DIA Regulatory Affairs Community
Regulatory Information Management (RIM)
Working Group

Regulatory Information Management Whitepaper V2.0

V. Balasubramanian[1], Vanessa Brewer-Yizar[2], Kathie Clark[3], Bernie Coney[4], Joel Finkle[5], Vahé Ghahraman[6], Sheila Mahoney-Jewels[7], Don Palmer[8], Keith Parent[9], Pat Shafer[10], Cary Smithson[11]

Abstract

The Regulatory Information Management Working Group (RIMWG) of DIA's Regulatory Affairs Community has identified significant potential value from development of a RIM Reference Model, a conceptual framework for Regulatory Information Management (RIM) systems and processes. The Reference Model is intended to aid organizations in structuring the complex organizational, data, process, information, and workflow issues as they implement or upgrade their RIM systems. The ultimate goal of these efforts is to enable RIM to be a strategic corporate asset that will have direct impact on a life sciences organization's operations as well as efficient and effective delivery of needed treatments to patients.

This Whitepaper reflects the experience of the authors, who have previously supported RIM initiatives within their companies or with their clients and addresses the multiple capabilities that define RIM. Version 2.0 builds upon the original Consensus Paper by updating content and adding capability areas. The key objective of this initiative is to define an "ideal RIM state" in the form of RIM Reference Model made of a collection of data, process and organizational constructs which could be used as a framework for sponsors, vendors and systems integrators to optimize Regulatory processes.

Keywords:
Regulatory Information Management, RIM, data governance, regulatory data quality, regulatory systems

[1] V. Balasubramanian, PhD, Senior Vice President, Life Sciences, Orion Innovation,
[2] Vanessa Brewer-Yizar, Senior Manager, SG Research International,
[3] Kathie Clark, Product Director, Ennov Software for Life
[4] Bernie Coney, Head of Assay Content Development and Product Labeling at Siemens Healthineers
[5] Joel Finkle, Associate Director, Regulatory Information Management, BeiGene
[6] Vahé Ghahraman, PhD, Senior Director, Global Regulatory Operations Head, Apellis Pharmaceuticals, Inc
[7] Sheila Mahoney-Jewels, CEO, Life Sciences Hub
[8] Don Palmer, MA, Senior Director, Regulatory Affairs, Business and Technology Transformation, IQVIA
[9] Keith Parent, CEO Court Square Group
[10] Patterson Shafer, Managing Director, FTI Consulting, Inc.
[11] Cary Smithson, MBA, Director, Transformation Advisory, Grant Thornton LLP

Contents

1. Introduction

Organizations engaged in drug development face an increasingly challenging environment: an expanding global footprint, evolving regulatory requirements, dynamic partnership models, new roles within the regulatory organization, and rapidly evolving technology. At the same time, many organizations are also innovating on the capture and use of regulatory data. Organizations, both sponsors and the vendors that serve them, have developed organic solutions that are fit for specific purposes. The resulting bespoke systems are not always harmonized in data structure, approach, or terminology, which compounds the complexity.

Based upon the successes in other industries, the global pharmaceutical, biotech and medical device sectors have recognized that data have a major and quantifiable potential impact on improving operational efficiency, decision making, and data security. Efficiently managing this complexity could be greatly enhanced by a unified description of an "Ideal State" of RIM, in terms of harmonized definitions of common processes and concepts, systems used, data entities, master data, and governance structures. This ideal state is unlikely to be achieved in full in actual practice, as many initial RIM approaches have already been implemented. In some cases, these approaches are, if not truly mature, individually entrenched, and are now causing companies to think about integrated solutions. However, as RIM evolves, the opportunity is increasing to capitalize on data to support improved regulatory planning. RIM is becoming an increasingly impactful asset.

2. Defining the Scope of Regulatory Information Management (RIM)

Regulatory Information Management means different things to different people. As part of harmonizing the terminology and defining standards, the first order of business for the RIMWG is to define RIM. Regulatory Information Management refers to the effective and efficient identification, collection, curation, communication, and management of regulatory information for products across the life sciences value chain. At a high-level, regulatory information includes regulatory and submission intelligence / health authority submission / reporting requirements, submission plans for new products and life cycle management activities including regulatory commitments and other obligations, product registration information, labelling, CMC, and safety submissions, communications from health authorities including but not limited to questions and answers during the submission/registration process, submissions (published, both electronic and otherwise), etc. Regulatory information can be in the form of data, meta-data, documents, and knowledge.

The work done by Steve Gens and Associates (Gens 2020) suggests a total of fifteen components being defined as an integral part of the end-to-end RIM landscape of capabilities, and 10 connection points.

15 RIM Categories
1) **Submission Forecasting and Resource Planning**
2) **Dossier Management** (content plan, distribution, archive)
3) **Submission Document Management**
4) **Submission Production** (assemble, publish, QC, dispatch)
5) **Submission Planning and Tracking**
6) **Product Registration Management**
7) **Health Authority Commitment Management**
8) **Health Authority Interactions** (Q&A, correspondence)
9) **Regulatory Archive**

10) **Label Management** (Content Control & Compliance Tracking)
11) **Reporting, Analytics, Dashboard**
12) **Data Standards and Governance Management**
13) **Design History File – Medical Device**
14) **Regulatory Intelligence**
15) **Ad / Promo**

10 Connection Points
1. **Product Change Control Process**
2. **Product Supply Release**
3. **Clinical (eTMF)**
4. **Clinical Trial Tracking (CTMS)**
5. **Label Artwork Management**
6. **Enterprise Portfolio Management**
7. **PLM** (typically Medical Device)
8. **Master Data Management**
9. **Data Lake** (pooling from multiple systems)
10. **Safety / PV**

While we acknowledge that RIM has broader reach and scope, we start with addressing some key components of RIM that are traditionally understood as in-scope for RIM. We welcome broader industry participation and the expertise of individuals who could join our efforts as volunteers to further the cause of this working group and contribute to the creation of artifacts to benefit the industry. As the paper evolves, we will be adding more comprehensive definitions and other components not initially covered by this version of the paper. We expect this to be a "living document" until it covers all the components that are being included within the scope of RIM.

3. Development of a Vision and Outline for a RIM Framework

The RIM Working Group's (RIMWG) genesis was at an "Ask the Experts" Panel at the May 2015 DIA eRegulatory and Intelligence conference. The discussion revolved around the unprecedented success of the DIA Trial Master File (TMF) Reference Model, the main deliverable of the TMF Working Group in the DIA's Document and Records Management Community. Parallels were drawn between RIM today and TMF's disorganized and problematic status when it started in 2008: both are critical to the efficient, effective work being done, but not directly related to regulations or submissions – which has been the primary driver of regulatory technology solutions to date. After the session, several participants including Sheila Mahoney-Jewels and Peter Terbeek (Terbeek and Mahoney-Jewels, 2017) co-founded the nascent RIM working group with the goal of replicating the TMF Reference Model's extraordinary self-organizing state of 2015.

The initial goal was to develop a RIM Reference Model, but the group decided that was too ambitious at that time[12]. Like RIM, TMF lacked agency guidance, however still had far more traditional structure than the wide-open space of RIM. The initial meetings were comprised of a small number of sponsor companies and service

[12] The lack of structure was a primary reason for tackling the Reference Model in 2018

providers that were passionate about improving RIM for Industry. Within a few months of the conference, the group transformed to a Working Group, with the intention of identifying specific deliverables over time.

