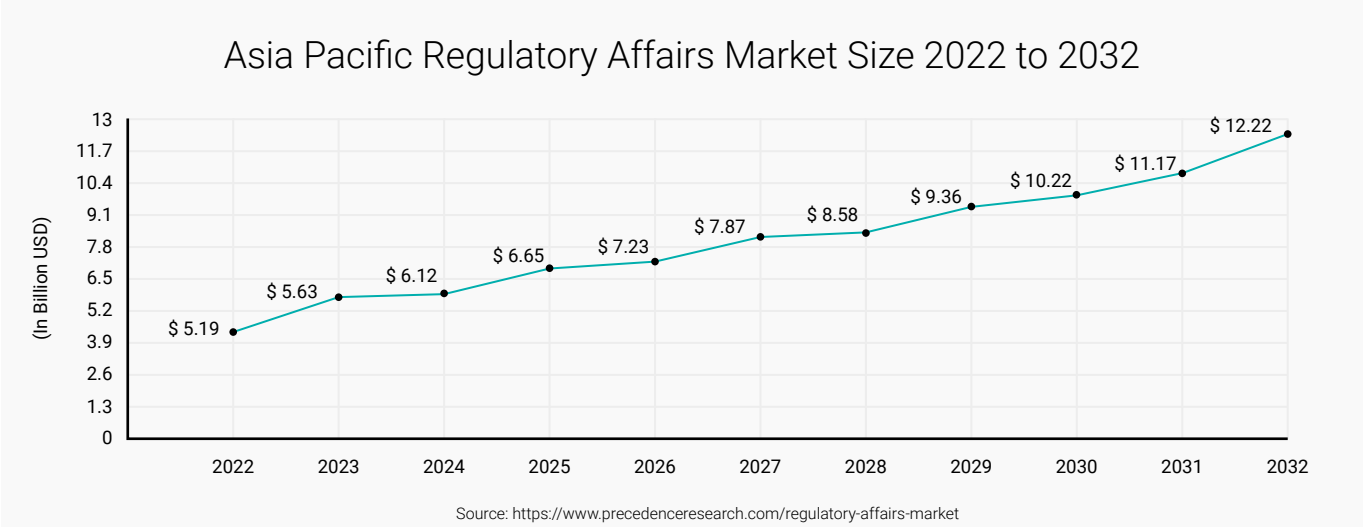
Pharmaceutical companies need to follow regulations set forth by respective regulatory agencies right from the pre-clinical to post-marketing phases of clinical development. Each and every regional agency has a wide range of stringent guidelines for various processes to ensure patient safety and product quality. New regulations are bound to be set to further enhance medical research as per changing industry trends. If any change occurs in regulatory regime, it is sponsors' responsibility to track the revisions/modifications from time to time to adapt and align with them. Regulations changed like before and after COVID-19. After COVID 19, global regulatory agencies made notable changes in regulations based on the unforeseen challenges, key learning and various observations from the development, manufacturing, and delivery of vaccines. Globally, Life Sciences and Pharmaceutical industry continues to adopt advanced technology and novel therapies to improve quality of medicines, medical devices and biologics.

The global regulatory affairs market size was estimated at USD 14.75 billion in 2023 and is expected to surpass around USD 31 billion by 2032 and is poised to grow at a compound annual growth rate (CAGR) of 8.6% during the forecast period 2023 to 2032.



Source: https://www.precedenceresearch.com/regulatory-affairs-market

<u>Asia Pacific Regulatory Affairs Market Size 2023 To 2032:</u> The Asia Pacific regulatory affairs market size was valued at USD 5.63 billion in 2023, grew to USD 6.12 billion in 2024, and is estimated to reach around USD 12.22 billion by 2032, growing at a CAGR of 9% from 2023 to 2032.



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Current Challenges in Regulatory Affairs for Sponsors

As Pharma industry continues to make strides into offering better quality of medicines, sponsors are still coming across challenges in both process and technology adoption.

