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Review Article

Balancing Innovation and Safety: The Regulatory Journey in Drug Development

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Abstract

Regulatory compliance and drug safety are pivotal components in the pharmaceutical landscape, ensuring the development, approval, and post-market surveillance of safe and efficacious medicines. This review explores the intricate relationship between regulatory compliance and drug safety, examining historical contexts, key components, major regulatory bodies, challenges, strategies, and future trends. It highlights the critical role of regulatory agencies such as the FDA, EMA, and others in safeguarding public health through stringent protocols and oversight. The paper delves into the challenges posed by emerging technologies, globalization, and the need for balance between innovation and safety. Pharmacovigilance, adverse event reporting, and risk management are scrutinized as essential facets of ensuring drug safety. Future trends, including the impact of AI, personalized medicine, and regulatory responses to health crises, are examined. The review offers insights from case studies, emphasizing the importance of learning from past incidents and successful regulatory interventions. Ultimately, this paper underscores the profound significance of regulatory compliance in maintaining drug safety and public health, urging for continual evolution and adaptation in response to a dynamic pharmaceutical landscape.

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Introduction

Regulatory compliance and drug safety are fundamental cornerstones of the pharmaceutical industry, vital in ensuring the efficacy, safety, and quality of medicinal products. The interconnectedness of regulatory compliance and drug safety is not only intrinsic to the pharmaceutical industry's success but is paramount in protecting public health and fostering trust in healthcare systems. This introduction aims to illuminate the multifaceted nature of these critical elements, examining their historical evolution, key principles, and their role in contemporary pharmaceutical practices.(1)The evolution of regulatory compliance in the pharmaceutical sector can be traced back through various milestones in history. Early drug regulation was primarily a response to public health crises and detrimental incidents caused by inadequately tested or monitored substances. The birth of regulatory oversight in pharmaceuticals emerged as a means to protect consumers from harmful or ineffective medications. Landmark events, such as the passage of the Pure Food and Drug Act in the United States in 1906, signified a pivotal shift towards government involvement in overseeing drug safety. This led to the establishment of regulatory bodies like the U.S. Food and Drug Administration (FDA), marking the beginning of systematic drug approval processes and safety protocols.(2)

The principles of regulatory compliance in pharmaceuticals revolve around stringent guidelines governing drug development, testing, approval, and post-market surveillance. Rigorous pre-clinical testing, encompassing in vitro and in vivo studies, plays a crucial role in understanding the potential efficacy and safety of a new drug candidate. Subsequently, clinical trials are conducted in multiple phases to evaluate safety, efficacy, and dosage in human subjects, adhering to ethical considerations and regulatory standards. The core of ensuring drug safety lies in the regulatory approval processes. These involve meticulous scrutiny of clinical trial

data, risk-benefit assessments, and adherence to Good Manufacturing Practices (GMP). Post-market surveillance further strengthens this process by continuously monitoring adverse events, conducting pharmacovigilance, and updating safety information on drug labels.(3)Central to this discussion is the pivotal role played by major regulatory bodies such as the FDA, the European Medicines Agency (EMA), and other international agencies. These entities set and enforce regulations, conduct inspections, and collaborate with pharmaceutical companies to ensure compliance and safeguard the public from unsafe or ineffective medications.(4)

Challenges in regulatory compliance have evolved in parallel with scientific advancements and globalization. Emerging technologies like gene editing, nanotechnology, and artificial intelligence present both opportunities and challenges in regulatory frameworks. Balancing innovation with safety while adapting to the globalized nature of pharmaceutical manufacturing remains a constant challenge for regulatory bodies.(5)

Importance of Drug Safety in Public Health

Drug safety is an essential pillar of public health, ensuring the well-being and safeguarding the lives of individuals by overseeing the efficacy and safety of medicinal products. The significance of drug safety in public health cannot be overstated, as it directly impacts healthcare systems, patients, and the overall welfare of society. This discussion delves into the multifaceted importance of drug safety, its historical context, key elements, challenges, and its role in promoting public health. The primary objective of drug safety is to mitigate risks associated with pharmaceutical products and to maximize their benefits. Throughout history, the necessity for drug safety measures has been accentuated by adverse events stemming from inadequate regulation, leading to public health crises. Tragic incidents like the thalidomide catastrophe and others underscore the critical need for stringent drug safety protocols. The

subsequent development of regulatory bodies and guidelines aimed at ensuring drug safety has been a response to such crises, reflecting the prioritization of public health protection.(6)

