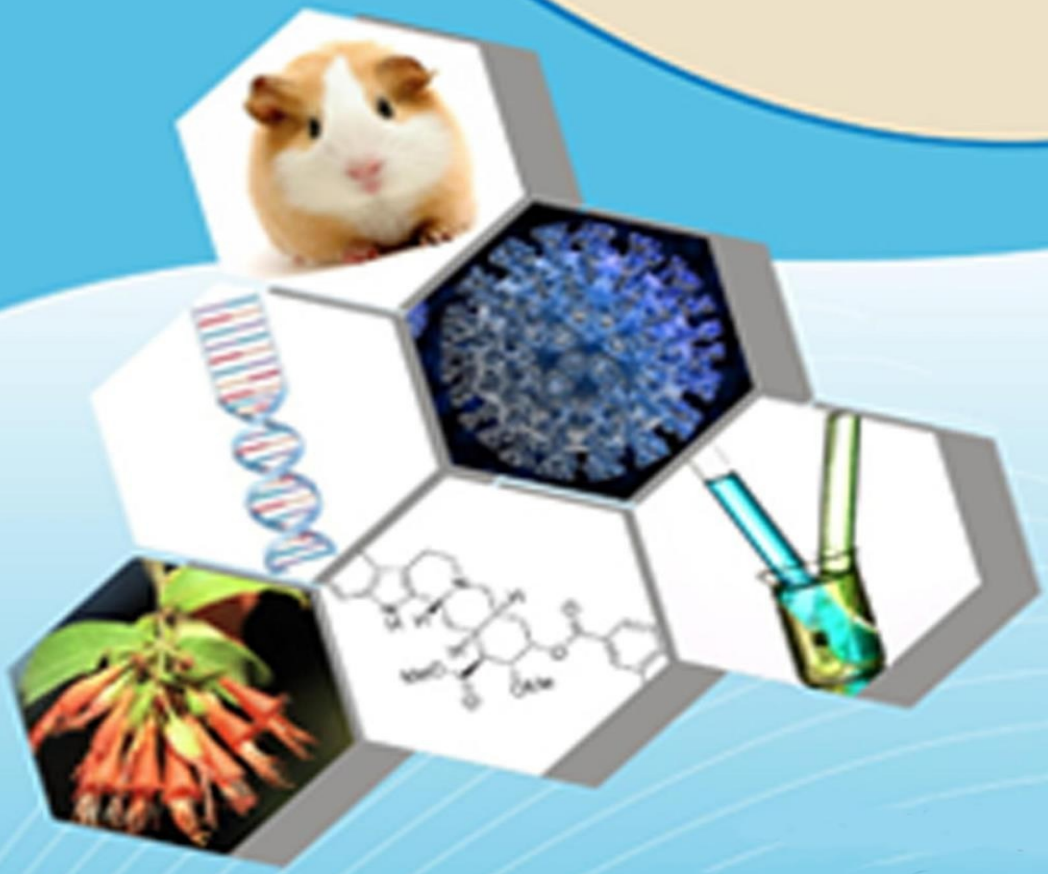
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OPTIMISING GLOBAL ECTD SUBMISSIONS: HARMONISATION CHALLENGES AND SOLUTIONS

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Abstract— *This research examines how to optimise both global eCTD submissions while identifying discrepancies and noting the lack of harmonisation between regulatory agencies in various countries. Through case study reviews and analysis of industry reports and secondary data, the research outlines barriers to creating, submitting, and marketing eCTDs, such as varying validation criteria, scalability, and human error. However, solutions are highlighted, such as automation and standardized processes, to help overcome these barriers. Ultimately, the research concludes a case for why pharmaceutical companies should be collaborating with regulatory agencies to eliminate barriers to global eCTDs and submission, and the time it takes to approve and remain compliant. Finally, recommendations for future solutions for optimisations are suggested.*

Index Terms— *"eCTD submissions, regulatory harmonization, automation tools, global compliance, pharmaceutical industry, submission challenges, approval timelines, validation criteria, scalability, automation, and regulatory agency"*

I. INTRODUCTION

A. Background to the Study

Recently, the *"Electronic Common Technical Document"* (eCTD) has become the accepted form of pharmaceutical regulatory submissions globally, creating globalised, consistent and efficient processes for industry. However, global eCTD submissions have to be optimised because of regionalised regulatory requirements. The eCTD framework has been created by the *"International Council for Harmonisation"* (ICH), but each regulatory agency, like the FDA (U.S.), EMEA (Europe), PMDA or MHLW (Japan), adds its region-related requirements. This creates complexities in the submission process [1]. Discrepancies in module structures, metadata specifications, and validation criteria complicate global compliance. In terms of meeting these challenges, regulatory agencies are engaged in a program, alignment with ICH M4 and structured data submissions [2]. A good optimisation strategy, including automation and standardised validation tools, is critically needed to get seamless global approvals.

