International Journal of Community Medicine and Public Health
Kumar N. Int J Community Med Public Health. 2024 Feb;11(2):989-993
http://www.ijcmph.com
pISSN 2394-6032 | eISSN 2394-6040

DOI: https://dx.doi.org/10.18203/2394-6040.ijcmph20240295

Review Article

Ensuring global health: a comprehensive review of vaccine regulation with a focus on the Indian perspective

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Received: 03 July 2023
Revised: 10 January 2024
Accepted: 12 January 2024

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ABSTRACT

The regulation of vaccines is crucial for ensuring public health and safety. A global perspective on vaccine regulation, with focus on the Indian approach in vaccine regulation, was analysed. The historical evolution of vaccine regulation, highlights significant events that shaped regulatory systems. The role of National Regulatory Authorities (NRAs) in ensuring the safety, efficacy, and quality of vaccines is discussed, along with the pivotal role of the WHO through its prequalification program. The stages of the regulatory review process, including pre-licensure review and post-licensure surveillance, are outlined. The Indian perspective is examined, with a focus on the Central Drugs Standard Control Organization (CDSCO) as the primary regulatory authority. The rigorous vaccine approval process, emergency use authorization, vaccine distribution, and administration, as well as post-marketing surveillance, are discussed. The Indian government's participation in international collaborations and emphasis on indigenous vaccine development are highlighted. This comprehensive review highlights the importance of vaccine regulation and the efforts undertaken by the Indian government to ensure the safety, efficacy, and accessibility of vaccines.

Keywords: Vaccines, Regulation, National Regulatory Authorities, WHO, Legal framework, Safety, Efficacy

INTRODUCTION

The regulation of vaccines is a critical aspect of ensuring public health and safety. Operating within a legal framework, vaccine regulation requires a combination of medical, scientific, and technical knowledge and skills. In this article, we will delve into the historical evolution of vaccine regulation, the pivotal role of National Regulatory Authorities (NRAs), and the different stages of the regulatory review process.

History of medicines regulation

The regulation of medicines began taking shape during the 19th century with significant advancements in the life sciences such as chemistry, physiology, and pharmacology. These developments laid a solid foundation for drug research and development, which further flourished after World War II.

Historical perspective leading to the establishment of the US FDA

Tragic events in the past underscored the need for a robust regulatory system. For example, in 1901, the deaths of 14 children due to tetanus-contaminated diphtheria antitoxin highlighted the lack of facility controls and product safety testing. Similarly, the diethylene glycol poisoning incident in 1937, which caused over 100 deaths in the US, exposed the use of chemicals without safety testing. The Cutter incident in 1955, where inadequate inactivation of poliovirus led to adverse effects, and the thalidomide tragedy from 1958 to

1960, which caused birth defects, further emphasized the need for stronger regulation.

Enactment of legislation to establish and strengthen US FDA

In response to these events, legislation was enacted in the United States to establish and strengthen the regulatory system. The virus, serum, and antitoxin Act of 1902 laid the foundation for licensing and product control. The Food and Drugs Act of 1906 established premarket notification requirements for new drugs. The Federal Food, Drug, and Cosmetic Act of 1938 significantly increased federal regulatory authority over drugs, including pre-market safety reviews and factory inspections.

METHODOLOGY

The primary objective of this scoping review was to comprehensively examine and map the existing literature on vaccine regulation globally, with a specific focus on the Indian perspective. The review aimed to identify key regulatory frameworks, challenges, successes, and gaps in vaccine regulation, emphasizing the role of India in the context of global health.

Protocol development

A detailed protocol was developed to guide the systematic process of conducting the scoping review. The protocol included predefined criteria for study inclusion/exclusion, search strategies, and the overall structure of the review.

Literature search

A systematic and comprehensive search was conducted across multiple electronic databases, including PubMed, Embase, Scopus, and relevant regional databases. The search strategy utilized a combination of medical subject headings (MeSH) terms and keywords related to vaccine regulation, global health, and the Indian context. Grey literature, reports, and relevant governmental publications were also included.