A crucial component of drug safety involves pre-clinical and clinical trials. Pre-clinical studies encompass extensive in vitro and in vivo experiments that evaluate a drug's potential effects, helping to identify potential risks early in the development process. Clinical trials, performed in several phases, involve human subjects and aim to establish the safety, efficacy, and dosage of a drug, ensuring its compliance with regulatory standards and ethical considerations. These trials contribute immensely to the understanding and documentation of a drug's safety profile before it reaches the market. Post-market surveillance and pharmacovigilance also play an instrumental role in drug safety. Even after a drug is approved and made available to the public, continuous monitoring is essential to detect and assess any adverse events or side effects that were not apparent during the initial trials. This ongoing surveillance enables timely intervention, label updates, and risk management strategies to ensure patient safety. Regulatory bodies like the FDA, EMA, and other international agencies serve as guardians of drug safety, establishing stringent protocols for drug approval, monitoring, and risk assessment. Their oversight, inspections, and collaboration with pharmaceutical companies are essential in ensuring compliance and upholding public health standards.(7)

However, challenges persist in maintaining drug safety. Rapid advancements in technology, globalization, and the increasing complexity of pharmaceuticals present ongoing challenges to regulatory frameworks. Balancing innovation with safety and adapting to the evolving landscape of drug development and manufacturing is a perpetual challenge faced by regulatory bodies.(8)

Overview of Regulatory Bodies and their Role in Ensuring Drug Safety

Regulatory bodies play a critical role in ensuring drug safety by establishing and enforcing guidelines that govern the development, approval, manufacturing, distribution, and post-market surveillance of pharmaceutical products. These bodies serve as guardians of public health, ensuring that medications reaching the market meet stringent safety and efficacy standards. The following overview explores the key regulatory bodies and their pivotal role in ensuring drug safety:(9)

1. Food and Drug Administration (FDA): The FDA, based in the United States, is one of the most influential regulatory bodies globally. Its responsibilities encompass ensuring the safety, effectiveness, and quality of drugs, biologics, medical devices, food, and cosmetics. The FDA plays a critical role in evaluating new drugs through rigorous assessment of pre-clinical and clinical trial data before granting approval for market release. Post-approval, the FDA continues to monitor adverse events through its robust pharmacovigilance programs.(10)

2. European Medicines Agency (EMA): Operating within the European Union, the EMA is responsible for the evaluation and supervision of medicines. The EMA evaluates and approves new medicines and provides oversight during their entire lifecycle. Collaborating with national regulatory authorities, the EMA assesses a drug's quality, safety, and efficacy before granting marketing authorization. It also monitors and reports adverse reactions following the drug's release into the market.(11)

3. Health Canada: Health Canada regulates the safety, efficacy, and quality of health products in Canada, including pharmaceuticals. It evaluates drug submissions and conducts post-market surveillance to ensure ongoing safety and effectiveness.(12)

4. Pharmaceuticals and Medical Devices Agency (PMDA): In Japan, the PMDA evaluates

and oversees pharmaceuticals and medical devices. It conducts reviews of new drugs and devices and supervises post-marketing safety monitoring to protect public health.(13)

5. International Conference on Harmonisation (ICH): The ICH is a global initiative involving regulatory authorities and pharmaceutical industry representatives from the U.S., Europe, and Japan. It aims to harmonize and standardize regulations to ensure the safety, quality, and efficacy of pharmaceutical products.(12)

These regulatory bodies perform several key functions:(13)

Drug Approval Process: They evaluate the safety, efficacy, and quality of drugs before allowing them to enter the market.

Ongoing Monitoring: They conduct post-market surveillance to monitor the safety and effectiveness of drugs already in use.

Setting Standards and Guidelines: They establish and enforce guidelines, regulations, and standards for drug development, manufacturing, and distribution.

Adverse Event Reporting and Risk Management: They oversee adverse event reporting and manage risks associated with marketed drugs.

