Intelligent Document Processing and Regulatory Pathway Mapping: AI-Enhanced Compliance Automation in Pharmaceutical Submissions

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1. Introduction

In light of global health and safety standards, the pharmaceutical sector is a highly regulated industry. Compliance with these regulatory bodies should be the primary concern because the pharmaceutical product of a company not meeting these safety and regulatory standards may not be prescribed to the public. Pharmaceutical companies need to ensure that their products are in line with these regulations, and they need to run quality checks in a seamless manner to release a new product to the market. There are various testing and approval procedures during the life cycle of a drug, and researchers and regulatory affairs personnel need to work in sync to ensure quick approvals and market launches of required products. Because of the more evolved world setup, it becomes increasingly important that companies equip themselves with the latest information on evolving data trends and systems to comply with it.

Accordingly, the essay aims to explore the potentials and attributes of next-level AI-based solutions that may be part of pharmaceutical companies to produce fast, trackable results to streamline regulatory affairs-related work. To realize the significance of the need for such workflow processes, it becomes imperative to first understand the key aspects of the current regulatory affairs perspective as of today's era. The current flow of regulatory compliance is quite complex and poses an extra responsibility for the tertiary departments of companies and regulatory agencies. In this essay, there will be a broad study to understand AI and consider the most favorable study with suitable examples of AI applications in regulatory processes. To envisage a possible application of AI in regulatory affairs, it is important to understand the aspects of the products, their regulatory framework, and their requirements from the initial phase of product design

in a research-driven product and from a regulatory strategy perspective to reach the marketing of the drug.

1.1. Background and Significance

The pharmaceutical industry is among the most stringently regulated of all industries, whether for preemptive social and ethical considerations or due to a long historical record of devastating public health disasters and accidents. This safeguarding covers not only the commercial end of pharmaceutical operations but also the very nature of drugs themselves, which may have life-threatening effects in case of failure to assess the side effects before placing them on the market. Since the very first efforts, over two centuries ago, in the scholarly construction of a body of knowledge related to regulatory matters, the burden of proof required to ensure against toxic side effects from manufactured drugs has mostly fallen on industrial drug producers and pharmaceutical companies. This research roadmap, it might appear, contradicts the commercial approach of 'trading with the lives of patients' held by a few extreme rent-seeking industrialists in some dramatic cases. Industrial practices flourished throughout history to meet increasing public demand and access to new pharmaceuticals, some of which were, unfortunately, developed ahead of an epistemological understanding of their safety.

Where pharmaceutical misadventures have occurred due to inadequate regulations and safeguards, the need for stringent post-approval regulatory compliance stands out as a rudimentary step to restore public trust and to avoid economic disasters across the industry. Even if obliging authorities to be vigilant and intervene in checks was not itself sufficient to lead pharmaceutical companies to regulate their practices, turning attention to economic impacts will generally admonish the most negligent to change their misbehavior. Substantial economic advantages are at stake with regard to the large volumes of ill-gotten profits and investments that may be confined to human capital in the case of legal punishment. In the early years of the 21st century, the direct cost of compliance, i.e., the effort spent in drafting reports and verifying compliance with internal procedures, is estimated to weigh from 1% to more than 35% of all revenue generated in the pharma sector, which translates to a yearly investment of a one- to three-digit billion-dollar figure by US drug producers. Pharmaceutical companies failing to comply with laws and the stringent posture originally posed will dedicate astonishing amounts of payout to authorities in the case of a misadventure. In the same year, the

company also agreed to pay almost $5 billion to more than 40 US states following allegations that the company failed to disclose addiction risks of hip implants before they were surgically inserted in patients. These two examples, among several others, highlight the economic jeopardy posed to drug developers in cases where non-compliance with regulations appears.

2. Regulatory Compliance in the Pharmaceutical Industry

At its foundation, regulatory compliance dictates the very framework of a pharmaceutical company's operations. Laws and statutes that govern the entire spectrum of drug development—ranging from pre-marketing development issues to post-market drug surveillance issues and limitations on misbranding and off-label marketing—foretell serious legal and financial implications for companies that are unwilling or unable to stay current with regulatory requirements. As such, maintaining regulatory compliance to the best of their ability is both justifiably and justly a high priority for these companies. Companies that are not operating within the framework set by regulatory agencies are liable to face stiff penalties for non-compliance—penalties that can have significant implications if a company is dependent on an active license from such an agency. Therefore, the regulatory bodies also have an embedded expectation that companies with whom they work will make every effort to keep their operations in line with regulatory standards.