For several months, during its early formation period, the group attempted to be part of the IRISS Forum or one of the Regulatory Affairs Communities under DIA. During this time, the Working Group did not widely advertise additional participation beyond the initial five to ten regulatory participants, due to the need for greater organization and ability to mobilize wider membership. Also, during this time, the group drafted an initial Charter, and began to identify potential deliverables of the WG. After several months of these foundational activities, a group vote was taken to decide that the Working Group become part of the DIA. This was due to:

- DIA's greater size, ability to reach greater numbers of more diverse types of regulatory professionals (membership over 10,000, vs. IRISS' approximately 4-500).
- The WG's closest inspirations and experiences resided in DIA, namely the TMF Reference Model and Electronic Document Management Reference Model.
- Whereas IRISS' main, and significant, attraction was its responsiveness to its members, its focused attention and impressive support tools, the WG felt IRISS' core focus on submissions and implantation of supporting systems was too restrictive for RIM, which, though related, is a much broader topic. The DIA's Regulatory Affairs Community (RAC) already had several long established and productive Working Groups such as Regulatory Intelligence and Labelling which were both complimentary to the RIMWG goals and potentially mutually beneficial.

2018 saw an updated vision for the deliverables:

1. RIM Whitepaper 2.0 (originally the RIM *Elements Catalog*): Basic definitions of main components or business capabilities recommended to move towards leading practice "RIM", broken out by the following capabilities:

    - Correspondence and Commitments
    - Labelling
    - Product Registration Management
    - Regulatory Analytics
    - Submission Planning and Tracking
    - Publishing and Submissions
    - CMC Submissions
    - Data Quality and Data Governance
    - Regulatory Intelligence
    - Cross Functional Touchpoints
    - Change Control and Variation Management
    - Advertising and Promotional Material
    - Opportunities for Artificial Intelligence

This also sought to identify common related systems, as well as data ownership/governance/consumption. The goal of RIM Elements was not to create a binding definition, rather an "ideal state" recommended by the WG, and thus become a clarification tool to help regulatory professionals implement sensible changes and move towards the ideal state over time. The ultimate objective of the RIM Elements catalog is to define a RIM Reference Model as a guide to sponsors, vendors, and systems integrators to adhere to some common terminologies and business/system capabilities.

2. RIM Reference Model: Before introducing the RIM Reference Model, it is helpful to look at the definition of a Reference Model, by the Organization for the Advancement of Structured Information Standards (OASIS), which states:

"A reference model is an abstract framework for understanding significant relationships among the entities of some environment, and for the development of consistent standards or specifications supporting that environment. A reference model is based on a small number of unifying concepts and may be used as a basis for education and explaining standards to a non-specialist. A reference model is not directly tied to any standards, technologies or other concrete implementation details, but it does seek to provide a common semantics that can be used unambiguously across and between different implementations."

In the spirit of the above OASIS definition, the objectives of the RIM Reference Model can be described as follows:

- Develop a core data/information model centered around the needs of RIM capabilities as addressed in this Whitepaper.
- Address common regulatory information needs of sponsors.
- Enable regulatory and other functional areas to have better line of sight around product information, regulatory activities, and other related information.
- Define commonly occurring objects/concepts, relationships, and related data in a simple and user-friendly manner.
- Define common terminology to enable effective implementation of Regulatory Information Management (RIM) solutions.
- Create a common understanding to increase inter-operability of RIM processes and systems, especially in situations around Mergers and Acquisitions.

Also, the RIM Reference Model is not a standard but a framework which provides the basis for common definitions and common understanding of RIM business processes and related objects. The Model was created based on detailed analysis of processes around investigational and marketed regulatory activities, initially for drugs and biologics, which can be extended to medical devices easily in future versions. While the Submission EDM and TMF Reference Models are based on artifacts such as documents and their meta-data, the RIM Reference Model is about RIM processes, related objects, and their attributes. Therefore, the RIM Reference Model is process- and data-centric, while the other models are document/metadata-centric.

3.1 Organization of the Reference Model

The reference model is organized using the framework shown below. At the highest level is the functional area supported, which in this case is Regulatory Affairs. A given functional area is responsible for a set of activities specific to that area to meet specific business objectives. For example, Regulatory Affairs is responsible for Investigational and Marketing Registration Activities to meet the objectives of initiating clinical trials and/or obtaining marketing approval. These activities drive processes. For example, an Investigational activity may drive the CTA Application Process. This process references certain other objects such as the specific Health Authority to which the Application is being submitted and the corresponding Application Object. The Health Authority or Application Object is defined by their Attributes such as Health Authority Name, Application Number, Status, etc. A given process may contain other processes within it. For example, the CTA Application Process may result in interactions with the Health Authority resulting in the creation of either Submission Objects or Correspondence Objects. Submission Objects are further defined by attributes such as Submission Number, Submission Format, etc.

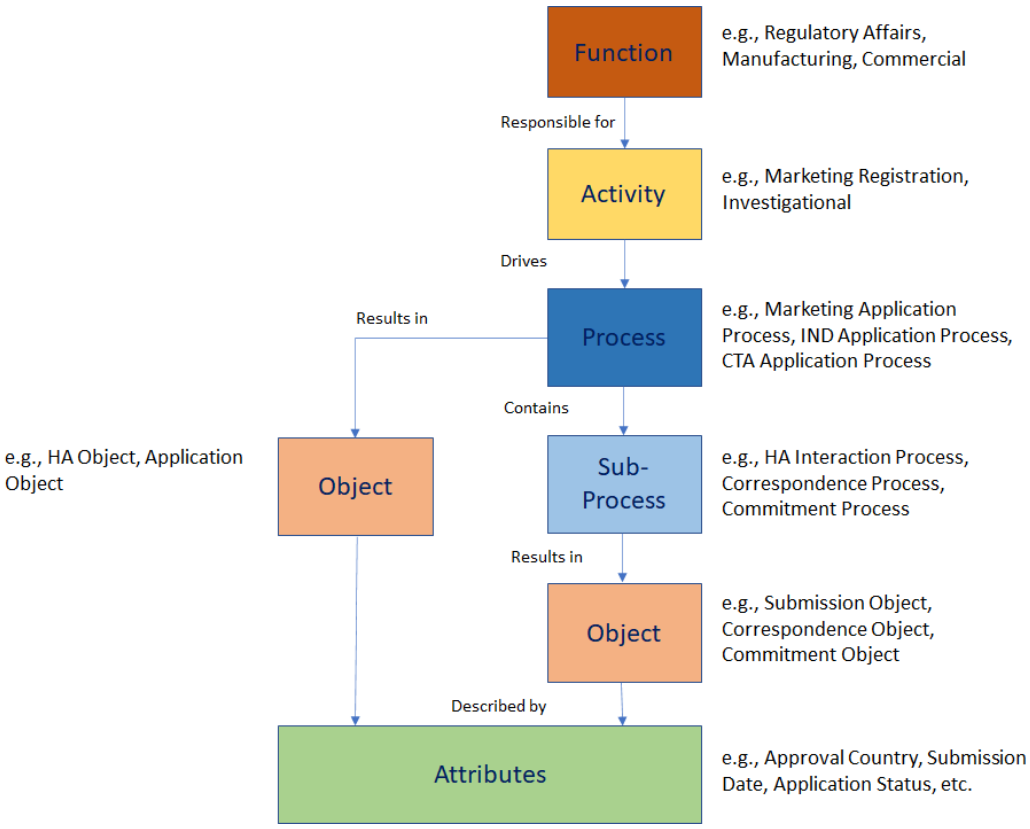


Figure 1. RIM Reference Model Framework

The combination of Function, Activity, Processes, and Object define the context of each attribute. For example, a Submission Type depends upon the context of the submission – Investigational Activity, IND Application Process, Health Authority Interaction Sub-Process, Submission Object. The values of Submission Type will differ based upon the context – e.g. for a CTA Application Process, IND Application Process, or a Marketing Application Process.