Process Challenges:

i. Obtaining regulatory approval for a drug is often time-consuming especially during the pandemic, which leads to higher costs, a more complex supply chain, and a requirement for refined systems to sustain regulatory compliance.

ii. Submission of adequate evidence by the sponsor from in vitro studies to confirm that the proposed clinical trial is reasonably safe.

iii. The marketing authorization application MAA must contain evidence of the drug's chemistry, manufacturing, and controls CMC (details of product manufacturing, product stability, and shelf-life), and preclinical studies of pharmacology, pharmacokinetics PK and ADME.

iv. Developing and maintaining country-specific versions of the same information in order to meet regional health authorities requirements.

v. Maintaining different processes for manufacturing the same product to ensure availability of product, which increases inventory segmentation and potential for errors in terms of producing and regulatory compliance.

vi. Managing GxP inspections that are required for approval of submissions.

Technical challenges:

i. Adapting to modern technology that is dynamically changing is laden with constant updates and usage of multiple electronics/software tools at times making the process tough.

ii. As novel approaches and techniques come to light, current study designs may not be compatible to determine the efficacy of the drug.

iii. As medical research keeps evolving, inventing new techniques and approaches are often a prerequisite to scrutinizing new medical research.

New Trends in Regulatory Affairs to Expedite Review Process: Pharma companies integrate the following approaches and redefine clinical development by accelerated digital adoption and innovation.

Adopting Real World Evidence (RWE): In 2017, the FDA relied on RWE to expand the use of Edwards Life sciences' trans-catheter 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 randomized controlled trials RCTs.

Adopting Virtual First Approaches: 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.

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 healthcare setting.

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:

i. Electronic health records (EHRs)

ii. Claims and billing activities

iii. Product and disease registries

iv. Patient-generated data

v. 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.

Telemedicine: Telemedicine involves the use of electronic communications to provide clinical services to patients without an in-person visit. Telemedicine technology is often used for follow-up visits, management of chronic conditions, medication management, specialist consultation and a host of other clinical services that can be provided remotely via secure video and audio connections. But telemedicine applications can be augmented to be used to effectively manage clinical trials and gather adverse event data.

Pragmatic Clinical Trials (PCTs): PCTs are defined as patient-centered, outcome-based trials examining the comparative benefits and risks of therapeutic interventions to inform clinical and/or policy decision-making. These trials often employ electronic health records EHR)-embedded research designs to rapidly test important clinical questions. PCTs, measure the effectiveness of an intervention in a real-world environment. There are typically few to no exclusion criteria in the population of interest and the intervention is provided along with routine care by a heterogeneous group of clinicians.

Big Data Analytics: Big data is a collection of a large volume of data that is generated in hospitals and clinics on a day to day basis with increased velocity and variety. Over a period of time, there has been another “V” that gained momentum – Veracity, which refers to the quality of the data.

Clinical trials: Big data can help in recruiting patients for clinical trials by tracking the genetic information and disease status of subjects most relevant to the study.

Drug discovery: This can support researchers in predictive modeling for drug discovery.

Precision medicine: This can enhance the diagnosis and treatment of several disorders by capturing and understanding a patient’s genetic make-up, environmental factors and behavioral patterns.

Research and Development: Leveraging big data in the pharmaceutical industry will aid businesses in gaining a holistic awareness of the variety of drugs and their development

Artificial Intelligence: Compared to traditional analytics and clinical decision-making techniques, AI allows better performance. Continuously learning algorithms interact with training data, allowing humans to gain unprecedented insights into diagnostics, care processes, treatment variability, and patient outcomes. They have the ability to improve the quality of data resulting in producing precise and accurate outcomes. The Pharma industry is significantly gaining from AI-driven efficiency improvements in R&D, manufacturing, sales and marketing.

Notable changes in different types of regulations

USA – United States Food and Drug Administration (USFDA)

The US FDA planning to introduce some changes in reviewing process as increasing concerns around patient safety, and growing.