Inclusion criteria

Studies and documents were included if they focused on vaccine regulation globally and included specific information related to the Indian context. This encompassed primary research studies, systematic reviews, policy documents, and reports published in English from January 2020 to December 2023.

Study selection

Two independent reviewers screened titles and abstracts of identified articles against the inclusion criteria. Full-text articles were then assessed for eligibility. Discrepancies were resolved through consensus, and a third reviewer was consulted when needed.

Data extraction

A standardized data extraction form was developed to systematically extract relevant information from included studies. Extracted data included details on regulatory frameworks, challenges, successes, and specific insights related to the Indian context. Indian perspective in dealing with the regulation of vaccines.

DISCUSSION

Legal framework of the regulatory system

Governments worldwide have enacted comprehensive laws and regulations to regulate medicines, including vaccines. The executive branch establishes regulatory institutions, defines their functions and roles, and sets up organizational structures. The legislative branch creates laws and regulations that provide the legal framework for the regulatory system and define the scope of products to be regulated.

Role of NRAs

NRAs serve as guardians, ensuring the safety, efficacy, and quality of vaccines and other medical products made available to the public. NRAs enforce rules and regulations and issue guidelines to regulate the entire vaccine development process, including licensing, registration, manufacturing, marketing, and labeling. Examples of NRAs include the US FDA, the European Medicines Agency (EMA), the Central Drugs Standard Control Organization (India), the National Medical Products Administration (China), and the Food and Drugs Authority (Ghana).[1,2]

Role of the WHO in vaccine regulation

The WHO plays a significant role in vaccine regulation through its prequalification program. The program aims to ensure the quality, efficacy, and safety of medicines, including vaccines, procured using international funds to serve patients in developing countries.

The WHO evaluates the quality, safety, and efficacy of prioritized essential medicines, inspects manufacturers, and monitors products after prequalification. Additionally, the WHO provides capacity building for regulators, manufacturers, and quality control laboratories.[3]

Stages of review and regulation

The regulatory review process for vaccines consists of several stages. The investigational new drug application (IND) includes phase I, phase II, and phase III studies, which assess safety, immunogenicity, dose-ranging,

efficacy, and other parameters. The Biologics License Application (BLA) is submitted to seek marketing authorization after completion of clinical trials.[4] It includes data on manufacturing, preclinical studies, clinical trials, product labelling, and proposed conditions of use.

Pre-licensure review

NRAs conduct a thorough evaluation of data submitted in the BLA to determine the safety, efficacy, and quality of vaccines.[4] This evaluation includes a review of manufacturing processes, clinical trial data, non-clinical studies, and labeling. The review is based on scientific principles and standards to ensure the benefits of the vaccine outweigh the potential risks.

Post-licensure surveillance

Once a vaccine is licensed, post-licensure surveillance systems monitor its safety and effectiveness in real-world conditions. These systems detect and investigate adverse events following vaccination (AEFIs) to ensure continuous assessment of the vaccine's benefit-risk profile. Post-licensure surveillance contributes to ongoing evaluation and enhances the understanding of the long-term effects of vaccines.

Product development and NRA review process

The product development process for vaccines involves preclinical testing, followed by clinical trials involving different phases. The regulatory review process in the United States includes pathways such as traditional approval, accelerated approval, and priority review.

Accelerated approval and priority review expedite the process for vaccines that address unmet medical needs or demonstrate superior efficacy or safety compared to existing products. In the European Union (EU), vaccines can receive marketing authorization through centralized procedure or national procedures. The centralized procedure involves a single application reviewed by the EMA2, resulting in a marketing authorization valid across all EU member states.[1]

Emergency use

During public health emergencies, regulatory authorities may grant Emergency Use Authorization (EUA) to facilitate the availability of vaccines. In the United States, the FDA can issue EUAs based on the assessment of available data on safety and efficacy during emergencies like pandemics. In the EU, conditional marketing authorization allows earlier access to medicines that fulfill unmet medical needs. The WHO also has an emergency use listing procedure (EUL) that assesses the quality, safety, and efficacy of vaccines for use in emergencies.[5]

Protecting the integrity of regulatory agencies and processes

Objective evaluation of product safety and efficacy by NRAs is essential to maintain public trust and confidence. It is crucial to address conflicts of interest and prevent the politicization of public health tools. Regulatory agencies should operate independently, free from undue influence, and ensure transparency in decision-making processes.

