JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

Overview On Pharmaceutical Regulatory Agencies

Aditi S. Haval, Trupti P. Lade , Suraj H. Kolekar,
Vaishnavi K. Lad, Pranali S. Mali
Rajarambapu College of Pharmacy, Kasegaon (MS) India
Correspondence Address:
Trupti P. Lade
Assistant Professor,
Rajarambapu College of Pharmacy, Kasegaon (MS) India

Abstract: Pharmaceutical regulatory agencies play a crucial role in ensuring the safety, efficacy and quality of medicinal products. This comprehensive review provides an overview of prominent pharmaceutical regulatory agencies worldwide, including the US FDA, European Medicines Agency (EMA), Japan's PMDA, China's NMPA, India's CDSCO and Brazil's ANVISA, Therapeutic Goods Administration (TGA), Health Canada (HC),Medicines and Healthcare products Regulatory Agency(MHRA).The pharmaceutical industry is heavily regulated to ensure public safety. Regulatory agencies oversee drug development, manufacturing and distribution. Pharmaceutical regulatory agencies safeguard public health by enforcing stringent regulations. Understanding their roles, responsibilities and requirements facilitates compliance and innovation.

Keywords: Pharmaceutical regulation, Regulatory agencies, Drug approval, Global health, Public safety.

Introduction:

Pharmaceutical regulatory agencies are vital governmental bodies responsible for ensuring the safety, efficacy, and quality of pharmaceutical products, medical devices, and biologics.

These agencies play crucial role in protecting public health by regulating the development, manufacturing, marketing, and distribution of medicinal products.[1]

Through rigorous scientific evaluation, inspection and enforcement, regulatory agencies

verify compliance with stringent regulations, guidelines and standards such as Good Manufacturing practice (GMP), Good clinical practice (GCP) and Good laboratory practices (GLP).By balancing regulatory stringency with industry

innovation, these agencies facilitate the development of new medicines, therapies, and technologies, while safeguarding patients from harmful or adulterated products.

Globally, prominent regulatory agencies, including the US Food and Drug Administration (FDA), European Medicines Agency (EMA), and World Health Organization (WHO), collaborate to harmonize regulations, share best practices, and address emerging challenges, ensuring the availability of safe, effective, and high-quality pharmaceuticals worldwide.[2]

Examples of regulatory agencies:[3]

1. US Food and Drug Administration (FDA)
2. European Medicines Agency (EMA)
3. Medicines and Healthcare products Regulatory Agency (MHRA)
4. Health Canada (HC)
5. Therapeutic Goods Administration (TGA)
6. World Health Organization (WHO)
7. Pharmaceuticals and Medical Devices Agency (PMDA)
8. National Medical Products Administration (NMPA)
9. Central Drugs Standard Control Organisation (CDSCO)
10. Brazilian Health Regulatory Agency (ANVISA)

1. United state food and drug administration (USFDA)

The United States Food and Drug Administration (FDA) is a federal agency responsible for protecting public health by ensuring the safety, efficacy and security

of human and veterinary drugs, biological products, medical devices, food supply, cosmetics and radiation-emitting products.

Established in 1906, the FDA is a vital component of the US Department of Health and Human Services, with a mission to promote public health, facilitate innovation and provide accurate, science-based information. Headquartered in Silver Spring, Maryland, the FDA regulates approximately 25% of consumer spending in the US, impacting nearly every American's life. Through rigorous scientific evaluation, inspection and enforcement, the FDA safeguards the nation's health, fostering trust in the pharmaceutical and food industries.[4]

Organization of FDA

The United States Food and Drug Administration (FDA) is organized into several centers, offices and divisions to efficiently regulate and oversee various industries. Here's an overview of the FDA's organization:[5]

Centers

1. Center for Drug Evaluation and Research (CDER): regulates human drugs, including prescription and over-the-counter medications.
2. Center for Biologics Evaluation and Research (CBER): regulates biological products, including vaccines, blood and biotechnology-derived products.
3. Center for Devices and Radiological Health (CDRH): regulates medical devices, radiation-emitting electronic products and mammography facilities.
4. Center for Food Safety and Applied Nutrition (CFSAN): regulates food, dietary supplements and cosmetics.
5. Center for Veterinary Medicine (CVM): regulates animal feed, drugs and devices.

Offices

1. Office of the Commissioner: provides leadership and direction for the FDA.
2. Office of Regulatory Affairs (ORA): conducts inspections, investigations and enforcement actions.
3. Office of International Programs: coordinates international regulatory activities.

4. Office of Scientific and Professional Development: provides training and development opportunities for FDA staff.

5. Office of Women's Health: promotes women's health initiatives and research.

Divisions

1. Division of Enforcement: conducts enforcement actions, including recalls and seizures.

2. Division of Compliance: ensures compliance with FDA regulations.

3. Division of Scientific Investigations: conducts scientific investigations and research.

4. Division of Risk Management: identifies and mitigates risks associated with regulated products.

5. Division of Information Management: manages FDA's information technology and data systems.

Other Organizations

1. National Center for Toxicological Research (NCTR): conducts research on toxicology and risk assessment.

2. FDA Laboratories: provides laboratory testing and analysis support.

3. Office of Criminal Investigations (OCI): investigates criminal violations of FDA regulations.[6]

Types of application

A) Investigational New Drug (IND) Application: This application is required for experimental drugs to be tested on humans. It's essentially an exemption from the federal law requiring FDA approval before transporting or distributing drugs across state lines.

B) New Drug Application (NDA): Once sufficient evidence on a drug's safety and effectiveness is gathered, the sponsor submits an NDA for FDA approval to market the drug in the US.

c) Abbreviated New Drug Application (ANDA): This application is for generic drugs,

demonstrating bioequivalence to the innovator drug.

Biologics and Devices

a) Biologics License Application (BLA): Required for marketing biological products, such as vaccines, blood products and biotechnology-derived products.

b) Over-the-Counter (OTC) Drug Applications: For non-prescription drugs, ensuring proper labeling and safety.

c) Medical Device Applications: For clearance or approval of medical devices, including radiation-emitting products.[7]

Other Submissions

a) Drug Master Files (DMFs): Confidential submissions by drug manufacturers, containing information about facilities, processes or articles used in the manufacturing, processing, packaging and storing of drugs.

b) Electronic Regulatory Submission and Review: For submitting regulatory information electronically.[8]

Case study:

The case study's objectives are to consider FDA laws pertaining to medical devices, examine how risks associated with the devices are classified, and examine the firms' recall processes as carefully monitored by the regulatory body.