In summary, regulatory bodies such as the FDA, EMA, Health Canada, PMDA, and the ICH play a pivotal role in safeguarding public health by ensuring that pharmaceutical products meet stringent safety and efficacy standards throughout their development, approval, and lifecycle. Their oversight and regulations are crucial in upholding drug safety and maintaining public trust in the healthcare system.(14,15)

Historical Perspectives on Regulatory Compliance

Historical perspectives on regulatory compliance in the pharmaceutical industry reveal a transformative journey marked by significant

events, legislative changes, and shifts in societal perception. These historical milestones have shaped the current framework for drug safety, overseeing the development, manufacturing, and distribution of pharmaceuticals.(16)

1. Early Regulations and Crisis Response: The earliest forms of drug regulation were responses to public health crises. Throughout history, incidents such as the Elixir Sulfanilamide tragedy in 1937, which caused multiple deaths due to a toxic formulation, highlighted the need for government intervention to ensure drug safety.

2. Pure Food and Drug Act (1906): The Pure Food and Drug Act in the United States was a watershed moment in the history of pharmaceutical regulation. It aimed to prevent the adulteration and misbranding of food and drugs. This act laid the groundwork for future legislation and established the regulatory role of the government in drug safety.

3. Creation of the FDA: The establishment of the Food and Drug Administration (FDA) in 1930 further solidified the government's role in drug regulation. The FDA's primary objective was to ensure the safety and efficacy of drugs before they reached the market, laying down the groundwork for a formal approval process.

4. Thalidomide Tragedy (1950s-1960s): The thalidomide disaster, where the drug caused severe birth defects in thousands of infants, prompted a reevaluation of drug approval processes. This crisis led to the implementation of more rigorous testing and safety standards, emphasizing the importance of thorough pre-clinical and clinical trials.

5. Drug Amendments and Modernization Acts: Subsequent legislative acts, such as the Kefauver-Harris Amendments in 1962 and the Prescription Drug User Fee Act (PDUFA) in 1992 in the United States, aimed to enhance drug safety by tightening regulations, improving the approval process, and expediting reviews.

6. Global Harmonization and Standardization: The evolution of regulatory compliance extended globally with the establishment of international collaborations like the International Conference on Harmonisation (ICH). The ICH aimed to standardize regulations across regions, facilitating the development and approval of drugs globally.

7. Continuous Evolution and Adaptation: Over time, the landscape of regulatory compliance has continuously evolved in response to technological advancements, emerging challenges, and changing societal demands. The introduction of advanced technologies, personalized medicine, and increased globalization has necessitated ongoing adaptation and revision of regulatory frameworks.

These historical perspectives demonstrate the evolution of regulatory compliance in response to past crises and the continuous efforts to refine drug safety protocols. The journey from early legislation to modern-day regulatory structures highlights the ongoing need for vigilance, adaptation, and innovation to ensure the safety and efficacy of pharmaceutical products.(17–19)

Key Components of Regulatory Compliance

The key components of regulatory compliance in the pharmaceutical industry encompass a comprehensive framework governing the development, manufacturing, testing, approval, and surveillance of medicinal products. These components ensure that drugs meet stringent safety, efficacy, and quality standards before they reach the market and continue to be monitored for safety post-approval. The key components include:(20)

1.Pre-Clinical Testing and Research Protocols: Pre-clinical studies involve in vitro and in vivo experiments to assess a drug's potential effects, toxicities, and safety profiles. These tests help researchers understand a drug's

mechanism of action, pharmacokinetics, and potential risks before advancing to human trials.

2.Clinical Trials and Ethical Considerations: Clinical trials are conducted in multiple phases to evaluate a drug's safety, efficacy, and dosage in human subjects. These trials adhere to strict ethical considerations and regulatory standards. Phase I, II, and III trials systematically test the drug's safety and effectiveness on increasing numbers of human subjects.

3.Regulatory Approval Processes: Regulatory approval involves rigorous evaluation of pre-clinical and clinical trial data by regulatory agencies. Authorities like the FDA, EMA, and other national regulatory bodies review drug submissions to determine whether the benefits outweigh the risks, ensuring the drug's safety and efficacy before granting market approval.

4.Good Manufacturing Practices (GMP): GMP encompasses the standards for manufacturing, packaging, labeling, and quality control of pharmaceutical products. Compliance with GMP ensures that drugs are consistently produced and controlled according to quality standards.