Country	Regulatory Authority
India	Central Drugs Standard Control Organization Drug controller general of India (DCGI)
US	Food and Drug Administration (US FDA)
UK	Medicines and Health care products regulatory Agency (MHRA)
Australia	Therapeutic Goods Administration (TGA)
Japan	Japanese Ministry of Health, Labour and Welfare (MHLW)
Canada	Health Canada
Brazil	Agency Nacional degradation Vigilancia Sanitaria (ANVISA)
South Africa	Medicines Control Council (MCC)
Europe	European Directorate for Quality of Medicines (EDQM)
	European Medicines Evaluation agencies (EMEA)

Figure 1: Diverse global regulatory bodies [2]

B. Overview

This research highlights the challenges and solutions around optimising global eCTD submissions. The main focus is on regulatory agency harmonisation. ICHR's framework has not been successful in removing regional

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discrepancies. An example is the type of lifecycle management utilised by the FDA which is unique to FDA enforcement of the ICH rules, but ICH submissions are not followed in-kind by the EMA. This results in pretty much all drug companies having to deal with the slow compliance from each of the agencies because they each have dissimilar criteria for validation [3]. Although research is being conducted into automated tools leveraged by AI, and looking at how to overcome these challenges via automating, the research also evaluates the impacts from these approaches towards improving global regulatory working process efficiency and reducing the submission workflow.

C. Problem Statement

When reconciling the obligation to submit to many regional regulatory authorities, global "electronic Common Technical Document" (eCTD) submissions are also confronted with major harmonisation challenges between regions. While ICH has developed a standardised framework, agencies such as the FDA, EMA, and PMDA have added differing validation criteria leading to disparate submission documents [4]. This is an important issue because regulatory expectations change with the digital transformation; automating and establishing a global collaboration about this will resolve it. The exploration of clinical trial application study identifies optimisation strategies for eCTD submissions, with the intent of accelerating approval timelines with the least compliance risk for all pharmaceutical sponsors globally.

D. Objectives

- To explore the shared harmonisation challenges related to global eCTD submissions as experienced by regulatory agencies.
- To assess the impact regional regulatory differences, have on submission efficiency and compliance times.
- To offer possible ways of optimising habitually global eCTD submissions with considerations including automation and AI-enabled validation tools.

E. Scope and Significance

This study will elucidate challenges to harmonisation around the world related to eCTD submissions, and will determine differences, when they arise, between regulatory agencies, including the FDA, EMA, and PMDA [5]. It will also examine the implications of those differences on compliance efficiency with eCTD submissions to propose a framework for global regulatory harmonisation. This study will give pharmaceutical companies a new understanding that could help them enhance their submissions' accuracy, diminish submission timing, and promote harmonisation between regulatory agencies. Ultimately, these results could support the timely availability of drug products across all healthcare markets.

II. LITERATURE REVIEW

Regulatory Discrepancies and Harmonisation Barriers in eCTD Submissions

The implementation of an electronic Common Technical Document (eCTD) has been introduced to global pharmaceutical submission processes to facilitate the regulatory aspects. While regulatory differences do exist globally, the ICH framework aims to harmonise these standards; however, the FDA, EMA and PMDA have differing requirements making compliance complex. Submitting an eCTD varies from the U.S. and Canadian submission process, primarily in dossier structure and lifecycle management rules [6]. Ultimately increasing the cost and time factor

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for the review which is contrary to the efficiency purpose of eCTD harmonisation.
Furthermore, another research claims that while using CTD and eCTD helps reduce compilation time, many countries have their specific modifications which impede global submission without much hassle [7]. Management of regulatory affairs of varying types of not only version control but metadata requirements varies. The FDA's granularity compared to the EMEA's strict baseline submission requirements is an additional regulatory burden.