In addition, a case study was carried out to determine which medical devices were recalled in 2020, as well as to look into the cause of the recall, its consequences on the system, and potential next steps for fixing the issues.The study focused on a number of causes for the 2020 medical equipment recalls. It issues a warning to businesses and consumers to adhere to the guidelines closely during the development and testing phases of their products in order to reduce the likelihood of malfunctions with medical equipment.[9]

Link : https://www.fda.gov/

2. European Medicines Agency (EMA)

The European Medicines Agency (EMA) is a decentralized agency of the European Union

(EU), responsible for the scientific evaluation of medicines for human and veterinary use. Located in Amsterdam, the Netherlands, the EMA plays a vital role in ensuring the safety, efficacy and quality of medicinal products within the EU. Established in 1995, the agency provides independent, science-based recommendations to the European Commission, enabling informed decisions on marketing authorizations for medicines. Through rigorous assessment and monitoring, the EMA safeguards public health, promotes innovation and facilitates access to effective treatments, ultimately enhancing the well-being of patients across the EU.[10]

Organization

The European Medicines Agency (EMA) is organized into several departments, committees and working groups to efficiently regulate and oversee medicinal products within the European Union.

Departments

1. Executive Director's Office: Provides strategic leadership and oversight.
2. Human Medicines Development and Evaluation: Evaluates medicinal products for human use.
3. Veterinary Medicines and Inspections: Oversees veterinary medicines and inspections.
4. Pharmacovigilance and Risk Management: Monitors adverse events and manages risks.
5. Scientific Advice and Clinical Trials: Provides scientific guidance and oversight.
6. Regulatory Science and Innovation: Supports innovation and regulatory science.
7. Communication and Stakeholder Engagement: Facilitates communication and stakeholder engagement.

Committees

1. Committee for Medicinal Products for Human Use (CHMP): Evaluates medicines for human use.

2. Committee for Medicinal Products for Veterinary Use (CVMP): Evaluates veterinary medicines.

3. Pharmacovigilance Risk Assessment Committee (PRAC): Monitors adverse events.

4. Committee for Orphan Medicinal Products (COMP): Supports rare disease treatments.

5. Committee for Advanced Therapies (CAT): Evaluates advanced therapies.

Working Groups

1. Working Group on Quality Review: Ensures quality of medicinal products.

2. Working Group on Efficacy and Safety: Evaluates efficacy and safety.

3. Working Group on Pharmacovigilance: Monitors adverse events.

4. Working Group on Clinical Trials: Oversees clinical trials.

Scientific Advisory Groups

1. Scientific Advisory Group on Clinical Trials: Provides guidance on clinical trials.

2. Scientific Advisory Group on Pharmacovigilance: Advises on pharmacovigilance.

3. Scientific Advisory Group on Regulatory Science: Supports regulatory science.[11]

Type of application

Marketing authorization application

A request for approval filed by a pharmaceutical company to release a medication (either a brand-new drug or a generic medication) into the market. The centralised marketing authorization application (MAA) scientific examination is the responsibility of the European Medicines Agency. The centralised marketing authorization is valid in all EU member states, including Iceland, Norway,and Lichtenstein, after it has been approved by the European Commission.[12]

Case study:

The amount of medications approved for use in children as well as the number of pediatric

studies that supported the Marketing Authorization (MA) were taken into consideration while evaluating the 1995–2005 balance of EMEA operations in the field of pediatric medicines.

Techniques Information on medications approved by EMEA was taken from European Public Assessment Reports, or EPARs. Anatomical, therapeutic, and chemical (ATC) codes, indications, ages, orphan status, active ingredient, year of approval, and registrative clinical study parameters were evaluated.

Outcomes 33.3% of drugs are approved for use in pediatric patients. When distinct categories of medications were taken into account, the proportion changed either way (drugs for children under two years old, 23.4%), N-ATC code medications, and orphan medications, 46.4%). The MA dossiers for 51 medications at the time had 165 trials in total.[13]

EMA link : https://login.ema.europa.eu/

3. Medicines and Healthcare products Regulatory Agency (MHRA)

The Medicines and Healthcare products Regulatory Agency (MHRA) is the UK's regulatory authority responsible for ensuring the safety, quality and efficacy of medicines, medical devices and blood components. As an executive agency of the Department of Health and Social Care, the MHRA safeguards public health by regulating and monitoring products throughout their lifecycle, from development to patient use. Established in 2003, the MHRA's comprehensive remit encompasses licensing, inspections, enforcement and advisory functions, providing reassurance to patients, healthcare professionals and the industry. Through science-based decision-making and collaboration with international regulatory partners, the MHRA promotes innovative healthcare solutions while protecting the UK's population from harmful or ineffective products.[14]

Organization of MHRA:

1. Unitary Board of Directors: The MHRA is governed by a unitary board of directors with an equal number of executive and non-executive directors, and a non- executive chairperson.

2. Executive Committee: The executive committee, also known as the senior leadership

team, is responsible for regulatory decisions affecting medicines or medical devices.

3. Board Assurance Committees: Three board assurance committees support the board of directors.

Independent Advisory Bodies:

1. Advisory Board on the Registration of Homeopathic Products: Advises on the safety and quality of homeopathic medicines.
2. Blood Consultative Committee: Develops advice and recommendations on regulatory aspects of blood banks, blood establishments and blood processes.
3. Commission on Human Medicines: Advises ministers on the safety, efficacy and quality of medicinal products.[15]

Type of application to MHRA:

The Medicines and Healthcare products Regulatory Agency (MHRA) receives various types of applications for medicinal products, medical devices and blood components.

Medicinal Product Applications

1. Marketing Authorization Application (MAA): For new medicines.
2. Generic Medicine Application: For generic versions of authorized medicines.
3. Biosimilar Application: For biological medicines highly similar to authorized reference medicines.
4. Hybrid Medicine Application: Combining existing active substances.
5. Variation Application: Changes to authorized medicinal products.
6. Extension Application: Adding new indications or patient populations.
7. Renewal Application: Periodic reassessment of authorized medicinal products.

Medical Device Applications

1. CE Marking Application: Demonstrating compliance with EU directives.
2. Medical Device Registration: Registering medical devices with MHRA.

3. Clinical Investigation Application: Approving clinical trials for medical devices.
4. Design Dossier Application: Submitting detailed design information.