Framework to Use Real-world Evidence to Mitigate 'Off-label' Drug Usage

The US FDA introduced framework to incorporate real-world evidence to mitigate the "off-label" drug use in regulatory approvals and thus create a rigorous safety profile. This framework was brought by using revolutionary '21st Century Cures Act'. For an unapproved indication, off-label drug usage may result in adverse events that could be tough to understand and address. The regulatory agency is seeking to track real-world evidence to get information not only to regularize and control such usage, but also to track the usage of product for new indication and in-time allow for its approval should it prove beneficial.

CMC Post-approval Changes for Biologics

By revision of guidance for 'CMC post-approval changes for biologics', changes have been established in the manufacturing process, the drug substance purification process, the starting materials and the container/closure system. CMC guidance update comprises of other changes such as inclusion of 'intermediate' word in glossary as per industry body suggestion, and an appendix recommending categories for manufacturing changes which are commonly reported.

Emergency Use Authorization for Vaccines to Prevent Health Disasters like COVID-19

The FDA has paved way for faster approval of vaccines Under Emergency Use Authorization (EUA). For studies and review of COVID-19 specific vaccines, new guidelines have been issued and this guidance combines other guidelines issued independently and develops a comprehensive set of recommendations for biologics sponsors planning to market/ currently marketing their product in the USA. This guidance in its final version shall remain active only for the duration of public health emergency COVID-19 pandemic and might become void unless the agency issues further guidelines. All the required details need to submit by sponsors to get EUA to market their vaccine.

i) Description of product along with its intended use in detail.
ii) Safety and efficacy data about the product (currently available).
iii) Sponsor might have all available information about risks and benefits including steps to mitigate risk, recommendations for safe use, contraindications and other essential information.
iv) Alternative approved products and adequacy for proposed use.
v) Information about manufacturing facility, any existing safety and efficacy and CMC data

European Union – European Medicines Agency (EMA)

Clinical Trial Regulation (CTR) & CTIS Portal

A major guidance for regulating clinical trials by the EMA, the Clinical Trial Regulation (CTR) introduces multiple proposed changes and those changes will result in harmonization of assessment and supervision processes across all EU trials, support sponsors achieving approvals in multiple EU regions with greater efficiency, and protect and improve patient safety.

A brief summary with important changes is listed below.

i) The CTR categorizes the clinical trial studies into three types
   a) clinical trials
   b) non- interventional studies and
   c) low-interventional clinical studies
ii) Auxiliary medicinal products will replace the existing terminology non-investigative medicinal products (NIMP)
iii) CTR will allow for the submission of a single application dossier to multiple EU countries, through a single portal controlled by the EMA
iv) Substantial modifications (replacing substantial amendments) will be similarly submitted through the Clinical Trials Information System CTIS portal
v) Although no date has been set, EMA is aiming to go live with CTIS by January 21, 2022. Suspected unexpected serious adverse reactions SUSARs) submission process will be simplified with the submission being made through the EMA database which will then be forwarded on to member states
vii) A summary of the clinical trial results must be submitted within one year after completion of clinical trials in all member states, accompanied by a layperson summary

IDMP Implementation Guide

Second version of Identification of Medicinal Products (IDMP) Implementation Guide was recently published EMA. This guide is useful for understanding and complying with regulations for submitting data on medicinal products and defines the implementation requirements of the ISO IDMP standards and terminologies in the EU. The guidance imparts information about the timelines, requirements, processes, technical specifications, data elements and associated business rules for the stakeholders. The latest revision of IDMP Implementation Guide has additional information about the following aspects.

i) High level principles of the target operating model for submission and maintenance of medicinal product data in the EU
ii) Extended guidance on how the PMS data elements to populate.
iii) The basis for medicinal product data exchange in the EU

Canada – Health Canada (HC)

Enabling the Biomanufacturing and Life Sciences Strategy – Modernizing Clinical Trials to Support Innovation

Under the Food and Drugs Act, Health Canada has proposed modernization of regulation of clinical trials by introducing the following changes

i) Introduction of a coherent risk-based approach to the regulation of clinical trials
ii) Streamline processes towards greater efficiency and clarity
iii) Afford greater flexibility in the safe development of innovative therapies and products, and innovative clinical trial designs
iv) Align with international best practices regarding clinical trial oversight and public access to information

The proposal intends to better align Health Canada's clinical trials framework across its business lines (human drug clinical trials, medical device investigational testing, non- prescription drugs and natural health product clinical trials,

and clinical trials for foods for a special dietary purpose).