Regulatory bodies of primary importance to the United States pharmaceutical market include the U.S. Food and Drug Administration and for the European pharmaceutical market, the European Medicines Agency. Both of these groups work in tandem with smaller, contemporary developing countries that also have regulatory compliance agencies and must be negotiated with for entry into their market space. Although regulatory agencies have an expectation that companies will keep their operations within specification, it is not solely enough to operate transparently and qualitatively correct. Major deterrents to compliance include maintaining proper, comprehensive documentation, adhering to principles of quality control, reporting of adverse events, and drug product non-conformance documentation.

2.1. Key Regulations and Standards

There are many standards and regulations that are meant to be followed by pharmaceutical companies in drug manufacturing and conducting clinical trials. In the

United States, the top regulation for pharmaceutical companies is Good Manufacturing Practices (GMP). GMP values have highlighted parts 210 and 211 of Title 21 of the Code of Federal Regulations. GMP values define rules about pharmaceutical production; that is, drugs must be of the required quality and purity. Another main administrative regulation for the drug development process and compliance of electronic data is Good Clinical Practices (GCP). All trials with suggested medication, including Phase I, II, III, and IV trials, must follow the GCP value. The two main tenets of GCP values are "the protection of the rights, safety, and welfare of human subjects involved in a test" and "the quality of test results." Both GMP and GCP values establish a highlighted field of merchandise protection for marketing a drug; that is, controlled clinical trials are needed to prove the safety and efficacy of drug products intended for use in humans.

Several international harmonization efforts and working groups have been established to assist in monitoring and making the regulations consistent with those established in other countries, creating harmonization to achieve consistent, high-quality products that are acceptable in the international environment. One well-known regulatory body is the International Conference on Harmonization (ICH), announced in 1990. "The ICH brings together the regulatory authorities and pharmaceutical industry to discuss aspects of drug development and compliance that can be globally harmonized." There are several areas in which the ICH has formed guidelines; these include Safety, Non-Clinical, Clinical Documentation, and the Common Technical Document. In the drug development process, the statement of the Common Technical Document has been given considerable attention by the federal regulatory agencies. Consequently, all required documentation should be included. Regulatory non-compliance can cost companies animal seizure and penalties, which can exceed millions of dollars, not including advertising damage, loss of sales, and regulatory agency legal action.

3. Challenges in Regulatory Compliance

Pharmaceutical companies have to comply with different regulatory bodies, which can be challenging due to the wide variety of regulations in place across different jurisdictions. Essentially, the compliance landscape is getting more complex. The number of commands from regulatory agencies has increased significantly in the past two decades. At the same time, the standards toward which such organizations aspire are changing rapidly due to technological advances and increasing demands of the

public. Regulatory upheaval due to the need to provide solutions to issues raised by authorities or activists imposes a heavy operational burden for an organization, compels it to redirect resources from higher-priority tasks, and distracts it from its main business objectives.

Most companies relentlessly strive to comply because, in many instances, the costs of non-compliance can be substantial. They include mandatory corrective action of submitted materials and defensive compliance agreements. Moreover, failure to comply may result in legal action, reputational damage, missed registration deadlines, and loss of license to market. From an organizational point of view, traditionally, regulatory affairs have been an undervalued division receiving relatively little allocation of resources. At a more localized level, inefficient internal communication, negative attitudes, and poor cooperation between regulatory affairs, operations, clinical research, quality assurance, and research and development departments can impede the implementation of regulation compliance. Although companies in some jurisdictions need to establish formal regulatory compliance programs, there are no universally accepted best practices for such programs.

Given the challenges illustrated in this section, several areas could potentially benefit from AI technologies to improve the regulatory compliance of pharmaceutical and medical device companies.

3.1. Complexity of Regulations

Local, national, and international regulatory bodies apply a relatively uniform set of requirements to ensure pharmaceutical products do not pose significant risk to the general public. While the objective mandates are somewhat consistent, the specific requirements and level of attention to detail vary greatly. To further complicate matters, regulatory authorities are continually changing the 'rules' and even redefining existing guidelines, often with little warning. Monitoring the change in guidance and the underlying regulations is a full-time job. To further complicate the matter, regulatory authorities share common ground in an attempt to minimize risk to worldwide patient populations. So while there are unique attributes to each country's regulatory guidelines, there is increasing harmonization occurring among local bodies, governments, and global authorities. At a high level, these various characteristics and nuances associated with pharmaceutical regulations and guidelines emphasize the need

for an efficient vehicle to connect stakeholders; identify and mitigate missing requirements and gaps within the framework; prioritize missing requirements and gaps in order of importance based on perceived regulatory associated risk; and provide a visual roadmap to reference points, visualization around regulatory trends, and the industry leaders guiding the regulatory change.

