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Advancing Pharmaceutical Regulatory Operations through Digital Submission Technologies: A Framework for Global Compliance

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ABSTRACT: This article explores the shift in pharmaceutical regulatory operations from document-based submissions relying on the electronic Common Technical Document of version 3.2.2 to data-based concepts underpinned by eCTD of version 4.0, which is based on the HL7 Regulated Product Submission standard with ISO Identification of Medicinal Products, Substance, Product, Organization, and Referential master data services. The core operational issues inherent in this transition process are then summarized, addressing the multi-year periods of cross-jurisdictional coexistence of both standards, the continual threat of gateway-level technical rejections due to errors in the XML backbone, metadata, and controlled vocabularies, as well as the inconsistent digital maturity of the principal regulatory bodies. A dual data-centric five-layer architecture to facilitate globally consistent compliance is supplemented by a five-level organizational maturity model, illustrative comparative jurisdictional timelines contrasting current requirements and future milestones, and a dual-pipeline implementation methodology which explicitly considers the transitional burden of operating parallel publishing environments. A brief description of the comparative regulatory methodology used and a transparent explanation of the study's limitations, especially regarding shifting agency timelines and the advisory nature of this framework, are provided.

KEYWORDS: eCTD v4.0, HL7 Regulated Product Submission, ISO IDMP, dual-standard transition, regulatory maturity model

I. INTRODUCTION

The current pharmaceutical regulatory landscape is characterised by a new era of product complexity, involving, but not limited to, ATMPs, combination products with medicinal and device attributes and digitally-enabled therapeutics, whose underlying algorithms and post-marketing real-world effectiveness evidences must be kept up-to-date, all of which produce disparate data flows-from cellular characterisation and viral-vector bio distribution studies to version-control of software and post-market algorithm efficacy measurement, which cannot be accommodated within the limits of traditional document-centric dossier infrastructures(Olesti Muñoz et al., 2024; Colloud et al., 2023). At the same time, the melting pot of globalized programs-of-development has tripled the number of simultaneous jurisdictional submissions with differing Module 1 regulations and validation procedures, whilst the hyper-speed of regulatory digital transformation has elevated structured data submission from a service for sponsors to an imperative for regulators (Miozza et al., 2024). The evolution of a regulatory submission has gone from a paper-only Common Technical Document (CTD), through an electronic non-eCTD Submission (NeeS) that was merely replacing paper with an unstructured set of PDFs, to the eCTD 3.2.2 version that has added an XML backbone for a hierarchical structure and additional lifecycle management (Suchanek & Ostermann, 2012). Even though eCTD v3.2.2 is now the most widely used version across all the main ICH regions and has greatly improved the navigation and version management, it has suffered from the document-centric design (fixed folder hierarchy and metadata limitations) that cannot fulfill the granular, re-usable and machine interpretable data requirements of the modern products and the future master-data standards like the ISO Identification of Medicinal Products (IDMP) and the associated Substance, Product, Organization and Referential (SPOR) services (Suchanek & Ostermann, 2012). The evolution to eCTD version 4.0, based on the HL7 Regulated Product Submission (RPS) standard, is a fundamental architectural evolution to a message-based, Controlled-Vocabulary-Driven design supporting a single XML exchange unit, UUID-based document reuse, and richer lifecycle operations (Sudesamithiran, 2023).

Beyond the technical development of submission formats and structures, the operational implications of a longstanding dependency on a document-centered document-centered paradigm have also become increasingly clear. Empirical

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research and conceptual arguments indicate that traditional eCTD working procedures entail high levels of repetitive authoring, rechecking, and version-management costs, particularly where chemistry, manufacturing and controls content needs to be adapted for each jurisdiction and stage of the product lifecycle (Algorri et al, 2020). Structured content and data management methodologies that treat regulatory information as reusable, semantically coded data components instead of fixed PDF pages can contribute to cost savings and enhanced data quality, as well as enabling downstream automation (Algorri et al., 2020; Beierle et al., 2023). As regulators steadily roll out IDMP-aligned master data specifications and continue to converge on eCTD v4.0, the organizational ability to sustain a single source of structured data for the whole product portfolio will be an important source of cost efficiencies, troubleshooting agility, and readiness for future requirements. This article therefore aims to provide a systematic, multi-tiered framework for supporting multi-site worldwide compliance over a multi-year period of dual standards, while analyzing the technical and operational challenges in the envisaged transition from document-oriented to data-oriented submissions. The regulatory comparison approach has been employed in this article with mainly the official guidances and implementation packages released by the U.S. Food and Drug Administration, the European Medicines Agency, the International Council for Harmonisation and the Pharmaceuticals and Medical Devices Agency of Japan, alongside the peer-reviewed literature after 2023; the illustrative cases have been limited to situations that are already known to the public such as the April 2026 PMDA eCTD v4.0 requirement.