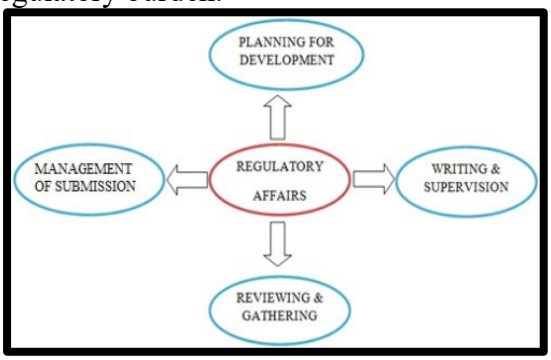


Figure 2: Overview of Regulatory Affairs [7]

Even within a unified CTD framework, discrepancies in validation rules result in a lot of rejections and resubmissions [8]. Approval timelines are extended due to the lack of standardisation of this drug, which in turn leads to its availability being delayed. Therefore, unless they were fully aligned, with validation and metadata requirements, eCTD's marketing promise would not come true.
However, these studies show that eCTD remains a step forward in the direction of harmonisation, but there are still barriers. Strong regulatory collaborations and technological developments like AI-driven validation tools are required to address them [7]. Global pharmaceutical firms will continue to experience hurdles that unnecessarily delay patient access to essential medicines unless they take proactive measures.

Consequences of Regional Regulatory Variations in eCTD Submissions

The goal of the eCTD framework is to standardise global regulatory submissions, but it poses major challenges to regional variations for pharmaceutical companies. Discrepancies in validation rules between the FDA, EMA, and PMDA foster lots of retrials and re-submissions [9]. It is not only a deterrent in drug approvals but also increases administrative costs for companies to comply with the multiple regulatory platforms.
Another study has shown that by reducing the preparation time for documents, eCTD has helped, but regulatory expectations have continued to cause problems. This means that simultaneous global submissions are highly complex as the baseline submissions are very stringent and they have to meet the requirements which require extensive lifecycle tracking [10]. The variations force companies to generate different regions targeted eCTD applications, which require a greater time and resource burden.

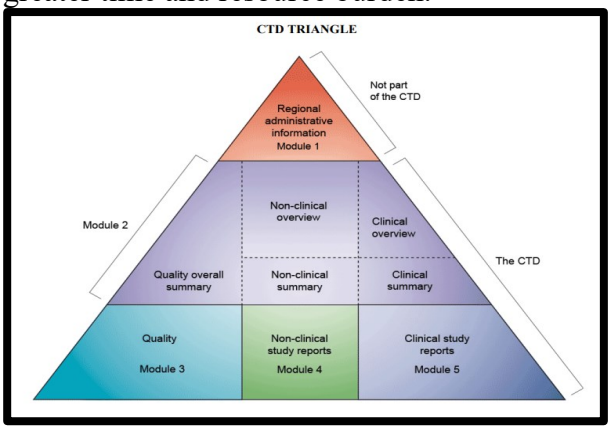


Figure 3: CTD Triangle [10]

Further, the regulatory requirements affect the availability of drugs. The US concentrates on the granularity and frequent updates in lifecycle management while the European agencies emphasize the consistency of submission format [11]. Due to the absence of harmonisation, companies have to find their way through region-specific compliance

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hurdles, thereby leading to delays in the process of market entry.

These studies indicate that, unless regulatory agencies adopt a true standardisation of eCTD, the pharmaceutical industry will experience inefficiencies. Therefore, considering the CTD triangle concept, there is a need for greater alignment, either through AI-driven validation and structured data submission, or other permissive mechanisms.

Optimisation Strategies for Streamlining eCTD Submissions

The intention of the eCTD framework to bring pharmaceutical firms closer to regulatory efficiency does not translate into reality as pharmaceutical firms continue to face inconsistencies in global submissions. Automation and AI-driven validation tools can reduce significant compliance errors and approval time [12]. Manual dossier preparation increases the risk that inconsistencies will occur, and the dossier will be rejected and have to be resubmitted, but they also underline. However, supporters of automation contend that overconcentration of automation can lead to regulatory subtleties that need to be handled manually.

Standardised templates and submission platform on the cloud as a means to streamline eCTD processes. However, the centrally administered document submission would invalidate suites of redundant document work. This approach saves efficiency, but it is often compromised by different data format requirements at regional levels. This results in the inability of such an approach to be truly globally harmonised.

More likely as a long-term solution in terms of regulatory collaboration, such as ICH M4 guidelines for the enhanced alignment [13]. Optimisation strategies are fragmented because they argue that without agency-level cooperation, they cannot operate. Yet, they recognise that global policy change takes time, so short-term solutions like AI-assisted compliance checks are feasible. So, for simplification of the eCTD submission process through automation, standardization, and regulatory engagement, their success is contingent on the opportunity for greater alignment between regulators and the incorporation of adaptive technologies.