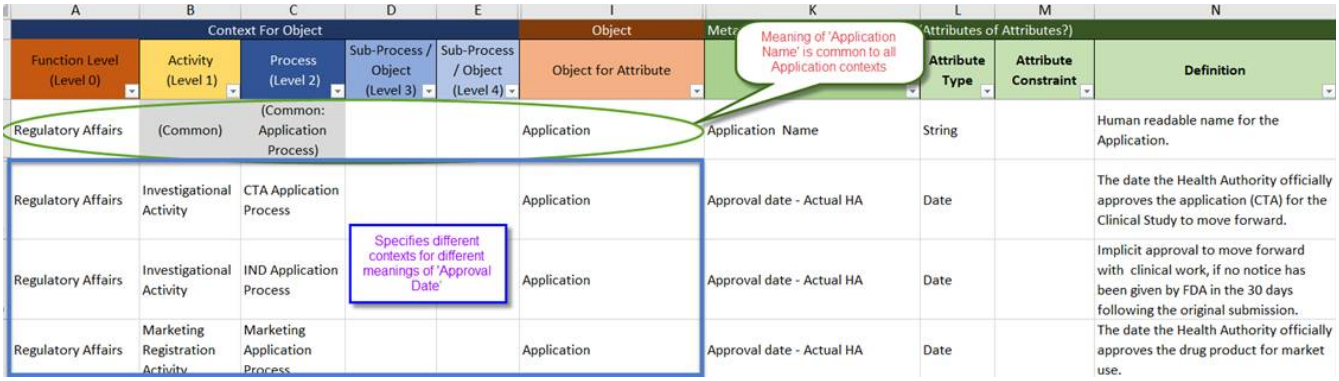
The initial draft of the Reference Model contains about 200 attributes spread across the following key Objects supporting regulatory processes:

1. Common [to all contexts]
2. Application
3. Regulatory Activity
4. Correspondence
5. Commitment
6. Organization
7. Label
8. Product
9. Submission

There are two important aspects to be noted in the Reference Model:

a. There are several places the word “Common” is used. This is to denote some commonality in processes and objects. For example, the attribute called Application Name is common whether it be an Investigational Activity such as a CTA or a Marketing Registration Activity such as MAA/NDA.

b. On the other hand, there are attributes which are context-specific whose meanings change based on the context. For example, the attribute called Approval Date has different meanings for different contexts, based on whether it is an Investigational Activity or a Marketing Registration Activity. For a CTA, Approval Date means when the clinical trial could start whereas for a MAA, Approval Date means when the product is approved for marketing in a given market. Approval Date for an IND indicates tacit approval (30 days after submission) to move forward.



A	B	C	D	E	I	K	L	M	N
Context For Object					Object	Meta	Attributes of Attributes?)		
Function Level (Level 0)	Activity (Level 1)	Process (Level 2)	Sub-Process / Object (Level 3)	Sub-Process / Object (Level 4)	Object for Attribute		Attribute Type	Attribute Constraint	Definition
Regulatory Affairs	(Common)	(Common: Application Process)			Application	Application Name	String		Human readable name for the Application.
Regulatory Affairs	Investigational Activity	CTA Application Process			Application	Approval date - Actual HA	Date		The date the Health Authority officially approves the application (CTA) for the Clinical Study to move forward.
Regulatory Affairs	Investigational Activity	IND Application Process			Application	Approval date - Actual HA	Date		Implicit approval to move forward with clinical work, if no notice has been given by FDA in the 30 days following the original submission.
Regulatory Affairs	Marketing Registration Activity	Marketing Application Process			Application	Approval date - Actual HA	Date		The date the Health Authority officially approves the drug product for market use.

Figure 2. RIM Reference Model Workbook

The activities and processes provide the various contexts which are key to how the Model is adopted and used. By identifying the context, we identify where different values, uses, and relationships apply.

The RIM Reference Model is available as an Excel Workbook with a set of instructions on how to use it. The Excel Workbook should be used in conjunction with the companion MindMap which describe contexts based on various types of activities and processes supported for managing regulatory information. The model can be expanded by 1) adding to the contexts described in the MindMap, 2) adding any new attributes (and objects) to the Excel table, and 3) adding rows in the Excel table when non-common contexts exist.

The Reference Model is a work in progress, and we are seeking validation and input from drug sponsors, vendors, and systems integrators in the spirit of industry-wide collaboration, adoption, and continuous improvement. The Model will be updated periodically.

4. Regulatory Intelligence

The US DIA Regulatory Intelligence Working Group defines regulatory intelligence as “*the act of gathering and analyzing publicly available regulatory information. This includes* ***communicating*** *the implications of that information and monitoring the current regulatory environment for opportunities to shape future regulations, guidance, policy, and legislation.”*

We believe that this definition of regulatory intelligence includes both strategic and operational aspects. Strategic aspects include understanding regulatory policies and their implications on regulatory and commercialization strategies. Operational aspects include understanding regulations, guidances, interpretations and industry best practices to implement a regulatory as well as a submission strategy, both for new drug applications and lifecycle

management activities. Both the strategic and operational aspects of regulatory intelligence are required throughout the regulatory value chain.

Many companies have defined Regulatory Intelligence, Regulatory Strategy and Regulatory Operations as three separate and distinct organizations, working on different activities across the regulatory value chain. However, traditionally, they have not always been working together. As shown in the figure below (Balasubramanian, 2018), most of the activities across the value chain require regulatory intelligence and understanding of regulatory requirements throughout the regulatory process. This is also true across the R&D and Commercialization value chains. Therefore, we believe the three key functions must work closely together because of the interdependencies shown below. In essence, regulatory intelligence and regulatory requirements form the backbone of the regulatory value chain and therefore must be treated as an integral part of the Regulatory Information Management strategy and capabilities for organizations.

Figure 3. Regulatory Intelligence as Backbone for the Regulatory Value Chain

Regulatory intelligence can include any data, metadata, knowledge, and experience that support regulatory activities. To help inform regulatory activities, companies may draw from on-the-ground experience with consortia, standard groups, or regulators; analysis and policy interpretation that can be product-specific or focus on specific countries; submission content and RIM metrics; HA meetings and correspondence; and published requirements and guidance. These elements of RI are also essential for effective submissions and maintaining compliance for marketed products, as they help improve submissions content, speed future response, and enable accurate approval forecasts to information change implementation. Throughout the product regulatory lifecycle, RI is considered at multiple points, and there is a growing list of RI applications with different value drivers. When companies make portfolio decisions, RI informs probability of regulatory success which in turn informs gating decisions. In planning and tracking the product lifecycle, 'actuals' from previous plans and RIM system provide continuous feedback to templates and forecasts. Another application of RI is in registration management, where published and unpublished requirements inform license maintenance activity.

5. Health Authority Interactions – Correspondence and Commitments

5.1 Correspondence

One of the broader activities within Regulatory is the management of correspondence and commitments, certainly in terms of the sheer number of documents. Considering that correspondence includes interactions between the company and potentially hundreds of health authorities, as well as interactions among partners, distributors and agents, the task of capturing, managing and archiving this material can become overwhelming.