II. REGULATORY LANDSCAPE AND THE SHIFT TO DATA-CENTRIC SUBMISSIONS

The global landscape for pharma submissions is evolving from document-based electronic Common Technical Document (eCTD) v3.2.2 arrangements to data-driven models based on eCTD v4.0 and the HL7 Regulated Product Submission (RPS) schema. Progress is very uneven across regions. Japan's Pharmaceuticals and Medical Devices Agency (PMDA) took the pioneering step of mandating eCTD v4.0 for all new applications from 1st April 2026, following a technical pilot in 2021 and voluntary use from 2022 (Pharmaceuticals and Medical Devices Agency, 2025–26). The European Medicines Agency (EMA) supports the centralized procedure, offering optional use of eCTD v4.0 from 22nd December 2025, with 'Mandatory use in the 1st quarter of 2027 and 'Mandatory use in the 1st quarter of 2028' (European Medicines Agency, 2025–26). Pilots are still in progress for updates to existing eCTD v3.2.2 dossiers. The US Food and Drug Administration (FDA) has accepted eCTD v4.0 submissions voluntarily since 16th September 2024, although a mandatory date has not been set and is expected to be proposed around 2029 (US Food and Drug Administration, 2024–26). The other agencies are at different points of readiness, leading to a multi-year window during which companies have had to support both standards.

Agency	Current Status	Next Milestone	Indicative Date	Primary Source
PMDA (Japan)	Mandatory for all new applications	Full mandatory use in force	1 April 2026	PMDA eCTD v4.0 Implementation Guide
EMA (EU)	Optional for new CAP MAAs	Strongly recommended use	Q1 2027	EMA eSubmission updates
EMA (EU)	Optional for new CAP MAAs	Mandatory for new CAP MAAs	Q1 2028	EMA eSubmission updates
FDA (United States)	Voluntary for new applications	Mandatory use (projected)	Around 2029	FDA eCTD Submission Standards
Health Canada	Optional / pilot stage	Mandatory use	2027–2028 (projected)	Health Canada draft guidance
Swissmedic	Technical implementation ongoing	Voluntary use followed by mandatory	2027 (voluntary) / later mandatory	Swissmedic implementation notices
TGA (Australia)	Planning / pilot stage	Voluntary then mandatory	Timeline under review	TGA eCTD communications

Table 1: The table presents a comparative evaluation of model performance across key documentation tasks, highlighting code comment quality, API documentation, repository summaries, and overall documentation scores for different AI model families.

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Several ICH guidelines support this change. ICH M4, the basic ICH structure support document, defines the overall content of an eCTD submission. M2, a precursor to M8, spells out the original rules for electronic submission transmissions. M8 defines the full technical specification for eCTD v4.0 and the associated controlled vocabularies. M5 defines the data elements and drug dictionaries, and M11 defines the clinical electronic structured harmonized protocol (International Council for Harmonization, 2015/2024–2026). M8, M5, and M11 support a move away from static folders and PDF-structured submissions to message-based units, enabling document and section reuse through globally unique identifiers, more dynamic lifecycle management, and additional metadata levels.

Legal requirements also contribute to the move to structured data. In the EU, Commission Implementing Regulation (EU) No 520/2012, Articles 25 and 26, mandate the use of internationally agreed terminology and formats, including the ISO Identification of Medicinal Products (IDMP) standards. This provides the legal basis for the Substance, Product, Organization and Referential (SPOR) services (European Union, 2012). The addition of matching FDA rules and guidance on electronic submissions and the Electronic Submissions Gateway Next Generation (ESG NextGen) creates similar requirements in the United States. At the same time, post-marketing safety reporting is evolving: from 1 October 2026, individual case safety reports submitted through ESG NextGen must adopt the ICH E2B(R3) data standard; the older E2B(R2) format will no longer be accepted (U.S. Food and Drug Administration, 2026).