Forward Regulatory Plan 2023-2025: Modernizing compliance and enforcement oversight for drugs

Enabled by the Health Canada under Food and Drugs Act, the Forward Regulatory Plan 2023-2025 would ease the burden associated with annual licence review and modernize provisions related to compliance and enforcement tools. This proposal is expected to increase regulatory decision-making efficiency and predictability concerning drug establishment licences, allowing an opportunity for industry stakeholders to streamline their compliance programs accordingly.

Regulatory cooperation efforts (domestic and international)

Forward Regulatory Plan 2023-2025 regulatory proposal would better align Canada's requirements with those of other jurisdictions such as the USA and EU.

Potential impacts on people in Canada, including businesses

i) Proposed amendments would apply to health and biosciences and agri-food stakeholders involved in the conduct of clinical trials in Canada.

ii) Regulatory proposal would improve clarity, predictability and transparency around the regulation of clinical trials for businesses, academics and people in Canada. Improved agility of the regulatory framework is expected to benefit researchers and industry by better accommodating innovative, non-conventional clinical trial designs; this could benefit people in Canada by improving access to clinical trials. The application of a risk-based approach would help reduce regulatory burden for some clinical trials conducted on marketed products.

iii) Canadian participants in trials would benefit from improved safety monitoring. Health care professionals would be able to apply for investigational testing of medical devices (without going through a manufacturer). As well, the agri-food business would be able to conduct clinical trials for infant formula and other prescribed foods for a special dietary purpose within Canada.

Japan – Pharmaceuticals and Medical Devices Agency (PMDA)

Regulatory Framework for Regenerative Medicines

The new Regulatory Framework for Regenerative Medicines (https://www.pmda.go.jp/files/000219466.pdf) defines regenerative medicines and establishes the guidelines to conduct studies for them under the PDM Act. This Act reduces the phased clinical trial period for regenerative medical products allowing them to be used on a conditional authorization basis, should there be a need. The facilitation of thorough regulation for this process is a major step forward for scientific regulation with the provision of early patient access to promising regenerative products. The data and knowledge gained from the clinical trials and post-marketing studies will help to identify issues to improve scientific regulations for approval of novel drug and medical device products.

Pharmaceuticals and Medical Devices Safety Information No. 407

In January 10, 2024, Revision of PRECAUTIONS (No.347) was made on Sertraline hydrochloride (and 11 others) drugs.

Australia – Therapeutic Goods Administration (TGA)

Australian Unique Device Identification (UDI) System

Aligning with global device identification systems, TGA is implementing its own UDI system to support manufacturers and sponsors of medical devices marketing in Australia in tracking their products throughout the supply chain and inventory management functions. Through UDI, TGA aims to reduce manual error in post-market surveillance and eliminate confusion in identifying the models of devices on both national and global basis. Currently, TGA's UDI system is in early stages. The system could come into implementation only after EU completes implementing the same as TGA plans to align with EU's system.

Other Regulatory Reforms

To accommodate regulation of evolving therapeutics and simplify regulatory processes for sponsors, TGA has come up with major regulatory reform activities for 2023-24

1. Regulatory functions by applying three principles of regulator best practice
    i) Continuous improvement and building trust
    ii) Risk based and data driven
    iii) Collaboration and engagement

2. TGA will continue to expand and evolve work-sharing product evaluations of new prescription medicines, extensions of indications to medicines and generic medicines with Australia-Canada-Singapore-Switzerland consortium ACSS partners and joint evaluations of new oncology medicines with the USA and Canada through Project Orbis.

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