The DIA RIM Reference Model Working group identified 2 of the 18 components of an end-to-end RIM system are “Health Authority Interactions (Q&A, Correspondence)” and “Health Authority Commitments”. Each of these is a separate component but they could be related depending on the context.

Managing correspondence is critical to compliance. Correspondence is subject to legal holds, and much of the correspondence requires timely and effective response. Commitments carry the greatest weight, as they, by definition, identify actions on the company’s part required by the Health Authority. The value of effective commitment and correspondence management goes beyond compliance. These messages and documents carry meaningful intelligence, insights into the expectations of the health authority. Leading companies are mining insights from their correspondence and commitments to achieve right-first-time quality and improved time-to-market.

Typical correspondence and communications both from and to the Health Authorities may include but are not limited to the following:

• Request for Advice • Advice • Approval Letter • Contact Report • Pricing and Reimbursement • Meeting Minutes • Briefing Book • Refusal to file	• Withdrawal Letter • Warning Letter • Request for Information (RFI) • Response to Question (RTQ) • Clinical Hold (added or removed) • No Objection Letter (NOL) • Request for Meeting • Q&A

Regulatory correspondence from the Health Authorities is typically not tied to any specific RIM capability but rather funnelled through a corporate-wide email system or other channels such as contact reports. Since most companies have disparate systems then integrating with an email system or content management system to track correspondence between multiple Health Authorities is imperative to provide a continuity of action based on the correspondence received. There exist some tools within certain applications that will interface with the existing email system and incorporate the correspondence from the health authorities to records within the system.

Many companies will then utilize that information and create spreadsheets detailing the correspondence and who has the responsibility to follow up. As a company submits data to multiple HAs then the effort required to track all of the correspondence multplies quickly. By moving this capability into the RIM system we should be better able to track correspondence globally. We would want to track correspondence by sequence, application, product or non-product specific characteristics.

This has been an exceedingly manual process as illustrated below:

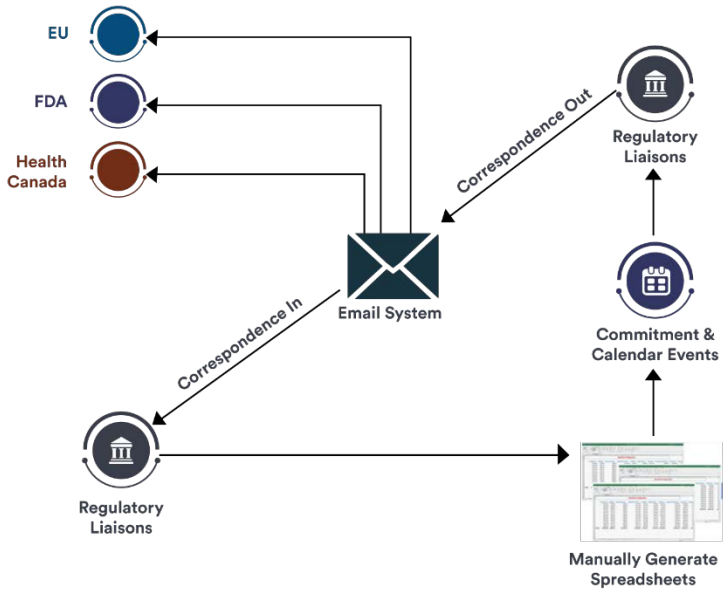


Figure 4. Health Authority Interactions

It's important that systems maintain the "thread" of correspondence. Correspondence is often related to previous communications. If these connections are broken, context is lost. This opens the company up to significant compliance risk.

As we shift from a document centric approach in regulatory systems to a more data centric approach it will be imperative that we determine the appropriate data elements to capture about each of the correspondence received. Refer to the RIM Reference model for recommended data elements.

An organizations communication practices could also encompass publishing partners, venture partners, CROs or other non-agency related entities are outside of the scope of this white paper.

We should look to have active links to the commitments, referenced documents and the appropriate version of those documents. Adding a knowledge base reflecting the correspondence received and the commitments identified in past correspondence would be a useful source of information for Regulatory Intelligence purposes. Development and clinical teams, Manufacturing, Supply Chain and other groups should utilize this information for more informed decision making.

5.2 Requests for Information (RFI) / Response to Questions (RTQ)

A subset of the agency communications are queries regarding submissions. Tracking the questions, the documents to which they pertain, and the responses (often sent as further submissions) is critical, especially as many agencies have expected time limits on such responses. These queries may not qualify as commitments, which require action, but do require response in the form of updated or additional documentation.

Tracking this information will include linking the communication to the relevant documentation in the previous submission and to the resulting additional submissions.

5.3 Commitments

Commitments are obligations that may be driven by regulations or specific contextual requirements (i.e. audit findings). The consequences of failing to meet your commitments may include non-approval or withdrawal of marketing authorization, delays to market, fines and even greater scrutiny by the health authorities.

All of these will need to be categorized and tracked and the default method of tracking these commitments has been to put them in a spreadsheet and review on a regular basis. We need to tie the data from the correspondence with the HA to specific actions required to be performed in a timely fashion. As we incorporate more process automation into our RIM environments we can see how ingestion of HA correspondence and the proper metadata design will allow for scheduling and alerting on activities to be performed.

Once the commitment has been agreed to with the Health Authorities then a series of events and actions will need to be scheduled and tracked. These should be incorporated into a system that will schedule and alert the appropriate resources to respond to any required activities.

We would want to start tracking metrics for different items that affect each company such as: percentage of commitments met on time, number of outstanding commitments in each market and any other number of metrics that different companies may chose.

Having the ability to translate the myriad of emails that inundate the people responsible for following up has been a manual task for a very long time. All of this hinges on our ability to ingest the correspondence and track the commitments necessary to satisfy the ad-hoc or predetermined requests from the authorities. As more advanced systems are developed we can automatically PDF the correspondence, file the correspondence in the appropriate location to tie it with the applicable submission, apply metadata specific to that correspondence and alert the appropriate resource of the new request and schedule the follow up all from a single system. This would be the ultimate integration that would allow for as seamless as possible to handle the growing complexity of multiple systems, Health Authorities requests and appropriate follow through.

6 Submission Planning and Tracking

Given the requirements of Registration Tracking, it becomes evident that significant effort will be placed in planning the submissions to regulatory agencies, whether they be applications for marketing new products, maintaining the registered status (Annual Reports, Periodic Reports, Renewals, and variations/supplements based on manufacturing and labelling changes), as well as other commitments and obligations.

Submission planning and tracking refers to planning, management and tracking a set of regulatory activities and individual submissions (sequences) needed during the life cycle of an application. These submissions are either planned as the information becomes available (e.g. IND, NDA, MAA, annual reports, routine amendments, PSURs, DSURs, commitments, Biologics Lot Release, etc.), or are more of an ad-hoc nature (such as expedited safety reports, agency request for information, certain CMC amendments, etc.).

Planning and tracking regulatory submissions is a foundational component of any regulatory information management (RIM) framework. It involves several distinct yet inter-related aspects including:

Figure 5. Submission Planning and Tracking

The role and impact of each of these aspects is described below.

6.1 Standards and Processes

Every company has a set of standards and follows certain processes for planning, preparing, dispatching, and tracking their submissions to health authorities. Managing these submissions and their due dates are key to ensuring smooth and uninterrupted conduct of regulatory projects and their activities.