The consequence of the resulting bi-modal environment, with disparate region-specific Module 1 requirements and differing submission deadlines, all integrated into a single operational environment, is the most pressing operational problem for global regulatory teams. The only compliance model that works allows simultaneous publishing streams, region-specific controlled vocabularies, and the convergence of pre- and post-approval data exchange standards.

III. OPERATIONAL CHALLENGES IN THE TRANSITIONAL ENVIRONMENT

Transitioning from eCTD v3.2.2 to eCTD v4.0 presents a set of operational challenges with implications for daily regulatory activities. The most tangible and immediately measurable hazard is rejection at the Gateway: erroneous XML backbone structures, incorrect or absent module-specific descriptive metadata, or use of uncontrolled vocabulary (or obsolete terms) regularly result in rejection at the next higher review activity (U.S. Food and Drug Administration, 2024–2026; European Medicines Agency, 2025–2026). Gateway rejection delays the review schedule and adds staff time for diagnostics and resubmission (Ahluwalia et al., 2025). Regional validation criteria vary dramatically, a package that passes one agency's schema validations and business rules will have parts rejected by a second agency due to differences in controlled vocabularies, Module 1 formatting, or stylesheet defaults (Kuwahara et al., 2025). Experience with digital transition efforts has shown that problems with analog transformation, legacy information systems, and incomplete evolution of host-to-source translation rules are common saddle points for projects during transition (Lyles et al., 2025). The observed result is not just navigational delay but a significant increment in operational cycle time as submission calendars spiral. At the same time, staff perform rework and retries or re-prioritize advanced activities to accommodate processing delays and internal QC loops. Without established infrastructure for validation and standardization, sponsors develop internal checks, which are useful but still add to global programs' cycle time; in tomorrow's market space, other programs cover various post-market lives.

A second large overhead is the need to operate two parallel publishing toolchains. Many sponsors are obliged to support eCTD v3.2.2 and eCTD v4.0 environments for several years, requiring duplicate software configurations and dual knowledge/skill sets, and often more reliance upon external publishing vendors. This leads to doubled expenditure on publishing licensing and validation, and doubled risk of mismatched content between the two format versions, due to inconsistent authoring practices, tool behavior, tool output, or target hierarchies. Managing parallel toolchains substantially increases the number of workflows needed to generate eCTD, significantly raising the overall total of authoring, validation, and publishing licenses or subscriptions, and creating divergent SOPs that can themselves need version control. Lessons learned from digital transformation projects have been drawn from companies that are still heavily dependent on document-based processes while supporting both message and document-centric backbone structures: ‘Supporting dual hierarchies producing the same content introduces inefficiencies’ (Ahluwalia et al., 2025). Published content can be converted once and still undergo reprocessing to produce both delivery formats, with the risk of content increments appearing in only one. Reconciling two sets of file versions and content is yet another operational challenge, adding to regulatory teams’ stressed workload.

Data integrity continues to be an issue. Under ALCOA+ (Attributable, Legible, Contemporaneous, Original, Accurate and Complete, Consistent, Enduring and Available), all transition formats or new systems must ensure the integrity of

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the underlying data carried across. Moving content from a document-centric to a data-centric architecture inevitably increases the risk of transcription errors, incomplete audit-trail histories or contextual loss, particularly where multiple systems, locations, or external agency interfaces are involved. The shift adds risk because the structured elements (UUIDs, controlled-vocabulary linkage, cross-sequence validity constraints) must be produced and reproduced, even tightened, in a single, strict, semi-structured, identifier-based paper files concept rather than the folder- and PDF-equipped breeze of v3.2.2. Incomplete mappings between regulatory information management systems, publishing engines, and agency portals often require workarounds, which then become sources of transcription error or audit-trail deficiency. More global contextual maturity-development studies demonstrate that those with immature data management practices experience higher challenges during the multi-standard coexistence phase (Chong et al., 2024). The result appears to be that implementing both standards is noticeably more complex operationally than either standard alone, not just for publishing logistics but also for fundamental issues of data quality, auditability, and internal capacity, which ultimately reveal whether the automation benefits promised by eCTD v4.0 can be realized without sacrificing compliance.

The restrictions imposed by interoperability add to the operational challenges. Data systems held by sponsors, contract research organizations, regulatory information management systems, and agency gateways often employ dissimilar data models and exchange formats. Partial mapping between these systems entails additional manual workarounds, longer data transfer times, and multiple quality assurance checks. Such frictions are aggravated for advanced therapy medicinal products and big multi-market programs, which produce intricate and voluminous data files.