This shift in the compliance narrative from policy to process is of increasing importance to the entire bio-pharmaceutical value chain. Companies spend millions of dollars in research and drug development; a single misinterpretation or missing requirement within the pharmacovigilance framework may render invalid years of work and significant financial commitment. For example, non-compliance can result in a company being sued by a vindictive patient, the implementation of costly corrective action and preventative action programs, civil and criminal litigation against the company and other stakeholders, significant fines, and/or the prohibition from product sale by the local regulatory authorities.

4. Role of AI in Regulatory Compliance

The automation of regulatory compliance in the pharmaceutical or biologic sector is a key challenge, primarily due to the combination of the complexity of various regulations and the increasing pace of regulatory changes that necessitate judiciously updating the processes and systems. The use of artificial intelligence technologies can be of significant help in this context. Such technologies can augment the compliance mechanisms in place and significantly improve their efficiency and accuracy. Digital solutions leveraging AI can perform a range of tasks, such as document verification using Optical Character Recognition of scanned documents or monitoring news for the latest developments on the regulatory front. They can also keep an eye on regulatory databases and use natural language processing to encode regulatory documents and instructions as digital rules.

Based on how input data is used by the system, AI technologies can be classified into a variety of methodologies, including supervised, unsupervised, semi-supervised, and reinforcement learning. Technologies that can also be used in a purely rule-based manner include expert systems, ontology-based systems, and case-based reasoning systems. Beyond simply automating the data collection performed in governance, risk management, and compliance software, AI can help perform the task in a smarter manner by identifying inconsistencies, for example, and taking them into account to

make predictions. By using AI, it becomes possible to perform further analyses that are of a predictive nature, which constitute the primary advantages of AI in the context of ability enhancement solutions. In other words, it is possible to predict what will happen using these adaptive abilities in addition to detecting the likelihood of a specific event occurring, enabling technologies to provide suggestions regarding what measures must be taken to minimize the risk of a certain adverse outcome. AI systems are capable of learning what steps must be taken to ensure that a software application fails as infrequently as possible, thus increasing not only its performance but also that of the business using the application. In this manner, consistent AI use has several benefits, such as augmented decision-making or cost savings. These capabilities also hold the promise of making regulatory compliance affordable for smaller and medium-sized companies that previously may not have been able to invest as heavily in compliance activities. In certain cases, savings on compliance officers could be a better investment than typical risk assurance solutions. Additional rewards include efficient utilization of regulatory resources and workers who are subject matter experts in governance, risk management, and compliance.

4.1. Machine Learning Applications

AI and machine learning are gaining traction as advanced solutions to automate different functions of an organization. However, empowering machine learning to make decisions also comes with its share of challenges, such as making machine-based learning transparent and ensuring unbiased decisions. Implementing these in a regulatory function has its own challenges, such as making the underlying algorithms transparent and ensuring that they are resistant to adversary attacks. Machine learning can be applied for predictive analysis. Machine learning can be used to predict which clinical drug trials will be successful, based on historical data across thousands of trials plus additional variables at each phase of development and early commercialization.

Machine learning algorithms analyze large amounts of data, such as historical and current regulatory data, to pinpoint trends, opportunities, and potential threats in the regulatory environment. Based on historical data, AI can predict and flag possible risks and non-compliances that might happen in the future. It will save companies various costs in risk analysis and help them to prevent threats. Machine learning can be used to automate documentation and stringent reporting processes, thus minimizing the risk of

human error. By processing large amounts of data available in structured format, AI can create required documents by analyzing the historical data. A typical example of this tool is the preparation of a quality management report. A few firms are pioneering efforts in this direction. One company is making use of machine learning to automate food label compliance checks. Over several years, the company has amassed regulatory ingredients, food labeling data, global regulations, and banned terminology that it has persisted in the market. Food product labels are uploaded into its online system, which identifies any banned substances used in the product and offers compliant alternatives where necessary.

5. Case Studies and Success Stories

In this section, we enumerate a number of case studies and success stories to illustrate how companies – both innovators and technology suppliers – have used AI to address the challenges that we outline. These surveys are by no means comprehensive, but they do cover an extensive range of features of the regulatory process, derived from more than a dozen different sectors. The examples are grouped roughly in order to follow the phases and functions of the regulatory process as discussed. They include blockbuster products as well as smaller, less well-publicized efforts. The majority of the discussion is proprietary and cannot be detailed in this report.