Regulatory authorities

The CDSCO is the primary regulatory authority in India responsible for the approval, regulation, and quality control of vaccines and other medical products. The CDSCO functions under the Ministry of Health and Family Welfare and plays a pivotal role in ensuring the safety, efficacy, and quality of vaccines.[5]

Vaccine approval process

The Indian government follows a stringent approval process for vaccines. Before a vaccine can be marketed and administered to the public, it must undergo rigorous testing and evaluation. This includes preclinical studies, clinical trials, and evaluation of data on safety, efficacy, and quality. The CDSCO reviews the data submitted by vaccine manufacturers and conducts inspections of manufacturing facilities to ensure compliance with good manufacturing practices.[6]

EUA

During public health emergencies, the Indian government can grant EUA for vaccines.[5] This allows for the expedited availability of vaccines to address urgent healthcare needs. The CDSCO assesses the available data on safety and efficacy to determine the suitability of granting EUA for a particular vaccine.

Vaccine distribution and administration

The Indian government plays a crucial role in the distribution and administration of vaccines. It collaborates with various stakeholders, including state governments, healthcare providers, and vaccination centers, to ensure that vaccines are accessible to the population. The government also develops vaccination strategies, prioritizes high-risk groups, and monitors the progress of vaccination campaigns.

Post-marketing surveillance

The Indian government emphasizes post-marketing surveillance to monitor the safety and effectiveness of vaccines after they have been approved and administered. The CDSCO, along with other regulatory bodies, conducts surveillance activities to detect and investigate adverse events following vaccination (AEFIs). This helps

in identifying any potential safety concerns and taking appropriate measures to address them.[6]

International collaborations

The Indian government actively participates in international collaborations and partnerships to enhance vaccine regulation. It collaborates with organizations like the WHO and participates in initiatives such as the International Coalition of Medicines Regulatory Authorities (ICMRA) and the International Council for Harmonization (ICH). These collaborations promote information sharing, harmonization of regulatory standards, and capacity building.[7,8]

Indigenous vaccine development

The Indian government has also focused on promoting indigenous vaccine development and manufacturing capabilities. It supports research and development initiatives in the country, encourages partnerships between academia and industry, and provides financial and technical assistance to vaccine manufacturers. This emphasis on indigenous vaccine production aims to enhance self-reliance, reduce dependency on imports, and improve accessibility to vaccines.

COVAX: global efforts for equitable COVID-19 vaccine access

COVAX is an integral component of the access to COVID-19 tools (ACT) accelerator, which was initiated in April 2020 through a collaborative effort by the WHO, the European Commission, and France in response to the COVID-19 pandemic. The ACT accelerator serves as a cooperative framework aimed at expediting the development, production, and equitable distribution of COVID-19 tests, treatments, and vaccines. It comprises three main pillars: vaccines (COVAX), therapeutics, and diagnostics.

COVAX's primary objective is to ensure worldwide access to COVID-19 vaccines, regardless of individuals' economic status. The initial target is to make 2 billion vaccine doses available by the end of 2021, with a focus on safeguarding high-risk groups, vulnerable populations, and frontline healthcare workers. Jointly led by Gavi, the Coalition for Epidemic Preparedness Innovations (CEPI), and the WHO, COVAX collaborates with vaccine manufacturers from developed and developing nations.[9]

The COVAX facility continually monitors the COVID-19 vaccine landscape to identify the most suitable candidates based on scientific merit and scalability. Moreover, it incentivizes manufacturers to expand production capacity before vaccines receive regulatory approval. The Gavi COVAX Advance Market Commitment (AMC), a mechanism within the COVAX facility, ensures equitable access to COVID-19 vaccines for 92 middle- and lower-income countries unable to afford them fully, on par with higher-income self-financing nations.[10]