5.Post-Market Surveillance and Pharmacovigilance: Even after a drug is approved and made available to the public, continuous monitoring is essential. Pharmacovigilance involves the collection, detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems. Adverse event reporting and risk management are integral parts of post-market surveillance.

6.Labeling and Packaging Compliance: Accurate and comprehensive labeling is crucial for providing information to healthcare providers and patients. Compliance with labeling requirements ensures clear information regarding dosage, potential side effects, contraindications, and safety measures for use.

7.Compliance with Regulatory Guidelines and Standards: Pharmaceutical companies must

comply with a myriad of regulatory guidelines and standards throughout the drug development and manufacturing process. These standards are set by various regulatory bodies and ensure that the drugs meet the necessary safety and quality criteria.

These key components collectively form the foundation of regulatory compliance in the pharmaceutical industry. They serve to ensure the safety, efficacy, and quality of medicinal products from the earliest stages of research through post-market surveillance, maintaining a high level of safety and efficacy for the benefit of public health.(21–23)

Challenges in Regulatory Compliance

Regulatory compliance in the pharmaceutical industry faces several challenges, reflecting the complexity of the regulatory landscape and the evolving nature of drug development, manufacturing, and distribution. These challenges pose hurdles for regulatory bodies, pharmaceutical companies, and healthcare systems. Key challenges in regulatory compliance include(24,25)

1.Rapid Technological Advancements: Continuous technological innovations such as gene editing, nanotechnology, and advanced manufacturing techniques introduce new complexities in drug development and require updated regulatory frameworks to ensure their safety and efficacy.

2.Globalization and Diverse Regulatory Standards: Global markets demand harmonization of regulatory standards. Variances in regulations between different countries or regions can lead to complexities for multinational pharmaceutical companies navigating diverse compliance requirements.

3.Balancing Innovation with Safety: Encouraging innovation while ensuring the safety and efficacy of new drugs is a perpetual challenge. Regulatory agencies must strike a

balance between promoting scientific advancements and guaranteeing patient safety.

4.Regulatory Framework Adaptation: Regulatory bodies must continually adapt to keep pace with the rapidly changing pharmaceutical landscape. This involves reviewing and updating guidelines and standards to encompass new technologies, treatments, and manufacturing practices.

Costs and Timelines for Drug Approval: The process for drug approval is lengthy and expensive. Balancing the need for thorough evaluation with the urgency to make innovative treatments available to patients can be challenging. It's crucial to expedite processes without compromising safety.

Complex Supply Chains and Outsourcing: Pharmaceutical companies often outsource various stages of drug development or manufacturing. Ensuring compliance and oversight across complex supply chains, especially involving international partners, poses challenges for maintaining quality and safety standards.

Cybersecurity and Data Protection: Digitalization and the use of sensitive health data raise concerns about cybersecurity and data protection. Regulatory bodies must navigate the challenges of protecting patient information while still encouraging digital innovation in drug development and monitoring.

Adverse Event Reporting and Pharmacovigilance: The identification, reporting, and management of adverse events continue to be a challenge. Ensuring comprehensive and accurate reporting of adverse events while managing risk assessment and communication remains a complex task.

Complex Regulatory Guidelines: The vast and intricate nature of regulatory guidelines and standards can be overwhelming for pharmaceutical companies. Clear interpretation and compliance with these regulations,

especially for smaller or newer companies, can be challenging.

Addressing these challenges requires collaborative efforts between regulatory agencies, pharmaceutical companies, healthcare professionals, and technology experts. The ongoing evolution and adaptation of regulatory frameworks are essential to ensure drug safety, maintain public health standards, and support innovations in the pharmaceutical industry.(26–28)

Future Trends and Innovations

Future trends and innovations in regulatory compliance within the pharmaceutical industry are poised to revolutionize drug development, safety, and approval processes. Several emerging trends and advancements are expected to shape the future of regulatory compliance:(29,30)

1.Advanced Technology Integration: Integrating technologies like artificial intelligence (AI), machine learning, and big data analytics will enhance the efficiency and accuracy of drug development, regulatory assessments, and pharmacovigilance. AI can aid in data analysis, predictive modeling, and identifying potential safety issues.