III. METHODOLOGY

A. Research Design

This research follows an ***explanatory research design*** to find the hurdles in harmonising the global eCTD submissions and optimisation strategies. Given its structure of regulatory discrepancy analysis, its adverse consequences and possible solutions, an explanatory approach is suitable. This design gives rise to a cause-and-effect exploration between regulatory framework variations and inefficiencies in eCTD submissions [14]. Through the case studies, qualitative data is gathered, which provides an in-depth look into real-world regulator challenges. Quantitative data, like industry reports and statistical trends, can also be used to validate findings with empirical evidence, while the other lends itself to qualitative data analysis.

B. Data Collection

The data are collected on a ***secondary basis, both qualitative and quantitative***. This is a combination of both data types that will give a robust, rounded analysis [15]. Case study analysis of pharmaceutical firms and regulatory agencies yields examples of practitioners' solutions in tackling eCTD submission challenges and optimising them. This also offers real-world regulatory hurdle case studies, which provide contextual understanding. Secondary sources in the form of graphs, charts, and statistical trends are quantitative data. The study's findings are supported by measurable trends in analysing numerical data that make a critical evaluation of regulatory inefficiencies possible.

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C. Case Studies/Examples

Case Study 1: Eisai Co., Ltd.- Enhancing eCTD Submission Efficiency with PharmaDoc Tools

Preparing submissions in different regions like Japan, the U.S., and Europe was a challenge that Eisai Co., Ltd., a global pharmaceutical company, had to address. Two key problems were fulfilling the competing regional compliance needs and handling the rising volume of eCTD documents. In order to solve these problems, Eisai designed ***PharmaDoc LeafChecker*** and ***PharmaDoc eCTD Supporter.*** The configuration of global standard compliance requirements was made possible by PharmaDoc LeafChecker for the validation of PDFs that would be submitted synchronously to multiple regions [16]. Nevertheless, performance issues were revealed when checking large numbers of files, and there was a demand for faster processing capabilities as eCTD document volumes increased. The PharmaDoc eCTD support userbase was able to effectively validate hyperlinks and bookmarks in PDFs thus dramatically reducing the time and effort previously required for manual checks.

Case Study 2: Orbis Consumer Product Limited- Accelerating Submission Preparation with eCTDBuilder® and a-Pulse®

This was designed to expedite the delivery of the new drug submission process of Orbis Consumer Product Limited, a UK-based generic drug producer. This used to take four weeks or more and required manual labour-intensive preparation. The company wanted to minimise errors and shorten cycle time. In November 2007, Datafarm's eCTDBuilder® and a-Pulse® software solutions were adopted by Orbis. The tools also automated the XML that regulators required, and simplified the building, preparing and checking PDFs. Orbis thus can reduce preparation submission time from four weeks to four hours [17].

Case Study 3: European Pharmaceutical Company- Outsourcing CMC Strategy and eCTD Publishing

A Medium-sized European pharmaceutical company wanted to outsource key functions, doing away with Chemistry, Manufacturing and Controls (CMC) strategy authoring and eCTD publishing. This was managing a portfolio with 35+ marketed products and handling hundreds of post-approval changes a year. G&L Scientific assembled a global delivery team (especially including 35 professionals across the UK, India, and the US) for the company [18]. Their support spanned the entire process from regulatory compliance to post-approval variations to issuing license renewals to planning and publishing submissions. Through the collaboration, the time to submit the dossier was improved, the quality of the dossier was improved, and the cost was reduced.

IV. RESULTS

A. Data presentation

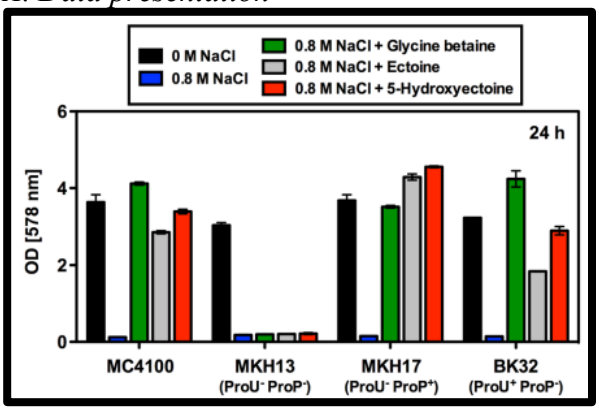


Figure 4: Growth Analysis

[19]

This is a bar graph of growth (OD at 578 nm after 24 h) of some E. coli strains under various osmotic conditions. Growth is impaired in high salt (0.8 M NaCl) stress (blue bars), but osmoprotectants such as glycine betaine, ectoine and 5 hydroxy

ectoine restore growth, in particular in ProP or ProU active strains.