Regional variation in technical validation requirements introduces a further challenge that at least offsets normalization-level process efficiencies gained during the dual-standard transition. Each regulatory authority has its own set of validation rules, controlled vocabularies, Module 1 definition, and business-rule engines. For example, a package validated successfully against one gateway is not necessarily validated against another because of differences in demand for the structure of the XML backbone, encoding of metadata, UUID positioning, or presence of authority-accepted terms. FDA, EMA, and PMDA published different guidance on technical conformance, perhaps harmonized to ICH M8 but differing largely in interpretation and implementation details (U.S. Food and Drug Administration, 2024–2026; European Medicines Agency, 2025–2026; Pharmaceuticals and Medical Devices Agency, 2025–2026). Therefore, sponsors are forced to adapt multiple packaging and validation toolsets for different regions, preventing horizontal scaling of the process to various portfolios. This results in greater resource requirements, potentially mismatched content between parallel pipelines, and extended timelines. Divergence in regional validation requirements may remain a cost-inflating bottleneck in multi-jurisdictional filing (Ahluwalia et al., 2025; Chong et al., 2024).

These factors ultimately decide how realistic the transition will be to implement in practice. It is a logistics problem requiring employees to retrain in new technical skills beyond their existing roles, as well as overhauls of organizational structures and other operating procedures. Simultaneously, the transition's reliance on more interconnected digital systems expands the attack surface for cybersecurity threats, requiring improved access controls, monitoring, and response capabilities. These factors together reveal that this transition is not just another technical upgrade but an organizational and operational issue.

IV. DIGITAL SUBMISSION TECHNOLOGIES AND STANDARDS

The regulatory submission packaging structure is being transitioned from a primarily document-based index with a data-centric approach (eCTD version 3.x & 3.2.2) toward a primarily data-centric model utilizing a compelling set of standards that combines a robust message transcript with strong controlled-vocabulary binding to track specific data content units throughout development and lifecycle model (eCTD version 4.0). The XML-based file index topology, based on a hierarchical directory structure, is extremely flexible about combining and repurposing different data content units; however, it constrains reuse and data-specific granularity (Tobias et al., 2014). Overall, the eCTD v4.0 structure is designed on the HL7 Regulated Product Submission (RPS) specification that allows explicit referencing of individual content units across lifecycle transitions in conjunction with product-specific combinations of data content units throughout the development process controlled vocabulary tagging is applied at many levels to enable tracking of content objects across submission units (universe of concatenated data content units) (International Council for Harmonization, 2015/2024-2026). The metadata-driven, content element-specific, process-centric model supports application of individual data content units to products throughout processing without universally re-issuing unchanged data content units. The FHIR standards are categorized as a separate interoperability construct, using the FHIR content

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specification to enable structured content transmission between application systems of organizations, sponsors, and agencies. It is not, however, recognized as the packaging "mechanism" of eCTD v4.0.

Electronic submission gateways serve as the initial transmission and automated validation point. The U.S. Food and Drug Administration Electronic Submissions Gateway has developed Next Generation infrastructure, including application programming interface (API) endpoints for machine-to-machine communication, advanced security with AS2 (Applicability Statement 2) protocols for secure point-to-point transmission, and a Unified Submission Portal with real-time status and acknowledgment messaging. Similar preparation infrastructure at the European Medicines Agency performs schema validation against regional Module 1 specifications and business rules before review access. These gateways enforce increasingly rigorous technical parameters, so that backbone structure, metadata coding, or the use of controlled vocabulary is immediately rejected for non-compliance before scientific review (U.S. Food and Drug Administration, 2024–26; European Medicines Agency, 2025–26).

Regulatory information management (RIM) systems are an integral element of all sponsor-centric data governance frameworks. They enable compliant, disciplined maintenance of business-critical master data governed to the four SPOR services: Substance, Product, Organization, and Referential Management Services, laid out within the suite of ISO IDMP standards applicable across the European Union for the life cycle of medicinal products. In conjunction with publishing engines, these appropriately tailor the RIM systems to serve as the single "on-line" source of information for both eCTD creation and agency portal submission interactions, naturally enforcing global consistency in the way trade names and non-proprietary names are used and minimizing transcription errors.