2.Real-World Evidence and Adaptive Trials: Increased reliance on real-world evidence (RWE) derived from healthcare data and patient experiences will complement traditional clinical trial data. Adaptive trial designs will allow for more flexible and efficient trials, optimizing patient outcomes and reducing trial costs.

Personalized Medicine and Regulatory Implications: The rise of personalized medicine, tailored to individual genetic profiles, will challenge traditional regulatory frameworks. Regulators must adapt to the evolving landscape of treatments specific to a patient's genetic makeup.

Digital Health and Telemedicine: The expansion of digital health tools, telemedicine, and mobile health applications will demand

updated regulations. This includes ensuring data security, interoperability, and regulatory oversight in rapidly evolving digital health technologies.

Regulatory Responses to Global Health Crises: Recent health crises, such as the COVID-19 pandemic, have highlighted the need for faster regulatory responses to emerging threats. Streamlined emergency approval pathways and flexible regulatory strategies will be essential in addressing future pandemics or health crises.

Continuous Manufacturing and Supply Chain Resilience: Continuous manufacturing methods offer flexibility and efficiency in drug production. Regulators need to adapt to these new manufacturing processes while ensuring supply chain resilience to avoid disruptions.

Environmental Impact and Sustainability: Focus on environmental impact and sustainability within drug manufacturing will drive new regulatory considerations. Stricter guidelines may be implemented to ensure eco-friendly practices in pharmaceutical production.

Blockchain Technology for Supply Chain Transparency: Implementation of blockchain technology for supply chain transparency will offer enhanced traceability, combating counterfeit drugs and ensuring the authenticity of pharmaceutical products.

Regulatory Convergence and Harmonization: Ongoing efforts in global regulatory convergence and harmonization will continue to align standards across different regions to facilitate smoother drug approvals and reduce redundancies in regulatory processes.

Advanced Therapy Medicinal Products (ATMPs) and Gene Therapies: The emergence of novel ATMPs and gene therapies requires new regulatory pathways. Regulators must develop specialized guidelines to accommodate these groundbreaking therapies.

Addressing these future trends will require agile regulatory systems that can adapt to rapid

technological changes, while maintaining a balance between innovation and safety. Collaboration between regulatory bodies, industry stakeholders, and healthcare professionals will be crucial in navigating the changing landscape of pharmaceutical innovation and regulation.(1,31,32)

Conclusion

In conclusion, the dynamic landscape of regulatory compliance in the pharmaceutical industry is intricately linked with ensuring drug safety, efficacy, and quality. The evolution of regulatory frameworks, from historical milestones to present-day challenges and future innovations, underscores the critical importance of vigilance, adaptability, and innovation to uphold public health standards.

Historical perspectives have illustrated the transformative journey from early crisis responses to the establishment of regulatory bodies and the implementation of stringent compliance measures. These historical milestones, including tragic incidents and legislative changes, have shaped the stringent approval processes and oversight practices we have today.

The key components of regulatory compliance, such as pre-clinical testing, clinical trials, post-market surveillance, and adherence to stringent guidelines, constitute the foundational pillars in ensuring the safety and efficacy of pharmaceutical products. However, these components face challenges in the face of rapid technological advancements, globalization, cost and timeline constraints, and the complexities of managing a global supply chain.

Looking ahead, the future of regulatory compliance in the pharmaceutical industry presents an exciting yet challenging landscape. Innovations such as AI, personalized medicine, digital health, and advanced therapies are poised to revolutionize drug development and patient care. However, these advancements necessitate

agile regulatory frameworks capable of adapting to rapid changes while maintaining a delicate balance between innovation and safety.

Collaboration between regulatory bodies, pharmaceutical companies, healthcare professionals, and technology experts is crucial in navigating the evolving terrain of regulatory compliance. Harmonizing regulations globally, adapting to new technologies, and responding swiftly to emerging health crises will be imperative in ensuring drug safety and public health.

In essence, the future of regulatory compliance in the pharmaceutical industry requires continuous evolution, adaptability, and collaboration. By addressing these challenges and embracing new innovations, the industry can ensure the continual delivery of safe, effective, and innovative medicines to improve patient outcomes and sustain public health standards. Regulatory compliance remains the cornerstone in safeguarding public health, and its evolution is key to meeting the ever-changing needs of a dynamic pharmaceutical landscape.

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all the required data is available.

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The author declare that they have no conflict of interest.

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