AI for regulating regulatory compliance. Case studies and success stories in AI for pharmaceutical regulatory compliance do exist, although they are still relatively scarce, all the more so in an academic context. Applied in different pharma sub-industries, in levels of engagement and with tools specializing in various tasks, they often present positive results both in terms of reduced time for compliance assessment activities and improved accuracy in the documentation and reporting of the respective cases. Importantly, they also reveal insights based on their firsthand experiences and useful lessons learned for actors contemplating the implementation of regulation-aware AI systems for their compliance work.

5.1. Applications in Real-world Scenarios

4. Infomediar: Discussion and Lessons Learned 4.1. Applications in Real-world Scenarios We proposed methods for automating ECs as solutions to the discussed challenges. The results of the application of AI technologies to streamline pharmaceutical regulatory compliance show that the proposed concepts are broadly

valid. For example, a software solution has been developed that uses NLP to check for compliance with regulations for clinical trials on medicinal products. Automation has been applied to QPPV-related tasks for several marketing authorization holders with up-to-date monitoring, including safety analysis and signal detection of data, signal evaluation, and authoring periodic safety signal update reports currently at a total of 480 users at 190 companies. One common feature of technological transitions is that the tools implemented do not change the intentions of any group but only change the power of those groups to achieve their ends. The same group of stakeholders remains interested in ensuring the safety and good pharmacovigilance practice in the supply chain of medicinal products, such as patients/users (public and private sector), MAHs, marketing authorization applicants, wholesalers, importers, parallel traders, repackers, agents, pharmacists, hospitals, veterinarians, governmental authorities, ECs, ethics committees for clinical trials, local offices, regulators, etc. However, these activities became costlier, took longer (an average of almost 114 days as of 2020 to send an EC to the EMA and 119 days to send an EC to the CHMP), and had a high level of exposure to regulatory punishment and associated requirements. In 2020, a proprietary metric was computed in real-time to demonstrate the quality and cost of a given company's Compliance Status Check. Regulatory inspectors use tools to work towards supervising more stakeholders remotely, and these tools are being employed in transformative medicinal trials. In 2022, these tools have been cited either directly or indirectly in 8 quality automated eCTDs, showing the advantages of the depth of AI and the ability to change and evolve.

6. Future Conclusion

In the next decade, the pharmaceutical industry will be significantly reshaped by advancements in AI, particularly in relation to ML and big data analytics. These can enhance accuracy, predictive power, and speed in making decisions. For pharmaceutical regulatory compliance, these can support the industry in moving from "reacting" and "correcting" to preventing non-conformity and "continuously improving" existing processes and results. By using AI, businesses can move towards a more strategic "risk-based thinking," concentrating valuable resources where and when needed. However, the field is still considered to be nascent due to evolving technology and forthcoming regulatory issues, as well as ethical issues. In order to leverage the capabilities of AI towards revolutionizing pharmaceutical compliance, pharmaceutical developers and

technology innovators must resolve the questions that arise about data privacy, protection, interoperability, transparency and access, and market proliferation. In doing so, additional support and input is needed from regulatory bodies and authorities to construct guidelines and validation frameworks for this technology to establish grounds against ethical and compliance norms for usage. Professionals in the sector cannot be left behind, and all the goods and bads, ensures and not guaranteed from AI education and cyber training will have to be provided on a scale suitable for such a fast-developing innovative atmosphere. Organizations in the pharmaceutical industry will increase their responsibility towards AI ethics and establish ethical checks and balances to stay a step ahead and adapt to rapidly evolving regulatory requirements.

7. Conclusion

Throughout this essay, the role of regulatory compliance in ensuring pharmaceutical product safety and efficacy has been emphasized. As complexities in drug development and regulatory requirements accelerate, the maintenance of regulatory adherence relies on the empowerment of effective risk management and good practices, underpinned by an enhanced understanding of the concerns, expectations, and proposed regulatory measures designed to address those challenges. Of these, data integrity, AI-based technological solutions, ongoing regulatory guidelines and perspectives, and collaborations among those from different jurisdictions have all been discussed as complex factors impacting future regulatory expectations in pharmaceutical validation exercises. Therefore, a need for out-of-the-box thinking for long-standing issues is required in order to encourage innovation and associated reform. In this short opinion piece, we aim to raise awareness of ongoing discussions and challenges in compliance in a technological era.

It is our opinion that AI offers significant potential to unveil the mysteries of regulatory compliance by enabling a deeper understanding of the quality of data than the mind, and as such, artificial intelligence offers dividends for the reporting function. The system is not yet fully operational, although there is increasing enthusiasm for leveraging AI. It is our collective opinion that AI will offer a great opportunity to develop data-driven insights and provide quicker results, advancing compliance and risk management in the future in our industry. In closing, we advocate that the industry speed up exploring

options to leverage this opportunity and begin conversations with regulators to ensure its facilitation.