Blood Component Applications

1. Blood Establishment Authorization: Licensing blood banks and establishments.
2. Blood Component Registration: Registering blood components.
3. Blood Product License Application: Authorizing blood products.[16]

Case study of MHRA:

Context In recent years, the field of digital mental health has experienced exponential expansion. The body of evidence has grown significantly, but the acceptance of this evidence within health and care services has been hampered by a number of issues, one of which is that academics are not well-versed in navigating the process for obligatory regulatory clearance. This document outlines the procedures that a group must follow in order to obtain the necessary clearances in order to conduct a study employing a cutting-edge digital mental health intervention. As a practical example, we employed a randomized controlled trial of a digital mental health intervention known as STOP (Successful Treatment of Paranoia).
Techniques The two primary goals needed to get regulatory clearance (MHRA Notification of No Objection) are explained in the techniques section.[17]

MHRA link: https://www.gov.uk/government/organisations/medicines- and-healthcare-products-regulatory-agency

4. Health Canada (HC)

Health Canada is the federal department responsible for helping Canadians maintain and improve their health. The Health Canada Regulatory Agency, also known as the Therapeutic Products Directorate, ensures that pharmaceuticals, biologics, medical

devices and natural health products available in Canada are safe, effective and of high quality.[18]

Organization

Health Canada's Regulatory Agency is organized into several branches and directorates to

efficiently regulate therapeutic products, medical devices and natural health products.

Branches:

1. Therapeutic Products Directorate (TPD): Regulates pharmaceuticals, biologics and medical devices.

2. Natural and Non-Prescription Health Products Directorate (NNHPD): Regulates natural health products, cosmetics and non-prescription medications.

3. Medical Devices Bureau (MDB): Regulates medical devices.

4. Biologics and Genetic Therapies Directorate (BGTD): Regulates biologics, vaccines and genetic therapies.Compliance and Enforcement Branch: Ensures industry compliance with regulations.

Directorates:

1. Regulatory Operations and Enforcement Directorate

2. Scientific Advisory and Regulatory Affairs Directorate

3. Policy and Strategic Planning Directorate

4. International Regulatory Affairs Directorate

5. Clinical Trials and Research Directorate

Offices:

1. Office of Clinical Trials

2. Office of Regulatory Affairs

3. Office of Science and Research

4. Office of Compliance and Enforcement

5. Office of International Regulatory Cooperation

Advisory Committees:

1. Scientific Advisory Committee on Pharmaceutical Sciences and Clinical Pharmacology

2. Advisory Committee on Medical Devices
3. Natural Health Products Advisory Committee
4. Biologics and Genetic Therapies Advisory Committee.

Type of application:

Health Canada receives various types of applications for therapeutic products, medical devices, natural health products and cosmetics.

Therapeutic Products

1. New Drug Submission (NDS): For new pharmaceuticals.
2. Supplemental New Drug Submission (SNDS): For changes to approved pharmaceuticals.
3. Abbreviated New Drug Submission (ANDS): For generic pharmaceuticals.
4. Biosimilar Submission: For biological medicines.
5. Clinical Trial Application (CTA): For conducting clinical trials.
6. Medical Device Licence Application: For medical devices.

Medical Devices

1. Medical Device Licence Application: For Class II, III and IV devices.
2. Medical Device Certificate Application: For Class I devices.
3. Clinical Trial Application (CTA): For medical device trials.
4. Medical Device Amendment Application: For changes to licensed devices.

Natural Health Products

1. Product Licence Application: For natural health products.
2. Site Licence Application: For manufacturing and packaging sites.
3. Clinical Trial Application (CTA): For natural health product trials.
4. Amendment Application: For changes to licensed products.

Cosmetics

1. Cosmetic Notification Form: For cosmetic products.

2. Cosmetic Ingredient Listing: For cosmetic ingredients.

Other Applications

1. Establishment Licence Application: For pharmaceutical and medical device manufacturers.

2. ood Manufacturing Practice (GMP) Certificate Application: For pharmaceutical manufacturers.

3. Foreign Site Reference Number (FSRN) Application: For foreign manufacturers.

4. Orphan Drug Designation Application: For rare disease treatments.

5. Pediatric Investigation Plan (PIP) Application: For pediatric populations. [19]

Case study:

The first five years of Canada's experience with Diane-35 (cyproterone acetate and ethinyl estradiol) is a case study in regulatory failure, if the goal of federal regulation of prescription pharmaceuticals is to safeguard public health and to encourage safe, effective, and informed medicine use. An analysis of the circumstances behind this failure serves as an illustration of the necessity for modifications to Canada's federal drug laws.

This document spans the time frame from late 2003's pre-market application to the first five years following license. The evidence supporting regulatory decisions both pre- and post-approval was examined through a systematic examination of the studies submitted to Health Canada in order to secure regulatory approval and a review of later published research.[20]

Link of health Canada: https://www.canada.ca/en/health-canada.html

5. Therapeutic Goods Administration (TGA)

The Therapeutic Goods Administration (TGA) is Australia's regulatory authority responsible for ensuring the safety, quality and efficacy of therapeutic goods, including medicines, medical devices, blood and blood components, and

biologicals. As a division of the Australian Department of Health, the TGA safeguards public health by regulating and monitoring products throughout their lifecycle, from development to patient use. Established in 1989.[21] Organization of TGA :

The Therapeutic Goods Administration (TGA) is organized into several divisions and branches to efficiently regulate therapeutic goods in Australia.

Organizational Structure

1. Office of the Delegate: Provides strategic leadership and oversight.
2. Regulatory Operations Division: Responsible for pre-market assessment, compliance and enforcement.
3. Safety and Surveillance Division: Monitors adverse events, recalls and post- market activities.
4. Scientific Evaluation Division: Conducts scientific assessments of therapeutic goods.
5. Compliance and Enforcement Division: Ensures industry compliance with regulations.
6. International and Technical Relations Division: Facilitates international cooperation and harmonization.
7. Corporate Services Division: Provides administrative support.

Branches

1. Medicines Branch: Regulates prescription and over-the-counter medicines.
2. Medical Devices Branch: Regulates medical devices and in vitro diagnostic devices.
3. Blood and Blood Components Branch: Regulates blood and blood components.
4. Biologicals and Cell Therapies Branch: Regulates biologicals, cell therapies and gene therapies.
5. Complementary Medicines Branch: Regulates complementary medicines.