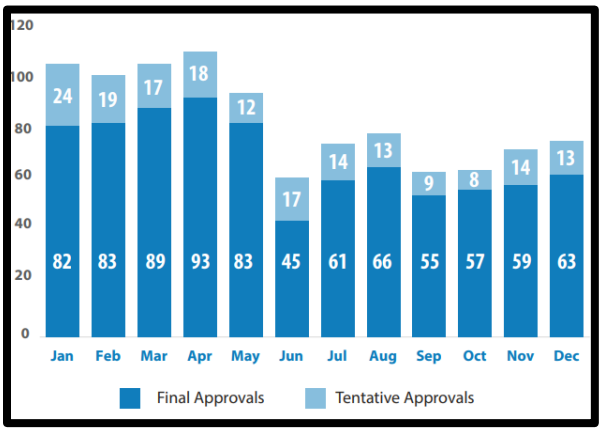


Figure 5: Generic Drugs Approved

[20]

This presentation shows that most of the drugs were approved from January to April, with an 82% to 93% final approval rate [20]. However, this has decreased from June to December. On the other hand, eCTD submissions were rejected due to a lack of lifecycle management. The first main reason for rejection was granularity, followed by templates. This signifies the challenges of the integrity of submission and integrity to eCTD technical requirements, where optimisation is essential.

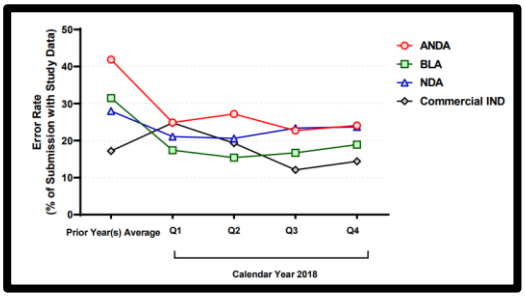


Figure 6: Conformance Trend for Validation Errors 1734 & 1736 in the Submissions

[21]

As per the above graph, submissions along with study data received during CY2018 showed overall decreases in Validation Errors 1734 and 1736 compared to prior years' average error rate [21]. In these cases, the submissions to Module 5 of this particular eCTD module have shown a substantial improvement relative to the quality and compliance, which is expected from tighter enforcement.

B. Findings

EctD is connected to this, and ectD encodes ectoine hydroxylase, which is necessary for the conversion of ectoine to 5-hydroxyectoine—a good osmoprotectant. EctD expression thus confers stress tolerance by allowing the use of 5 hydroxyectoine in response to osmotic stress [19]. This refers to an increased complexity and a need to gain specialised expertise in navigating regulatory requirements, including eCTD submissions. Such a trend suggests that benefits pertaining to harmonised global standards and ready to use tools to manage this complexity can come about.

Although the drug approval rate was higher from the month January to April [20]. There are 'Duplicate Sequence' and 'High Validation Errors' suggesting underlying issues in data management and technical compliance (Figure 6). There are errors in the submissions due to a lack of lifecycle management.

As seen in Figure 3, the positive result of stricter compliance with specific regulatory criteria translates to better submission quality (smaller number of FDA technical rejections post-enforcement). This therefore has a strong importance on clear, enforced guidelines and how harmonising those guidelines globally could significantly reduce errors. Together, these findings reinforce the importance of avenues to optimisation. This implies the need for solutions that can make the submission process easier.

C. Case study outcomes

Case Study	Key Outcomes	Relevance to the Study

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Eisai Co., Ltd.	Implemented PharmaDoc tools to streamline global eCTD compliance and automate validation. Reduced errors but faced performance issues with large volumes.	Demonstrates the importance of automation in optimizing eCTD submissions while highlighting scalability challenges.
Orbis Consumer Product Ltd.	Adopted eCTDBuilder® and a-Pulse® to reduce submission time from four weeks to four hours. Minimized manual errors and improved workflow efficiency.	Highlights the role of automation in expediting regulatory processes and reducing resource-intensive manual efforts.
European Pharma Company	Outsourced CMC strategy and eCTD publishing, improving submission timelines, dossier quality, and cost efficiency.	Emphasizes outsourcing as a viable strategy for optimizing eCTD submissions in resource-constrained settings.