Artificial intelligence and machine-learning applications can also be characterized by their levels of maturity within the regulatory domain. Operational use cases involve automated validation against region-specific common technical document (CTD) modules, metadata integrity, controlled-vocabulary similarity, and content matching, as well as automated classification into appropriate eCTD module structures. Applications still emerging but not currently in production include, for example, generative functionality supporting first-draft content generation, predictive functions for estimating adherence scores from historical rejection trends, and fully automated CTD assembly. These higher-order use cases are constrained by limitations in data quality, human oversight, and validated regulatory pathways for the provision of AI-generated products (Kargren et al., 2023).

Distributed-ledger-based frameworks to date, however, have not moved beyond thinktank pilot stages and settlements, whether regulatory or content-publishing authorities sanction such artifacts as mandatory components of a submission. To be fit-for-digital submission, architectures must therefore enable the semantic and technical interoperability of submission content with clinical, chemistry-manufacturing-control (CMC) and pharmacovigilance ontologies and data-sets; metadata-tagged structured content methodologies, such as modular content, enable the componentization of information at scale, systems/market-wide, to be multiplexed across multiple eCTD modules, and future lifecycle streams, without the need to duplicate manual transcription processes(Kargren etal, 2023).

V. A FRAMEWORK FOR GLOBAL COMPLIANCE: ARCHITECTURE, MATURITY, IMPLEMENTATION AND OUTLOOK

The persistent coexistence of eCTD version 3.2.2 and eCTD version 4.0, the varied jurisdictional preparedness, and the concurrent development of master-data and safety-reporting standards call for a coordinated organizational approach. The five-layer structure shown in the diagram is just that. Rather than restating the content of each layer, the discussion that follows explores how the architecture operates holistically as a system, how organizations can evaluate their preparedness via a complementary maturity model, and what immediate and future-oriented issues emerge during rollout.

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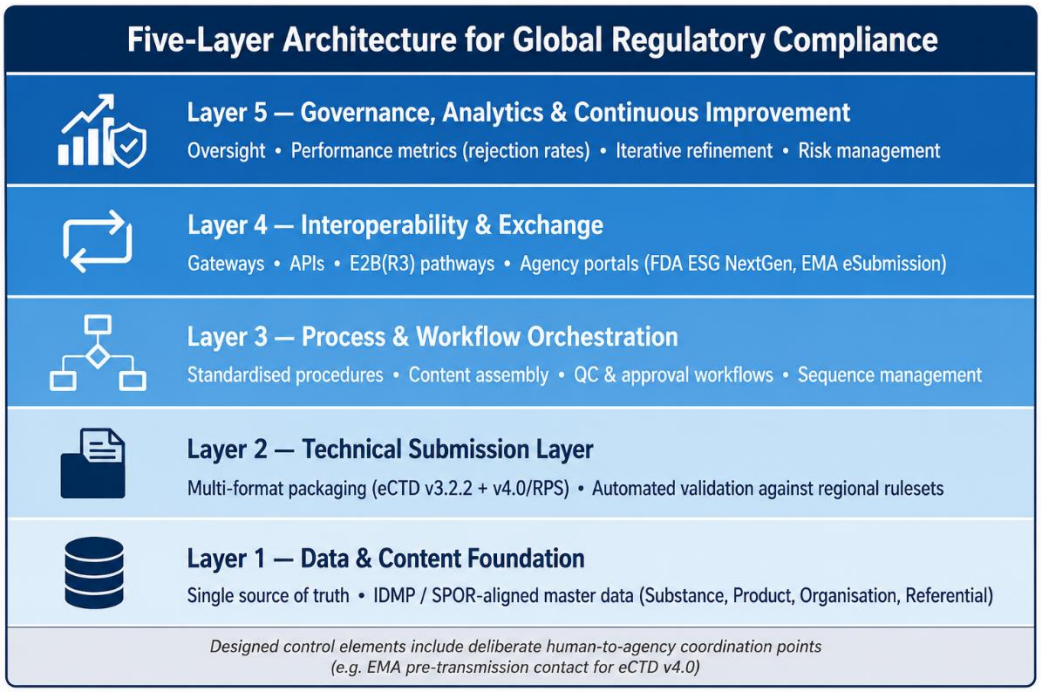

Figure 1. Five-layer architecture for global regulatory compliance, illustrating the integrated foundation, submission, workflow, interoperability, and governance components supporting regulatory submissions.