Advisory Committees

1. Advisory Committee on Medicines (ACM): Provides expert advice on medicines.
2. Advisory Committee on Medical Devices (ACMD): Provides expert advice on medical devices.
3. Advisory Committee on Blood and Blood Components (ACBBC): Provides expert advice on blood and blood components.

4. Advisory Committee on Complementary Medicines (ACCM): Provides expert advice on complementary medicines.[22]

Types of application:

The Therapeutic Goods Administration (TGA) receives various types of applications for therapeutic goods, including medicines, medical devices, blood and blood components, and biologicals.

Therapeutic Goods Applications

1. New Medicine Application: For new prescription or over-the-counter medicines.
2. Generic Medicine Application: For generic versions of approved medicines.
3. Biosimilar Application: For biological medicines highly similar to approved reference medicines.
4. Medical Device Application: For Class I, II, III or IV medical devices.
5. Blood and Blood Component Application: For blood and blood components.
6. Biological Application: For biologicals, cell therapies and gene therapies.
7. Complementary Medicine Application: For complementary medicines. Variation Applications

1. Minor Variation Application: For minor changes to approved therapeutic goods.
2. Major Variation Application: For significant changes to approved therapeutic goods.
3. Extension Application: For adding new indications or patient populations. Clinical Trial Applications

1. Clinical Trial Notification (CTN) Scheme: For conducting clinical trials.
2. Clinical Trial Approval (CTA) Scheme: For conducting clinical trials requiring TGA approval.

Other Applications

1. Establishment Licence Application: For manufacturing and supplying therapeutic goods.
2. Good Manufacturing Practice (GMP) Certificate Application: For pharmaceutical manufacturers.
3. Sponsorship Application: For sponsors of therapeutic goods.
4. Orphan Drug Designation Application: For rare disease treatments.

5. Priority Review Application: For expedited review of therapeutic goods.[23]

Case study:

The public, medical experts, and policy makers all generally agree that new medications always result in treatment innovations and improved health outcomes. The purpose of this study is to compare two categorization methods to assess the therapeutic value of newly marketed medications in Australia.

Methodology: The Australian Therapeutics Goods Administration (TGA) classified all approvals for new medications between 2005 and 2007 based on their therapeutic value using the Motola's and Ahlqvist-Rastad's methods.

Based on the Prescribe review papers and Public Summary Documents, the three writers independently assigned scores.

Findings: A total of 217 recommendations for approval were made, 81 (37.3%) for new indications and 69 (31.8%) for new medications. Of the 59 medications, 31 (52.5%) were graded using Motola's rating approach.[24]

TGA link: https://www.tga.gov.au/therapeutic-goods-administration-tga

6. World Health Organization (WHO)

The World Health Organization (WHO) is a specialized agency of the United Nations responsible for international public health. Established in 1948, WHO promotes health, keeps the world safe and serves the vulnerable through its leadership on global health matters.[25]

Organization of WHO :

The World Health Organization (WHO) is a specialized agency of the United Nations that promotes health and safety globally. Its organizational structure is divided into several key components.

Governance Structure

The WHO is governed by the World Health Assembly (WHA), comprising 194 member states that elect an Executive Board of 34 health specialists The WHO sets goals, priorities

and approves the budget and activities.

Key Divisions

- Director-General's Office: Provides strategic leadership.
- Executive Board: Advises and oversees WHO's work.
- Regional Offices: Six regional offices worldwide, including Africa, Americas, South-East Asia, Europe, Eastern Mediterranean and Western Pacific.
- Country Offices: Over 150 offices globally.

Departments and Programs

- Health Systems and Innovation: Strengthens health systems.
- Health Security and Preparedness: Responds to emergencies.
- Family, Women, Children and Adolescents: Focuses on maternal and child health.
- Communicable Diseases: Addresses diseases like HIV/AIDS, malaria and tuberculosis.
- Non-Communicable Diseases: Tackles conditions like cancer and heart disease.[26]

Types of application:

The World Health Organization (WHO) receives various applications across different programs and departments. Here are some examples:

Programmatic Applications

1. Global Health Programme Applications
2. Disease-Specific Applications (e.g., HIV/AIDS, malaria, tuberculosis)
3. Health System Strengthening Applications
4. Health Emergency Response Applications
5. Research and Development Applications

Regulatory Applications

1. Pre-Qualification Applications (medicines and vaccines)
2. Medical Device Applications (certification)
3. Pharmaceutical Product Applications (registration and certification)
4. Clinical Trial Applications (approval)
5. Good Manufacturing Practice (GMP) Certificate Applications Partnership and Collaboration Applications

1. Collaborating Centre Applications
2. Partnership Applications (collaborative partnerships)
3. Membership Applications (advisory committees)
4. Observer Applications (non-governmental organizations) Funding and Grant Applications

1. Global Fund Applications (HIV/AIDS, tuberculosis and malaria)
2. WHO Fellowship Applications (research fellowships)
3. Technical Assistance Applications (health system development)
4. Grant Applications (specific health projects) International Health Regulations (2005) Applications

1. National IHR Core Capacity Applications
2. Event Reporting Applications (public health emergencies)
3. IHR Implementation Applications Medical Product Applications

1. Essential Medicines List Applications
2. Vaccine Pre-Qualification Applications
3. Medical Device Registration Applications
4. Pharmaceutical Product Registration Applications

Research and Development Applications

1. Research Proposal Applications
2. Clinical Trial Protocol Applications
3. Investigational New Drug (IND) Applications Electronic Submission

WHO accepts electronic submissions through:

1. WHO's online portal
2. Electronic Application System (EAS)
3. Common Technical Document (CTD) format.[27]

Case study of WHO:

In low-resource settings, the World Health Organization's (WHO) case definition for children pneumonia, which consists of basic clinical symptoms including coughing, breathing difficulties, and rapid breathing, is frequently used to direct the treatment of acute respiratory infections. Additionally, the term is frequently employed as an endpoint or entry criterion in several intervention and disease burden studies.

Techniques: A retrospective review of clinical and laboratory data, such as C- reactive protein concentration and chest radiograph findings, was carried out by a group of pediatricians on Filipino hospitalized children at Bohol Regional Hospital who were part of a pneumococcal vaccine efficacy study and had a respiratory episode that met the WHO case definition for clinical pneumonia. Our objective was to assess whether disease entities are genuinely captured by the WHO.[28]

WHO link: https://www.who.int/

7. Pharmaceuticals and Medical Devices Agency (PMDA)

The Pharmaceuticals and Medical Devices Agency (PMDA) is Japan's regulatory authority responsible for ensuring the safety, efficacy and quality of pharmaceuticals, medical devices and other healthcare products.[29]

Organization of PMDA

The Pharmaceuticals and Medical Devices Agency (PMDA) in Japan has the following

organizational structure:

Governance

1. Minister of Health, Labour and Welfare: Oversees PMDA's activities.
2. PMDA President: Leads the organization.
3. PMDA Board: Provides strategic guidance.