Table 1: Case Study Outcomes
(Source: Self-created)

In Eisai Co., the establishment of eCTD compliance with PharmaDoc tools was faced when scalability was an issue. eCTDBuilder with a-Pulse reduced submission time, and improved efficiency. The European Pharma Company outsourced CMC strategy and eCTD publishing with an aim to improve timelines and cost efficiency and show various optimisation strategies.

D. Comparative analysis

Author(s)	Focus	Key Findings	Gaps
[6]	eCTD challenges in the US and Canada	Identified compliance issues and delays due to inconsistent eCTD validation across regulatory agencies.	Limited focus on non-Western countries' regulatory challenges.
[7]	eCTD implementation in the pharmaceutical industry	Highlighted the role of eCTD in reducing time for regulatory approvals but faced regional adoption differences.	Lack of in-depth exploration of industry-specific challenges across regions.
[8]	Global regulatory challenges in eCTD	Discussed the evolving role of eCTD in harmonizing submissions but identified	Limited examination of the technological advancements that could bridge

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		gaps in global standardization.	regulatory gaps.
[9]	Management of deficiencies in CTD dossiers	Emphasized differences in requirements between the US, EU, and Australia, affecting submission quality.	Did not explore how advanced technologies can overcome these regulatory discrepancies.
[10]	Post-Approval Change in Manufacturing Site	Detailed global requirements for manufacturing site changes in post-approval submissions.	Does not address the broader implications for eCTD adoption in other regions.
[11]	eCTD adoption strategy in China	Discussed challenges and strategies for eCTD implementation in China based on ICH experiences.	Focused only on China, lacking comparative analysis with other emerging markets.
[12]	Medical writing competency model	Identified essential skills and knowledge for regulatory writing in the eCTD context.	Does not fully address regulatory challenges in the eCTD process or its impact on submission efficiency.
[13]	Clinical Development Design (CDD) Framework	Introduced an information model for decision-making throughout the medical product lifecycle, enhancing submission consistency.	Did not explore specific barriers to eCTD implementation in diverse regulatory environments.

Table 2: Comparative Analysis
(Source: Self-Created)

This table suggests a major gap in the scope of eCTD global regulatory challenges. While there are a lot of studies oriented to specific regional challenges (the US, EU, China), technological advancement and cross-regional solutions as a solution are usually ignored. Regulatory discrepancies are most often identified by studies but are not addressed as to how AI or automation can try to standardise and streamline global

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submissions. Also, few authors have described in depth the industry-specific (or country-specific) problems.

V. DISCUSSION

A. Interpretation of results

This study presents results that point to severe optimisation problems in global eCTD submissions, mainly related to the existing inconsistencies in the regional regulatory set-ups, technological barriers and variations in the implementation of eCTD standards. Automation and specialised tools do show promise in generating more efficient automation, but scaling is not there yet. The findings emphasise the importance of harmonising submission processes and adopting advanced technologies. This will further streamline compliance in various regulatory environments to reduce submission time and reduce error rates.

B. Practical Implications

In the practical implications of the research, the pharmaceutical companies should invest on advanced automation tools and standardize eCTD across regions to overcome the regulatory discrepancies. Harmonized approach to submission formats with limit of technology can reduce submission error, increase compliance and short need cycle of approvals thus increasing the market access.

C. Challenges and Limitations

One challenge of this research is to rely on secondary data, which may not provide real-time insights or variances on a regional basis. Moreover, the variance of eCTD adoption across different countries does not allow generalisation of findings. Limitations of the study include reduced opportunities to access proprietary industry data.

D. Recommendations

This research suggests that pharmaceutical companies should focus on the implementation of standardized eCTD submission formats around all the regions of the world with minimum differences. Investing in automation tools to speed up the processes related to compliance and reduce errors will benefit them. Also, regulatory bodies should work together to establish the global harmonization standards for the eCTD submissions.

VI. CONCLUSION AND FUTURE WORK

Conclusion

This research concludes that global eCTD submissions require optimisation to improve regulations efficiency. In terms of tackling regional differences, automating, harmonisation and advanced technological processes can alleviate the submission process, and reduce errors. In terms of maintaining consistent and global compliance the collaboration between the pharmaceutical companies and the regulatory bodies is very essential.

Future Study

Future studies could examine real-time case studies in various regions and industries to evaluate the efficacy of automated solutions, regional harmonisation, and the role of regulatory authorities in prompting global standardisation.

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