The regulatory owner (Global or Local Lead, RA Clinical, RA-CMC, Labelling, AdPromo, etc.) schedules a submission(s) for a regulatory activity, in alignment with the company's Clinical, Regulatory, or Commercial development strategies, or in response to inquiries from health authorities. Contribution and input from several functions (Clinical, Medical, Nonclinical, CMC, PV, QA, Bioanalytical Sciences, Regulatory, etc.) are typically required in planning and preparing major submissions. Each submission event, with all relevant metadata including applicable dates, is entered into a tool than generates a global submission calendar, normally with a targeted timeframe, which in turn triggers a host of activities involving different stakeholders.

The way submission activities are prioritized, planned, and managed depends on the following factors, among others:

Submission type	Scope	Complexity	Size	Format	Regulatory & Commercial Impact
Major application Vs Minor amendment	Global Vs Local	Major CMC variations Label change	Large Vs Small	eCTD NeeS paper	Commitment Response to agency inquiry

Figure 6. Factors influencing Submissions

Additionally, tracking the progress and status of the submission and its components can be extremely complex, especially for a global company having many products in several markets. Failure to effectively plan and track submissions will impact maintenance of product registrations, availability of products, safety of patients, compliance with local and global requirements, and sustainability of the enterprise and its development programs.

Implementing processes for successful and efficient outcomes requires establishment and adherence to clear and stringent, yet pragmatic, procedures and a set of standards and quality checks for consistent, high-quality outputs.

6.2 Systems and Tools

Once the standards and processes are in place, technology systems and tools are utilized to facilitate these processes and automate the aspects that greatly improve and enhance the productivity and quality of the outcomes and deliverables.

This involves utilizing project management tools (spreadsheets, checklists, smartsheets, project management) potentially integrated with other RIM components (document management, change management, labelling tracking, publishing, and review, etc.). Here, the concept of master data management, establishing the authoritative source for any information, is key to data integrity.

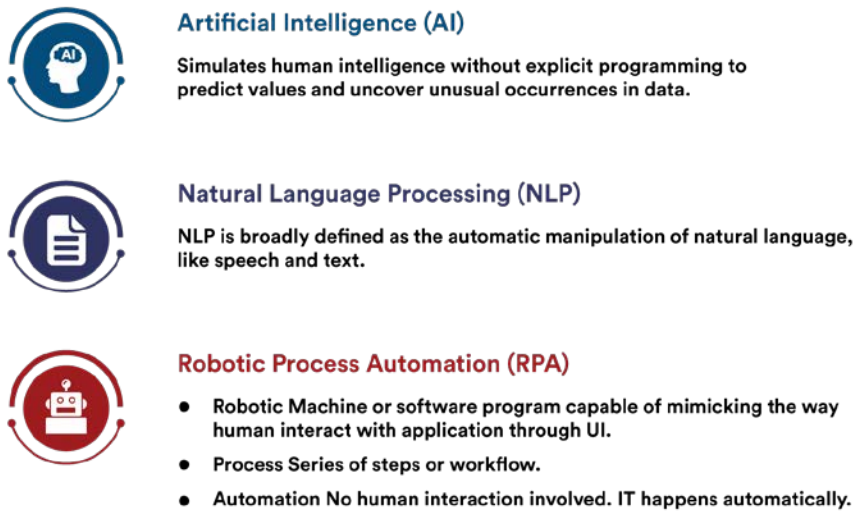


Figure 7. Role of AI, NLP and RPA in Regulatory

Most recently, development of automated and intelligent tools and processes such as artificial intelligence (AI), natural language processing (NLP), and robotic process automation (RPA) have enabled some extremely labor-intensive activities, such as manual information gathering and performing repetitive tasks, to be performed in an efficient, consistent and intelligent manner.

As part of their best practices, some companies leverage templates (both submission content and project plan) to speed the planning and tracking process. Experience and regulatory intelligence are used to update these

templates to reflect a continuously changing regulatory environment. Companies will need a process to review and update templates.

Creation and maintenance of submission content via a content plan presents another essential component of submission planning and tracking activities. RIM vendors are currently offering tools to automate creation and management of content plans. Often this remains very much a manual process, especially in smaller companies. In either case, managing the content plan still requires human intervention, as both the content and the timelines for delivery of submission documents are constantly in flux.

6.3 Expertise and Resources

As companies adopt new technologies to support Regulatory processes, new roles and skills are needed. These include expertise in data governance, data stewardship, data analytics, and data quality, along with advanced tools such as AI, NLP, and RPA.

6.4 Strategy

An organization may opt for a centralized vs decentralized approach for planning and managing its submissions. Typically, entities with a global footprint utilize a decentralized process, relying heavily on direct input and involvement from local affiliates (or partners). Smaller entities with less commercial activity tend to adopt a more centralized process, managed via a dedicated team. A hybrid model is the most common approach.

Another aspect relates to the nature and scope of outsourcing activities. This in turn impacts the way companies utilize the processes, systems, and expertise of the vendor. In those cases, vendor qualification and management become a critical activity, which may require establishment of a separate function, or groups within functions, to ensure data integrity, consistency, quality, and compliance. It also ensures that activities conducted and deliverables by vendors are managed in a timely manner.

6.5 Information and Data Governance

Other important aspects of submission planning and tracking activities are the flow of information, data ownership, and resource management. Establishing the data ownership and identifying the most reliable source of data should be of high importance and something that needs to be managed during the implementation of the system.

Capturing overall submission metrics, including handoffs, delays, missed submission due dates against established timelines, and service level agreements (SLAs), will allow proper resource forecasting and management. It will also allow for periodic gap analysis, reforecasting, process improvements, and on-time performance.

6.6 Summary

Planning and tracking submissions are essential components of regulatory information management for every company. These activities require a high level of diligence, detailed planning, careful design, and close attention to proper implementation and maintenance in every aspect (processes, standards, expertise, technology, and strategy). Most importantly, given the fact that many of the foundational data elements of RIM are captured via this component, an in-depth analysis and assessment of the information to be captured is key, the primary goal of the RIM Reference Model.

Almost every action taken by a Publishing and Submissions team either inputs or consumes critical RIM data, all while under intense time pressure. For example: from the last complete document to the ability to share that dossier with the health authority is a finite set of time. To ensure quality, validity and accuracy of that dossier, the Regulatory Operations team must go through a series of processes for every document and dataset included in the dossier. Therefore, it is paramount to be able to track KPIs on how long those processes take and optimize them to allow the contributors time to ensure the quality of their deliverables.

This trickle-down and consequence-driven transaction between contributors, operations professionals and global health authorities requires a tremendous amount of coordination. Anyone who's lived through an NDA filing the week before a major holiday understands this pressure.

7 Publishing, Dispatch and Archiving of Submissions

Once submission content (source documents) has been assembled, edited, reviewed, reference checked and quality checked, it is typically passed, in whole or in sections, to the Regulatory Operations team for publishing and submission. Unique submission requirements for each health authority, whether relating to format, structure or content, introduce considerable complexity.

Health authorities expect content and data in defined formats. These include the Electronic Common Technical Document (eCTD) structure, a Non-eCTD Electronic Submission (NeeS), or a paper submission. The Publishing team prepares and verifies all documents comply with the correct standards, navigation, tables of contents, cross referencing, and technical validation of the final submission against health authority specifications.