Departments

1. Pharmaceuticals and Medical Devices Evaluation Department: Evaluates new pharmaceuticals and medical devices.
2. Safety Division: Monitors adverse reactions and conducts post-marketing surveillance.
3. Inspection and Compliance Division: Conducts inspections and ensures compliance.
4. International Affairs Division: Collaborates with international regulatory agencies.
5. Clinical Trial Department: Evaluates clinical trial applications.
6. Medical Device Certification Department: Certifies medical devices.
7. Pharmaceutical Affairs Department: Handles pharmaceutical-related affairs.

Divisions

1. New Drug Evaluation Division: Evaluates new pharmaceuticals.
2. Generic Drug Evaluation Division: Evaluates generic pharmaceuticals.
3. Medical Device Evaluation Division: Evaluates medical devices.
4. Biologicals and Vaccines Division: Evaluates biologicals and vaccines.
5. Pharmacovigilance Division: Monitors adverse reactions.
6. Good Manufacturing Practice (GMP) Division: Ensures GMP compliance.
7. Good Clinical Practice (GCP) Division: Ensures GCP compliance.

Offices

1. Tokyo Office: Headquarters.
2. Osaka Office: Western Japan regional office.
3. Nagoya Office: Central Japan regional office.

Centers

1. Center for Pharmaceutical and Medical Device Evaluation: Conducts evaluations.
2. Center for Clinical Trial Information: Manages clinical trial data.
3. Center for Post-Market Surveillance: Monitors adverse reactions.

Committees

1. Pharmaceuticals and Medical Devices Advisory Committee: Provides expert advice.
2. Clinical Trial Advisory Committee: Provides expert advice on clinical trials.[30]

Type of application

The Pharmaceuticals and Medical Devices Agency (PMDA) in Japan receives various types of applications related to pharmaceuticals, medical devices and cosmetics.

Pharmaceutical Applications

1. New Drug Applications (NDA)
2. Generic Drug Applications
3. Biosimilar Applications
4. Vaccine Applications
5. Pharmaceutical Variation Applications
6. Clinical Trial Applications (CTA)
7. Investigational New Drug (IND) Applications Medical Device Applications

1. Medical Device Certification Applications
2. Medical Device Registration Applications
3. Medical Device License Applications

4. In Vitro Diagnostic (IVD) Device Applications

5. Medical Device Clinical Trial Applications

Cosmetic Applications

1. Cosmetic Notification Applications

2. Cosmetic Ingredient Listing Applications

3. Cosmetic Product Registration Applications Regulatory Applications

1. Good Manufacturing Practice (GMP) Certification Applications

2. Good Clinical Practice (GCP) Certification Applications

3. Good Laboratory Practice (GLP) Certification Applications

4. Pharmaceutical Inspectorate Applications Post-Market Surveillance Applications

1. Adverse Event Reporting Applications

2. Recall and Safety Alert Applications

3. Post-Market Clinical Follow-up (PMCF) Applications International Applications

1. Mutual Recognition Procedure (MRP) Applications

2. Decentralized Procedure (DCP) Applications

3. Centralized Procedure (CP) Applications[31]

Case study :

Japan's Pharmaceuticals and Medical Devices Agency (PMDA) requires marketing authorization holders (MAHs) to report adverse events (AEs) to them within 15 days, sometimes even 30 days.

Techniques: Sixty-one reports for five different kinds of cardiovascular devices were obtained in order to examine the promptness of AE reporting to the PMDA. Two timestamps were computed: (1) the interval between the AE occurrence date and the MAH capture date (DOC: days); and (2) the interval between the MAH capture date and the MAH report date (DCR: days).

Calculations were also made for the number of DOC N 15 days (DOC15) and delayed reports (DCR N 15 or 30 days).

Findings: 9.2% of AEs resulted in fatalities, and 7.5% in non-recoveries. 51.0% and 10.9%, respectively, of reports were DOC15 and delayed.[32]

PMDA link : https://www.pmda.go.jp/english/

8. National Medical Products Administration (NMPA)

The National Medical Products Administration (NMPA), formerly the China Food and Drug Administration (CFDA), is China's regulatory authority responsible for overseeing medical products, including pharmaceuticals, medical devices, and cosmetics. Established in 2018, NMPA ensures the safety, efficacy, and quality of medical products through rigorous evaluation, inspection, and monitoring.[33]

Organization of NMPA:

The National Medical Products Administration (NMPA) in China has a complex organizational structure, with various departments and affiliated institutions.

Leadership Structure

The NMPA is led by Commissioner Li Li, who is also the Secretary of the NMPA Leading Party Members' Group . The other key leaders include Deputy Commissioners Xu Jinghe, Zhao Junning, Huang Guo, and Lei Ping.

Departments

Some of the key departments within the NMPA include:

- Department of Comprehensive Affairs, Planning, and Finance Affairs: responsible for routine operations, information, security, and statistics.
- Department of Policies and Regulations: conducts research on policies for drug, medical device, and cosmetic regulation.
- Department of Drug Registration: oversees drug registration, Chinese Pharmacopoeia, and drug standards.

- Department of Medical Device Registration: responsible for medical device standards, classification, and registration.

- Department of Cosmetics Regulation: regulates cosmetic products

- Department of Science, Technology and International Cooperation: handles international cooperation, scientific research, and technological development.[34]

Type of application :

The National Medical Products Administration (NMPA) in China receives various types of applications related to pharmaceuticals, medical devices and cosmetics.