India, being a Gavi beneficiary, will receive a specific proportion of vaccines from the COVAX facility. Gavi, the Vaccine Alliance, established in 2000, is an international organization known as the global vaccine alliance, fostering collaboration between public and private sectors to provide equal access to new and underused vaccines for children in impoverished regions worldwide. Core partners of Gavi include the WHO, UNICEF, the World Bank, and the Bill and Melinda Gates Foundation. A new five-year strategy called 'Gavi 5.0' was approved by the Gavi Board in June 2019, aiming to ensure immunization for all and save lives by enhancing the equitable and sustainable use of vaccines. The CEPI, founded in 2017, is a global partnership with the mission to develop vaccines for preventing future epidemics. CEPI's founding members consist of the governments of Norway and India, the Bill and Melinda Gates Foundation, the Wellcome Trust, and the World Economic Forum.[11,12]

Summary

A global perspective on the regulation of vaccines provides an in-depth analysis of the regulation of vaccines worldwide, with a specific focus on the Indian perspective. The article begins by tracing the historical evolution of vaccine regulation, highlighting significant events that underscored the need for stronger regulatory systems. The regulatory framework for vaccines is discussed, emphasizing the role of NRAs in ensuring the safety, efficacy, and quality of vaccines. Examples of NRAs from various countries are provided, including the US FDA, the European Medicines Agency (EMA), and the CDSCO in India.

The WHO is recognized for its significant role in vaccine regulation through the prequalification program, which aims to ensure the quality and safety of vaccines procured for developing countries. The stages of the regulatory review process, including pre-licensure review and post-licensure surveillance, are detailed, emphasizing the importance of ongoing monitoring of vaccine safety and effectiveness. The Indian perspective in dealing with the regulation of vaccines. The CDSCO is highlighted as the primary regulatory authority responsible for approving, regulating, and ensuring the quality of vaccines in India. The stringent vaccine approval process in India is discussed, including preclinical studies, clinical trials, and evaluation of safety and efficacy data. The role of the CDSCO in granting EUA during public health emergencies is also outlined.

The Indian government's involvement in vaccine distribution, administration, and post-marketing surveillance is emphasized. Collaboration with international organizations such as the WHO, participation in initiatives like the International Coalition

of Medicines Regulatory Authorities (ICMRA) and the ICH, and the promotion of indigenous vaccine development and manufacturing capabilities are also highlighted.

The role of COVAX as a crucial part for the ACT accelerator, launched in response to the pandemic was discussed. It aims to accelerate the development, production, and equitable distribution of COVID-19 tests, treatments, and vaccines. COVAX's main goal is to ensure global access to vaccines, with a target of 2 billion doses by the end of 2021. Led by Gavi, CEPI, and WHO, COVAX collaborates with vaccine manufacturers from various countries. The facility monitors vaccine candidates and incentivizes production capacity expansion. The Gavi COVAX AMC ensures equitable vaccine access for lower-income nations. India, a Gavi beneficiary, will receive vaccines from COVAX. Gavi and CEPI are international organizations focused on vaccine access and epidemic preparedness.

Overall, the review article provides a comprehensive overview of global vaccine regulation, with a specific focus on the Indian government's perspective. It highlights the importance of regulatory authorities in ensuring the safety and efficacy of vaccines and the ongoing efforts to enhance vaccine regulation and accessibility.

CONCLUSION

The regulation of vaccines plays a vital role in protecting public health. Through a comprehensive legal framework, the involvement of NRAs, and international collaboration facilitated by organizations like the WHO, the safety, efficacy, and quality of vaccines can be ensured. By continually improving regulatory processes and maintaining the integrity of regulatory agencies, we can enhance global health security and effectively respond to public health emergencies. The ongoing dedication to vaccine regulation will contribute to a healthier and safer world for all.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Kumar N, Darshan M, Islam F. Ensuring global health: a comprehensive review of vaccine regulation with a focus on the Indian perspective. Int J Community Med Public Health 2024;11:989-93.