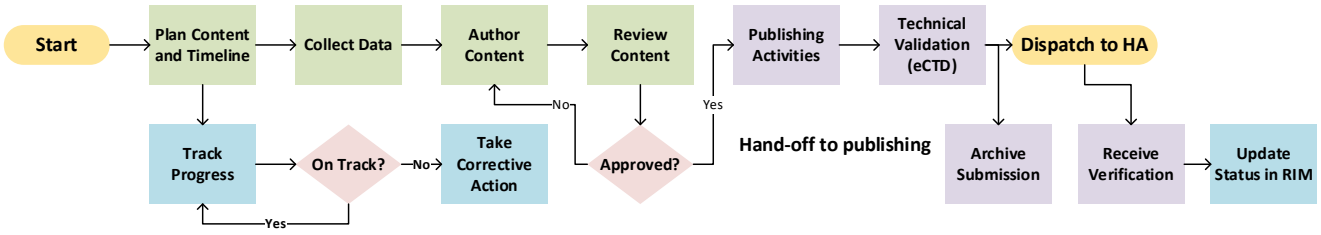


Figure 8. Publishing Process

Throughout the authoring process, from planning through final quality check, RIM captures the details such as time stamps, document status and progress of each dossier. The submission team can follow and track the status of each section until it is fully validated and ready for submission.

The methodology for compiling and transmitting the submission to health authorities varies. The publishing team must validate that the dossier is in conformance with each health authority's requirements. This includes both technical validation and quality checks. The industry has adopted automated validation tools, some of which are part of the RIM solution.

The team then dispatches submission content, whether through an agency gateway using an industry standard, by secure email, or by shipping a paper or physical digital media submission. In some cases, local affiliates will receive the dossier from the global team and then prepare and dispatch submissions locally. A copy of the exact submission for each health authority should be archived, as well as any acknowledgement from the authority,

such as an electronic eCTD verification or written confirmation of receipt. A central view of every submission and all correspondence is critical to support decision-making, lifecycle maintenance, and ensure ongoing compliance.

The data and metadata associated with the submission can tell a great deal about submission process efficiency. Over time, the organization can start to see trends and opportunities within their system as well as ways to streamline the process and the amount of data they provide.

8 Labelling

In many ways, the label is the distillation of all of the regulatory activities that preceeded it: It's the summary of what has been proposed to or approved by a regulatory authority, including clinical, nonclinical, manufacturing and safety details, as well as the authorization of a product to be on the market. The approved label is only one piece of labelling, as there are documents which can be considered its children, including Instructions for Use (IFU), Package Inserts, Physician Instructions, Medication Guide, and artwork files to produce the physical package labels and inserts.

Most companies work with a concept of a Company Core Data Sheet (CCDS) which is the global master version of the label including the superset of indications for use, safety warnings, etc., from which each locally-approved label is derived. The CCDS may be built upon the Investigator Brochure (IB) or upon the Target Product Profile (TPP) which is defined early in the development process. Companies using a CCDS will require that the regional regulatory affairs staff seeking approval of a label (whether or not they're part of the central company regulatory or local affiliates) base their version upon the CCDS. This means that a new verison of a label for a variation or supplement is likely to have two parents: The local specific edits to the previous version of the label as well as the CCDS's changes.

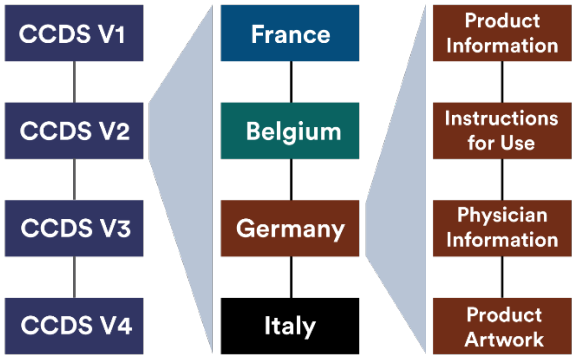


Figure 9. Labeling Artifacts

While the CCDS is not approved by agencies, there is typically a Global Labelling Committee that ensures consistency across global labels and sets the corporate goals for the product's approval [green in diagram below]. During this time, the changes to the CCDS are compared, section by section, to the local labels for each country to ensure consistency.

The workflow for labelling may be quite complex, meaning that labelling should be a critical part of consideration for regulatory Content Management and Workflow systems. The label may develop along multiple branches

where the versions are simultaneouly proposed, approved, in use. Challenges arise both in status and version tracking. Labelling is also tightly woven into the manufacturing change control process, with many changes requiring changes to the labels as well, with additional impact to ERP systems.

The local approval may require numerous submission cycles for negotiation, and in some regions (US and EU in particular) culminates with submission of key label facts in a structured data format (SPL Drug Listings in the US, XEVPRM – and soon IDMP – in Europe) [blue in diagram below]. Submission of the content of labelling may also require specific structured formats: Currently only the US requires the content of labelling in SPL (Structured Product Labelling) format, but Health Canada is readying a Structured Product Monograph guidance, and the European Union is developing Electronic Product Information (ePI), which has an additional challenge of numerous languages. Local labelling teams may also request exceptions to content in the CCDS, which then typically get routed back through the GLC for approval.

Labels during the investigational process may not follow all of the workflow steps – registration data such as EMA's XEVMPD and IDMP, or FDA's Drug Listings may not be required prior to approval. Labels in the first countries studied may not (but could and likely should) be based on a global core document.

Translations impose an additional burden. Companies have a limited time after the English label is approved to complete translations. Companies make efforts to include multiple translations on a single label (international labels) however space restrictions often complicate this approach. Multilingual countries (such as Switzerland) require original submissions in all required languages. Braille is required for many countries. Some companies are also exploring elabels (web-based) as an approach to managing translations.

Upon approval, there may be a period where existing artwork continues in production until the new approved packaging, inserts, etc. can be distributed. This requires an implementation plan for getting the completed materials into circulation, and tracking when this has been achieved in each country or region [red in diagram below]. While this is often part of Supply Chain/ERP systems and not RIM, it is critical that the implementation dates get back to regulatory, making integration of ERP master data critical.

The need to do comparisons on a section-by-section basis, and the need to create structured formats for particular agencies has meant that narrative labelling has moved toward Structured Content Authoring (SCA) also called Component-Based Authoring (CBA). This provides the following abilities that benefit labelling:

- tracking individual sections of documents and the sources from which they are derived
- automatically reformatting common content across a variety of output formats
- tagging of sections with the type of content they contain
- controlling the cost of translations by limiting to sections that are modified
- automatic import of metadata from the RIM and content management systems into the content of the document