Pharmaceutical Applications

1. New Drug Applications (NDA)
2. Generic Drug Applications
3. Biosimilar Applications
4. Vaccine Applications
5. Pharmaceutical Variation Applications
6. Clinical Trial Applications (CTA)
7. Investigational New Drug (IND) Applications
8. Import Drug Applications
9. Domestic Drug Applications Medical Device Applications

1. Medical Device Registration Applications
2. Medical Device Certification Applications
3. In Vitro Diagnostic (IVD) Device Applications
4. Medical Device Clinical Trial Applications
5. Medical Device Import Applications
6. Domestic Medical Device Applications Cosmetic Applications

1. Cosmetic Registration Applications
2. Cosmetic Notification Applications
3. Cosmetic Ingredient Listing Applications
4. Cosmetic Product Registration Applications
5. Import Cosmetic Applications
6. Domestic Cosmetic Applications Regulatory Applications

1. Good Manufacturing Practice (GMP) Certification Applications
2. Good Clinical Practice (GCP) Certification Applications
3. Good Laboratory Practice (GLP) Certification Applications
4. Pharmaceutical Inspectorate Applications Post-Market Surveillance Applications

1. Adverse Event Reporting Applications
2. Recall and Safety Alert Applications
3. Post-Market Clinical Follow-up (PMCF) Applications International Applications

1. Mutual Recognition Procedure (MRP) Applications
2. Decentralized Procedure (DCP) Applications
3. Centralized Procedure (CP) Applications[35]

Case study of NMPA:

The first monoclonal antibody for treating postmenopausal women with osteoporosis who are at high risk of fractures was approved by the National Medical Products Administration (NMPA) in the People's Republic of China on June 23, 2020. The drug is called denosumab, or Prolia®. With the implied meaning of "to give strength to everyone," its brand name in Chinese is 普罗力, a transliteration of the English name "Prolia" and a fitting moniker for a strong anti-resorptive therapy. The approval was backed by a novel marketing authorization application (MAA) that contained information from Prolia's global clinical trial program demonstrating favorable efficacy and safety, as well as findings from a real-world evidence

(RWE)

study verifying Prolia's efficacy and safety in Taiwanese and Hong Kong clinical practice. [36]

NMPA link: https://english.nmpa.gov.cn/

9. Central Drugs Standard Control Organisation (CDSCO)

The Central Drugs Standard Control Organisation (CDSCO) is India's national regulatory authority for Indian pharmaceuticals, medical devices and cosmetics. Established in 1948, CDSCO ensures the safety, efficacy and quality of drugs, medical devices and cosmetics. [37]

Organization

The Central Drugs Standard Control Organisation (CDSCO) in India has a structured organization to regulate pharmaceuticals, medical devices and cosmetics.

1. Director General of Health Services (DGHS): Highest authority, responsible for overall policy and guidance.

2. Drugs Controller General of India (DCGI): Head of CDSCO, responsible for regulatory decisions.

3. Central Drugs Standard Control Organization: Main regulatory body, divided into:

1. Headquarters: New Delhi

2. Zonal Offices: 4 zones (North, South, East, West)

3. Sub-Zonal Offices: 14 sub-zones

4. State Drug Controllers: Implement regulations at state level

Departments

1. Drugs Division: Regulates pharmaceuticals, including approvals, inspections and enforcement.

2. Medical Devices Division: Regulates medical devices, including certification,

registration and standards.

3. Cosmetics Division: Regulates cosmetics, including registration, notification and standards.

4. Inspection and Enforcement Division: Conducts inspections, enforces regulations and monitors compliance.

5. Standard Setting Division: Develops and maintains Indian Pharmacopoeia, drug standards and medical device standards.

6. Clinical Trials Division: Regulates clinical trials, including approvals and monitoring.

7. International Cooperation Division: Collaborates with international regulatory agencies.

Committees

1. Drugs Technical Advisory Board (DTAB): Advisory body on pharmaceutical regulations.

2. Medical Devices Technical Advisory Board: Advisory body on medical device regulations.

3. Cosmetics Technical Advisory Board: Advisory body on cosmetic regulations.[38]

Type of application :

The Central Drugs Standard Control Organisation (CDSCO) in India receives various types of applications related to pharmaceuticals, medical devices and cosmetics.

Pharmaceutical Applications

1. New Drug Applications (NDA)

2. Generic Drug Applications

3. Biosimilar Applications

4. Vaccine Applications

5. Pharmaceutical Variation Applications

6. Clinical Trial Applications (CTA)
7. Investigational New Drug (IND) Applications
8. Import Drug Applications
9. Domestic Drug Applications
10. Drug Manufacturing License Applications

Medical Device Applications

1. Medical Device Registration Applications
2. Medical Device Certification Applications
3. In Vitro Diagnostic (IVD) Device Applications
4. Medical Device Clinical Trial Applications
5. Medical Device Import Applications
6. Domestic Medical Device Applications
7. Medical Device Manufacturing License Applications Cosmetic Applications

1. Cosmetic Registration Applications
2. Cosmetic Notification Applications
3. Cosmetic Ingredient Listing Applications
4. Cosmetic Product Registration Applications
5. Import Cosmetic Applications
6. Domestic Cosmetic Applications Regulatory Applications

1. Good Manufacturing Practice (GMP) Certification Applications
2. Good Clinical Practice (GCP) Certification Applications
3. Good Laboratory Practice (GLP) Certification Applications
4. Pharmaceutical Inspectorate Applications

Post-Market Surveillance Applications

1. Adverse Event Reporting Applications
2. Recall and Safety Alert Applications
3. Post-Market Clinical Follow-up (PMCF) Applications International Applications

1. Mutual Recognition Procedure (MRP) Applications
2. Decentralized Procedure (DCP) Applications
3. Centralized Procedure (CP) Applications [39]

Case study

The spontaneous adverse drug reaction (ADR) reporting form is an essential instrument for gathering data on ADRs, assisting in the creation of a signal and the establishment of the causative assessment. This can be achieved if health care professionals (HCPs) transcribe high-quality data into the reporting form.

Therefore, the purpose of the current study was to assess how well HCPs translated potentially dangerous drug information from spontaneous reporting forms, as well as to compare the length of pharmacovigilance training across various nations and the ADR reporting forms used. Approaches: Fifty physicians, fifty nurses, and fifty pharmacists participated in a cross-sectional research whereby they were requested to complete several reporting forms (Medwatch, CDSCO form, Yellow card, and Blue form) with various simulated ADR case reports. Forms that were completed were examined for information and content.[40]

Link : https://cdsco.gov.in/opencms/opencms/en/Home/

10. Brazilian Health Regulatory Agency (ANVISA)

The Brazilian Health Regulatory Agency (ANVISA) is Brazil's national regulatory authority for health products, including pharmaceuticals, medical devices, cosmetics and food. [41]

Organization :

The Brazilian Health Regulatory Agency (ANVISA) is an autonomous agency linked to the Ministry of Health, responsible for regulating health products and services in Brazil. Its organization structure includes:

- Collegiate Board of Directors: A 5-member board that oversees the agency's activities.
- Thematic Directorates: Five directorates that focus on specific areas, such as pharmaceuticals, medical devices, and cosmetics.
- Oversight Structure: A 5-tier system that ensures accountability and transparency.
- General Office of Medical Devices Technology: A department specifically dedicated to regulating medical devices.
- Departments: ANVISA has various departments, including Pharmaceuticals, Medical Devices, Cosmetics, Food, and Inspections.[42]

Type of application:

The Brazilian Health Regulatory Agency (ANVISA) receives various types of applications related to health products and services.