Treating human-to-agency co-ordination as a deliberate control process rather than an informal exception, the EMA's guideline that sponsors must make contact before submitting an initial eCTD v4.0 dossier for a new centrally authorized product is an example of this. The same liaison approach is being adopted with other regulators. It is expected to mitigate obvious and remediable technical rejections, and demarcate region-specific understanding of controlled vocabularies and validation requirements. This framework can be mapped onto current agency expectations: the data layer can underpin the ISO IDMP requirements and the SPOR services; the technical, interoperability, and the business or workflow layer can implement the ICH M8 specifications, the FDA technical conformance guidance, and the EMA gateway; and the governance layer can enumerate the internal quality-system functions and the external horizon responsibilities PMID-26958950.

Organizational capability improvements could be tracked along a five-step maturity model that sequences capability development. The first maturity level refers to an organization that maintains residual paper-based or non-eCTD electronic operations. The second level is an operational state in which an organization meets the transition baseline of stable eCTD version 3.2.2 compliance. The third maturity level involves an organization whose information management system is integrated with systematic master-data management. The fourth maturity level is where an organization endorses active participation in eCTD version 4.0 pilots while maintaining a dual-pipeline capability. The highest maturity level is defined by a fully structured, data-driven operation that can support simultaneous multi-jurisdictional filings with very low manual overhead. Similar constructs have been successfully implemented in related pharmaceutical areas of practice, such as risk-based quality management of clinical trials, and show that staged maturities are likely to have many uses, including diagnostic functions and planning (Florez et al., 2025).

Implementation requires dedicated focus on the dual-standard environment. Organizations must sustain parallel publishing systems, develop dual technical capabilities, and create cross-disciplinary governance that combines Regulatory operations, Information Technology, QA, and PV teams. The most significant risks are increased rejection rates and high ongoing costs. Proactive engagement with agency-specific technical contacts from an early stage can alleviate these risks. State-enabled critical path milestones, mandatory adoption of eCTD version 4.0 by Japan from 4/26, phased migration of centrally authorized products by EMA, and optional adoption of version 4.0 by the FDA, followed by E2B(R3) from 10/26, offer firm indicators of progression. However, using these milestones as the basis for

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quantitative performance estimates should be approached with care; to date, independently validated comparative statistics are sparse.

Expected advantages include minimizing the replication of repetitive work, advancing uniformity of a global information 'brand', a steady decline in technical rejection levels, and increased ability to cope with complex global portfolios. Continuing hurdles are the resource cost of running two flows, ongoing regional variation in validation standards, and the organizational change required to adopt data- vs. document-centric working practices. Key factors to success are continued senior management support, rigorous master-data governance, and proactive communication with regulatory agencies prior to major format changes.

For the future, this two-tier characterization of AI applications still seems relevant. Applications providing automated validation and QC can be integrated online into operational workflows in the near future. More advanced applications, such as generative dossier support, are not likely to emerge before well -validated data models and proven organizational infrastructures exist. Evidence of such a trend is provided by the recent pilot trial using digitalized CMC dossiers and applications and E2B(R3) safety reporting, concurrently accepted by two separate Agencies, validating the dynamic but also organizational resources still required to reach that point (Algorri et al., 2026). Ultimately, one single interconnected regulatory information universe is the end state, with E2B(R3) safety reporting, eCTD v 4.0 and IDMP/SPOR master data forming its nuclei.

Significant limitations apply to the analysis performed. The regulatory timelines for eCTD ver4.0 mandates, SPOR rollout, and E2B (R3) deadlines remain pending. The architecture and maturity model presented are conceptual reference artifacts and should not be interpreted as validated implementation benchmarks; publicly available quantitative data for efficiency or cost performance is limited.

VI. CONCLUSION

The paradigm shift from document-centric eCTD version 3.2.2 filings to the inherently data-centric architecture of eCTD version 4.0 constitutes a global change to pharmaceutical regulatory operations, demanding that organizations evolve beyond familiar publishing workflows to interconnected, standards-compliant electronic compliance ecosystems. Ongoing compliance across the dual-standard transition will rely on harmonized HL7 RPS, ICH M8, ISO IDMP/SPOR, and regional technical validation processes, with concurrent publishing channels, effective data governance, formal quality control procedures, and interaction with regulators. As the industry adapts to converged electronic regulatory environments based on interoperable neutral structured data, organizations that embed these capabilities will be able to leverage digital regulatory operations as a competitive advantage that optimizes compliance and increases global regulatory agility.

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