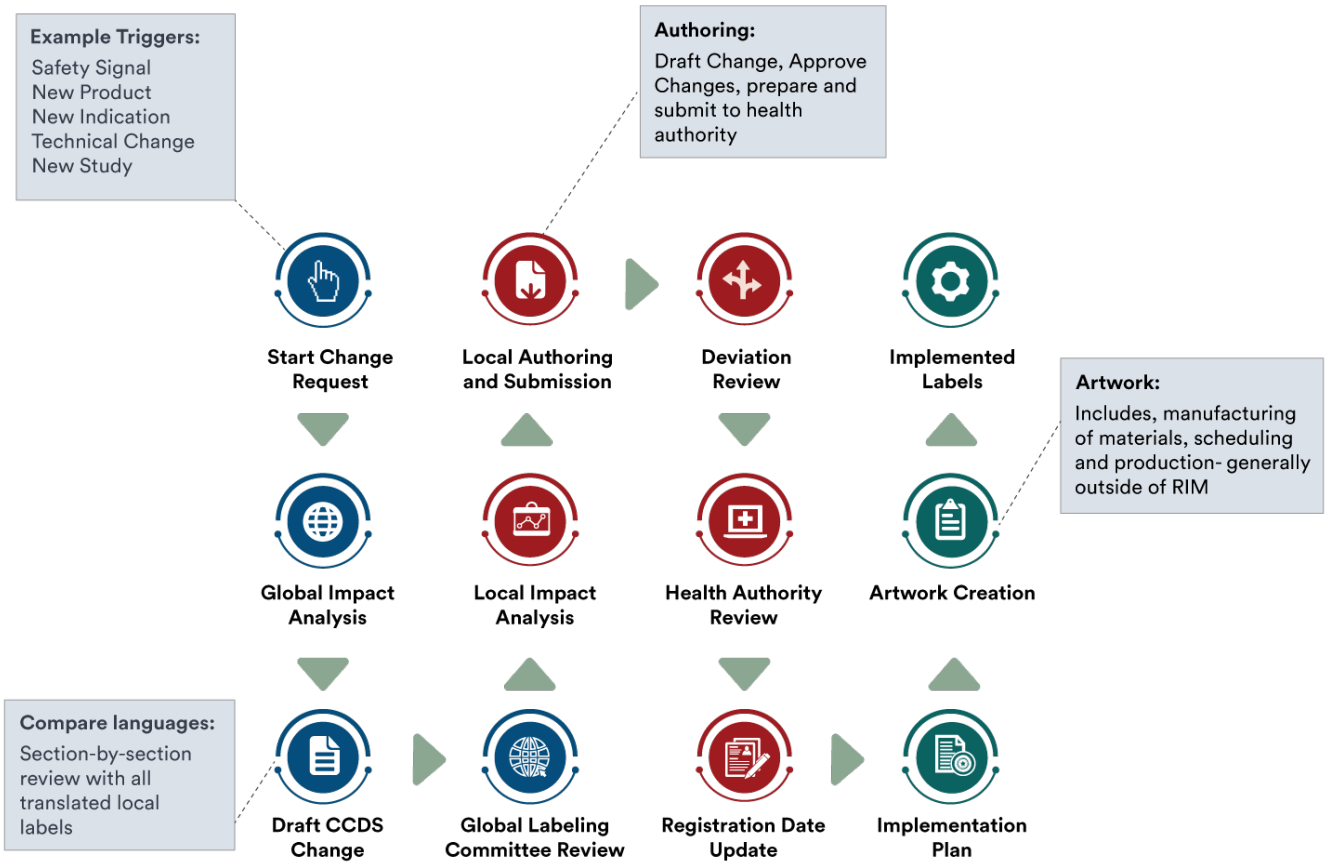


Figure 10. Labeling and Artwork Process

However, SCA has additional costs related to increased complexity of content management and workflow, and training to use the software tools. While some such products integrate with common off-the shelf word processing, many may require expertise in XML-based editors, or have limited web-based editing capabilities which may frustrate authors used to tools such as Microsoft Office™. Companies are also exploring use of Artifical Intelligence to verify local label compliance to the CCDS.

Labelling also must address the need for serialization to limit counterfeiting and mis-directed shipments.

Because of its importance in the approval of products, and the need to integrate content management, authoring, workflow, RIM metadata, and ERP implementation plans, full integration of labelling is only beginning to become part of companies' core RIM systems. This is growing as end-to-end RIM becomes more common.

A primary goal of managing labelling in RIM is to develop a definitive list of what labels are proposed, approved or in use in every market. RIM systems should support links to current and previous versions of all artwork.

9 Advertising and Promotional Material

9.1 Business Purpose

A wide variety of materials are used to promote pharmaceutical products and medical devices. These include materials that advertise or promote products to health care professionals, consumers, and other organizations such as payers. A wide variety of media are used, including print, television, radio, electronic (such as web sites and eDetail aids), email, and even physical items such as giveaways, and booths and displays used at conferences.

Regulation of the promotion of pharmaceutical products and medical devices is entirely controlled by individual Health Authorities (HAs); there is no international standard or guidance. Regulations vary significantly among Health Authorities.

To remain compliant with regulatory and legal requirements, organizations must submit, and sometimes seek approval, of advertising and promotional materials in compliance with the legal and regulatory framework in each country.

Although this section discusses promotional materials, some considerations also apply to non-promotional materials such as conference presentations and general disease awareness materials.

9.2 The Promotional Material Management Process

Advertising and promotional (Ad/Promo) materials are generally reviewed and approved by an internal team which may consist of team members representing medical, legal, regulatory and marketing functions, among others. The organizational structure and reporting authority can vary from company to company. Materials must be reviewed for compliance and accuracy before use.

Submission and approval pathways are numerous. Health Authorities rules vary extensively based on many factors, including but not limited to:

- Audience: Health Care Professional, (if allowed) consumer
- Whether prior submission is needed before use
- Whether prior approval is needed before use, and if so whether submission is explicit or implied after a time period has elapsed
- Whether rules differ for different classes of drugs (e.g., OTC vs prescription, controlled substances, drugs subject to abuse or addiction…)
- Whether rules differ for different media (print, TV, eDetail Aids…)
- Whether the HA has a specific timeline for receiving and reviewing submissions (e.g., once per quarter)
- Whether supporting references (such as clinical study reports, journal articles, etc.) can or should be submitted

In addition to required submissions, sponsors may seek advisory comments on proposed introductory advertising and promotional labelling materials prior to publication or dissemination. The following figure summarizes possible submission and pathways for Ad/Promo materials.

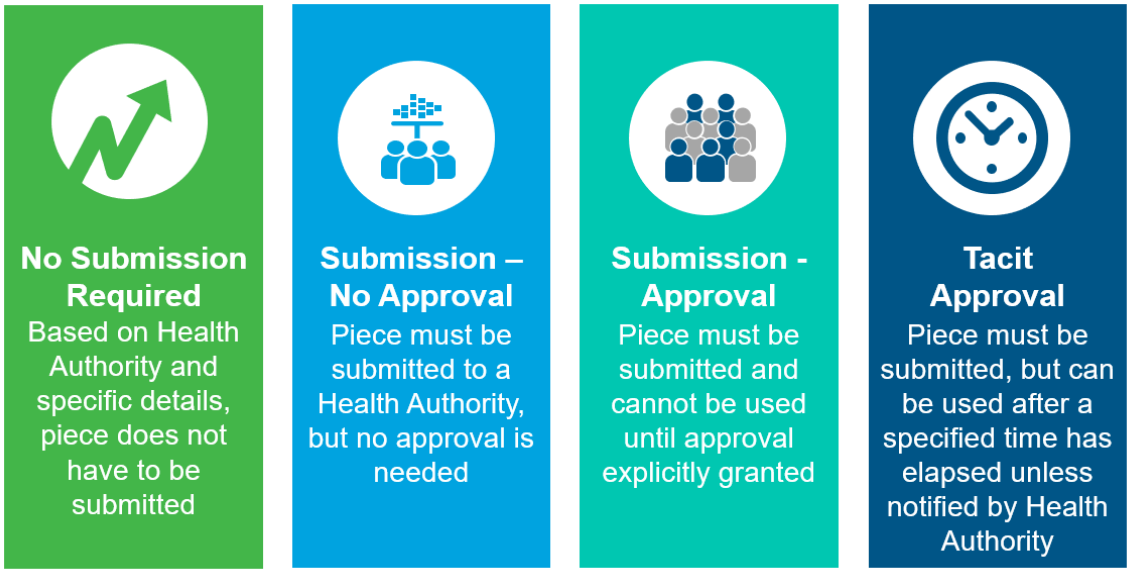


Figure 11. Promotional Material Approval

Once materials are cleared for use, that approval (whether tacit or explicit, internal or from a regulatory body) is usually considered to expire after a certain period of time. This time period may be different based on details of the materials. For example, in the US, materials referring to new products expire after six months; other materials generally expire after twelve months or more.