Pharmaceutical Applications

1. New Drug Applications (NDA)
2. Generic Drug Applications
3. Biosimilar Applications
4. Vaccine Applications
5. Pharmaceutical Variation Applications
6. Clinical Trial Applications (CTA)
7. Investigational New Drug (IND) Applications
8. Import Drug Applications
9. Domestic Drug Applications
10. Drug Manufacturing License Applications Medical Device Applications

1. Medical Device Registration Applications

2. Medical Device Certification Applications
3. In Vitro Diagnostic (IVD) Device Applications
4. Medical Device Clinical Trial Applications
5. Medical Device Import Applications
6. Domestic Medical Device Applications
7. Medical Device Manufacturing License Applications Cosmetic Applications

1. Cosmetic Registration Applications
2. Cosmetic Notification Applications
3. Cosmetic Ingredient Listing Applications
4. Cosmetic Product Registration Applications
5. Import Cosmetic Applications
6. Domestic Cosmetic Applications Food Applications

1. Food Registration Applications
2. Food Notification Applications
3. Food Ingredient Listing Applications
4. Food Product Registration Applications
5. Import Food Applications
6. Domestic Food Applications Regulatory Applications

1. Good Manufacturing Practice (GMP) Certification Applications
2. Good Clinical Practice (GCP) Certification Applications
3. Good Laboratory Practice (GLP) Certification Applications

4. Pharmaceutical Inspectorate Applications Post-Market Surveillance Applications

1. Adverse Event Reporting Applications

2. Recall and Safety Alert Applications

3. Post-Market Clinical Follow-up (PMCF) Applications. [43]

Case study :

The pharmaceutical industries are nonetheless susceptible to producing medications with quality variations, resulting in marketed items that fall short of the acceptable standards and need to be recalled from the market. This is true even with the greatest care used during the production process. This study's goal was to assess the factors that contributed to Brazil's medication recall throughout the time under review.

Methods This is a descriptive study on the recall of subpar medications listed on the National Health Surveillance Agency (ANVISA) website from 2010 to 2018, conducted through document analysis. The types of pharmaceutical dosage forms (solid, liquid, semi-solid, and parenteral preparation), the kind of medication (reference, generic, similar, specific, biological, herbal, simplified notification, novel, and radiopharmaceutical), and the cause for recall were the factors examined.[44]

Link : https://antigo.anvisa.gov.br/en/english

References :

1. Maggetti, M. (2010). Legitimacy and Accountability of Independent Regulatory Agencies: A Critical Review. *Living Reviews in Democracy*, *2*.

2. Christensen, T., & Lægreid, P. (2007). Regulatory agencies—The challenges of balancing agency autonomy and political control. *Governance*, *20*(3), 499-520.

3. Christensen, T., & Lægreid, P. (2007). Regulatory agencies—The challenges of balancing agency autonomy and political control. *Governance*, *20*(3), 499-520.

4. Meesters, R., & Voswinkel, S. (2018). Bioanalytical method development and validation: from the USFDA 2001 to the USFDA 2018 guidance for industry. *J. Appl.*

Bioanal, *4*(3), 67-73.

5. Kumar, T. S., & Kamaraj, R. (2024). Compliance challenges in clinical research organizations: A USFDA inspection retrospective. *Journal of Pharmacy & Pharmacognosy Research*, *12*(1), 91-98.

6. Sharma, A., Gamta, V., & Luthra, G. (2023). Regulatory Compliance in the United States: A Comprehensive Analysis of USFDA Guidelines and Implementation Strategies. *Journal of Pharmaceutical Research International*, *35*(17), 41-50.

7. Holbein, M. B. (2009). Understanding FDA regulatory requirements for investigational new drug applications for sponsor-investigators. *Journal of investigative medicine*, *57*(6), 688-694.

8. Enforcement, A. (2020). FDA.

9. Kamisetti, R. R. (2022). Regulatory control on medical devices-A case study on device recalls by USFDA. *Journal of Intellectual Property Rights (JIPR)*, *27*(3), 190-201.

10. Pignatti, F., Gravanis, I., Herold, R., Vamvakas, S., Jonsson, B., & Marty, M. (2011). The European Medicines Agency: an overview of its mission, responsibilities, and recent initiatives in cancer drug regulation. *Clinical Cancer Research*, *17*(16), 5220-5225.

11. Kingham, R. F., Bogaert, P. W., & Eddy, P. S. (1994). The New European Medicines Agency. *Food & Drug LJ*, *49*, 301.

12. Flynn, R., Plueschke, K., Quinten, C., Strassmann, V., Duijnhoven, R. G., Gordillo-Marañon, M., ... & Kurz, X. (2022). Marketing authorization applications made to the European medicines agency in 2018–2019: what was the contribution of real-world evidence?. *Clinical Pharmacology & Therapeutics*, *111*(1), 90-97.

13. Ceci, A., Felisi, M., Baiardi, P., Bonifazi, F., Catapano, M., Giaquinto, C., ... & Wong, I. (2006). Medicines for children licensed by the European Medicines Agency (EMEA): the balance after 10 years. *European journal of clinical pharmacology*, *62*, 947-952..

14. Richards, N., & Hudson, I. (2016). UK medicines regulation: responding to current challenges. *British Journal of Clinical Pharmacology*, *82*(6), 1471-1476.

15. Aziza, F. N. Review and Comparison of Food Drug Administration (FDA) and Medicines and Healthcare products Regulatory Agency (MHRA) on Good Manufacturing Practice (GMP) Implementation. *Majalah Farmaseutik*, *18*(2), 236- 240.

16. Aziza, F. N. Review and Comparison of Food Drug Administration (FDA) and Medicines and Healthcare products Regulatory Agency (MHRA) on Good Manufacturing Practice (GMP) Implementation. *Majalah Farmaseutik*, *18*(2), 236- 240.

17. Pariente, A., Daveluy, A., Laribière-Bénard, A., Miremont-Salame, G., Begaud, B., & Moore, N. (2009). Effect of date of drug marketing on disproportionality measures in pharmacovigilance: the example of suicide with SSRIs using data from the UK MHRA. *Drug safety*, *32*, 441-447.

18. Douglas, V. (2013). *Introduction to Aboriginal health and health care in Canada: bridging health and healing*. Springer Publishing Company.

19. Sass, R. (1989). The implications of work organization for occupational health policy: The case of Canada. *International Journal of Health Services*, *19*(1), 157-173.

20. Abelson, J. (2001). Understanding the role of contextual influences on local health-care decision making: case study results from Ontario, Canada. *Social Science & Medicine*, *53*(6), 777-793.

21. McEwan, J. (2007). *A history of therapeutic goods regulation in Australia* (pp. 45-50). Canberra, Australia: Therapeutic Goods Administration.

22. Lexchin, J. (2022). Use of priority and provisional approval pathways by the Australian Therapeutic Goods Administration in approving new medicines: a cross-sectional study. *Australian Health Review*, *46*(3), 309-315.

23. Etheridge, M. L., Campbell, S. A., Erdman, A. G., Haynes, C. L., Wolf, S. M., & McCullough, J. (2013). The big picture on nanomedicine: the state of investigational and approved nanomedicine products. *Nanomedicine: nanotechnology, biology and medicine*, *9*(1), 1-14.

24. Jones, C. M., Shaheed, C. A., Ferreira, G., Mannix, L., Harris, I. A., Buchbinder, R., & Maher, C. G. (2022). Spinal cord stimulators: an analysis of the adverse events reported to the Australian therapeutic goods administration. *Journal of Patient Safety*, *18*(5), 507-511.

25. World Health Organization. (2007). Working for health: an introduction to the World Health Organization.

26. WHO, C. O. (2020). World health organization. *Air Quality Guidelines for Europe*, (91).

27. Taylor, A. L. (1992). Making the World Health Organization work: a legal framework for universal access to the conditions for health. *American Journal of Law & Medicine*, *18*(4), 301-346.

28. Klarner, P., Probst, G., & Soparnot, R. (2008). Organizational change capacity in public services: The case of the World Health Organization. *Journal of change management*,

8(1), 57-72.

29. Kuribayashi, R., Nakano, A., Hariu, A., Kishioka, Y., & Honda, F. (2023). Historical overview of regulatory approvals and PMDA assessments for biosimilar products in Japan during 2009–2022. *BioDrugs*, *37*(4), 443-451.

30. Nishiyama, K., Toyoshima, S., Yamada, H., Suzuki, H., & Nagai, N. (2018). Relationship between the review time and various PMDA consultations in recent new drug approval cases in Japan. *Therapeutic Innovation & Regulatory Science*, *52*(6), 731-738.

31. Mori, K., & Toyoshima, S. (2009). Recent approaches by the PMDA to promoting new drug development: change in the status of the PMDA in relation to new drug development over the last five years. *Drug Information Journal*, *43*(1), 47-55.

32. Hamada, S., Shibata, A., Urushihara, H., Sengoku, S., Suematsu, C., & Kawakami, K. (2014). Transaction cost analysis of the new drug application process: A case study of a multinational pharmaceutical company in
Japan. *Therapeutic Innovation & Regulatory Science*, *48*(3), 371-377.

33. An, S., Wang, L., Xie, F., Jiang, D., Huang, G., Liu, J., ... & Wei, W. (2024). Pathway to approval of innovative radiopharmaceuticals in China. *Journal of Nuclear Medicine*, *65*(Supplement 1), 72S-76S.

34. Li, W., & Chen, J. (2021). Institutional framework for the management of human genetic resources in China. *Human Gene Therapy*, *32*(23-24), 1495-1500.

35. Zhao, Q., Han, Z., Wang, J., & Han, Z. (2021). Development and investigational new drug application of mesenchymal stem/stromal cells products in China. *Stem cells translational medicine*, *10*, S18-S30.

36. Storm, N. E., Chang, W., Lin, T. C., Lange, J. L., Bradbury, B., Critchlow, C. W., & Galson, S. K. (2022). A novel case study of the use of real-world evidence to support the registration of an osteoporosis product in China. *Therapeutic Innovation & Regulatory Science*, *56*, 137-144.

37. Sharma, A. K., Shrivastava, T. P., Singh, M. A., Ahuja, J., & Goyal, R. K. (2024). Regulations in India. In *Global Regulations of Medicinal, Pharmaceutical, and Food Products* (pp. 133-152). CRC Press.

38. Evangeline, L., Mounica, N. V. N., Reddy, V. S., Ngabhushanam, M. V., Reddy, D. N., & Bonthagarala, B. (2017). Regulatory process and ethics for clinical trials in India (CDSCO). *The Pharma Innovation*, *6*(4, Part C), 165.

39. Chaudhury, R. R., & Mehta, D. (2016). Regulatory developments in the conduct of clinical trials in India. *Global Health, Epidemiology and Genomics*, *1*, e4.

40. Kumar, A. (2018). Pharmacovigilance and Adverse Drug Reaction (ADR): A case study. *International Journal of Research in Informative Science Application & Techniques (IJRISAT)*, *2*(1), 28-41.

41. Huynh-Ba, K., & Beumer Sassi, A. (2018). ANVISA: an introduction to a new regulatory agency with many challenges. *Aaps Open*, *4*(1), 9.

42. Peres, K. C., Buendgens, F. B., Prates, E. A., Bonetti, N. R., Soares, L., Vargas-Peláez, C. M., & Farias, M. R. (2021). Vaccines in Brazil: historical analysis of the Sanitary registration and vaccine availability in the Brazilian Unified Health System. *Ciência & Saúde Coletiva*, *26*, 5509-5522.

43. Carmo, A. C. M. D., Piras, S. S., Rocha, N. F. M., & Gratieri, T. (2017). Main reasons for registration application refusal of generic and similar pharmaceutical drug products by the Brazilian Health Regulatory Agency (ANVISA). *BioMed Research International*, *2017*(1), 7894937.

44. Geyer, A. R. C., Sousa, V. D., & Silveira, D. (2018). Quality of medicines: Deficiencies found by Brazilian Health Regulatory Agency (ANVISA) on good manufacturing practices international inspections. *PLoS One*, *13*(8), e0202084.