> "OPDP [The Office of Prescription Drug Promotion] generally considers that "New" is an accurate description of the marketing phase for six months from the time a product is initially marketed. This should be distinguished from the time the product is cleared by FDA for marketing."

Expirations must be tracked, and materials updated and re-approved if appropriate.

9.3 Process Triggers

Triggers for submission of promotional materials can include:

- An initial product launch in a specific market
- A sales or marketing campaign
- A change in product (for example, a new dosage form or the addition of a black box warning)
- An event such as a conference
- A periodic update

For each triggering event, an index of materials is usually planned. An assessment is then needed to determine the submissions that are needed in the specific market.

9.4 Regulatory Intelligence

Since requirements vary so extensively for each Health Authority, sound regulatory intelligence that is market-specific is a prerequisite for both efficiency and compliance for planning, developing, and maintaining promotional material approvals.

A strategy for obtaining, organizing, and maintaining this information, whether through the use of internal resources or an external regulatory intelligence database, is part of an overall RIM strategy.

9.5 Competitive Intelligence

Often, studying competitors' materials (both approved and rejected) provides information that can inform an organization's strategy in determining materials that will be acceptable to HAs. The FDA's "Bad Ad" program and warning letters provide excellent insight into the expectations of that agency.

9.6 Medical, Legal, Regulatory Review

Regulatory review is a critical part of the Medical, Legal, Regulatory (MLR) review process for promotional materials. Key aspects include:

- Ensuring that a qualified regulatory reviewer is available for each market in which promotional materials are submitted
- Scheduling time for the reviewer to review materials, attend meetings and respond to comments
- Providing a feedback loop so that the regulatory reviewer's comments are understood by creative agencies and other team members, resulting in increased compliance and decreased need for comments in future reviews

9.7 Submissions, Approvals and Tracking

Submission and approval strategy is again very specific to the Health Authority receiving the submission. Depending on the market, submissions may be paper or electronic. Currently, only the US FDA accepts promotional material submissions in eCTD format.

Clear responsibilities and processes must be established for promotional material submissions.

- Who is responsible for submissions? Depending on the company size and organization, this may be the same group that does other submissions, or a dedicated team).
- In the US, will materials be submitted in eCTD format? Will a block of sequence numbers be reserved? Will grouped submissions be used to submit to multiple eCTDs? Note: the FDA strongly recommends a sample submission for organizations that have not submitted promotional materials in eCTD format before.
- How will rich media be submitted (websites, eDetail aids, video, audio)?
- How often will promotional material submissions be made? When submitting eCTD sequences, submissions may be planned periodically (such as every two weeks). Other submission planning may be based on health authority acceptance and review windows.
- Who is responsible for preparing needed forms and cover letters?

- Are any necessary copies of or references to labels needed?
- When will promotional material content be received? What is the cut-off before submission planning? How are materials delivered to the publishing/submission group?
- How are agency comments shared with interested parties so that HA opinions can be considered in the future?
- Will requests for advisory comments be utilized?

Regulatory professionals or other employees responsible for content will need to know details such as:

- How packages are submitted (mail, gateways, eSubmissions, email…)
- What formats are acceptable
- What forms and certifications are required?
- How materials must be packaged and labeled

Tracking the approval status of materials is key to ensuring that they are not disseminated before the proper processes are followed. Some key decision points include:

- Who is responsible for tracking submissions, acknowledgements, approvals or rejections? Is this information available as part of a RIM system or via some other mechanism?
- Does RIM have any role in tracking expiration dates and extensions, or is this the responsibility of the marketing/commercial group?

9.8 Challenges

There are a number of significant challenges encountered that are related to Ad/Promo materials.

Ensuring Compliance of Content – Promotional content must be balanced in disclosure of risks and benefits, based upon scientifically sound sources, and compliant with Health Authority regulations. A robust Medical, Legal and Regulatory review process, with a process to adequately address all comments and concerns, is essential to maintaining compliance.

Controlling Dissemination – In many markets and for many types of promotional items, Health Authorities prohibit distribution of materials before required processes are complete. However, organizations must prepare to distribute materials in advance of approval/release dates. A process must be in place to confirm that all regulatory clearances have been obtained before materials are pushed to sales people, published, broadcast, or distributed. Distribution of unapproved or violative materials can lead to fines and other judgments.

In some cases, materials must be withdrawn, which can include collection of physical materials. It's important to know where each promotional piece has been distributed or published so that it can be withdrawn in a timely manner.

Supporting desired timelines – As noted, product launches and other events follow designated timelines. Often, review and submission activities for promotional materials compete with other priorities such as a commitment,

critical regulatory business, or other submissions. If materials are not prepared, reviewed, and submitted in a timely manner, these timelines can be jeopardized.

Tracking – It's important to establish a capability for tracking status, submission and approval dates, and expiration and renewal dates for all materials, along with any constraints around how materials should be used. This could be done in a promotional materials management system, RIM, or elsewhere, but location and responsibilities should be clear. In some cases, this might need to accommodate outsourced management or submission activities.

9.9 Leading Practices

Regulatory Intelligence – Regulatory intelligence is crucial to developing and releasing compliant promotional materials. Regulatory intelligence can be maintained in house or obtained from a service or consultancy. With any option, it's crucial to understand:

- Requirements for submission of different materials in each market
- Review schedules in each market
- Timelines for tacit approval or expected times for explicit approval

Organizations should clearly document the source of all information that is needed, a methodology for keeping information up to date, and a strategy for making information available to all stakeholders.

Project Planning – Ad/Promo submissions often use the same resources as other regulatory submissions. This is especially true in the US when submissions are made using the eCTD format and therefore must be coordinated with other submissions for a product. Organizations should define a procedure for planning, resourcing and completing Ad/Promo submissions.

Metrics – Key metrics around Ad/Promo submissions might include:

- MLR approval times and rework cycles and reasons
- Time for approval (when explicit approval needed)
- Percentage on-time submissions
- Number and type of submissions per year and market (including advisory)
- Number and type of health authority comments/rejections per year and market
- Time spent in MLR review and in submission preparation
- Percentage of activities (such as publication or sales launch) delayed due to late availability of promotional materials (note that this can be for many reasons)

9.10 RIM's Role in Managing Ad/Promo Submissions

RIM's contribution to managing Ad/Promo could include:

- Providing insight on product status across markets
- Submission planning and tracking

- Contributions to metrics
- Resource management

RIM must support preparation, review, submission and tracking of promotional materials and their status. Management of advertising and promotional materials can be as complex and as important as the management of the product itself. High-quality, compliant promotional materials are critical to success.

10 Product Registration Management

In general, submission and approval of a marketing authorization application is a prerequisite to launching a product in each country. Obtaining such approval can be achieved by following different registration paths and regulatory procedures in a specific market, depending on the regulatory requirements in that market. For example, in the European Union (EU), currently there are four different procedures, namely Centralized, Decentralized, Mutual Recognition and National ones for approvals. Some markets may require approval from a major health authority (e.g., US, EU, JP), by requesting a Certificate of Pharmaceutical Product (CPP) to issue approval in that market.

While gaining initial marketing approval may be the first critical step in placing a product in a market, maintaining its lifecycle and tracking its registration status, is another important and challenging activity. The Marketing Authorization Holder (MAH) is tasked with ensuring compliance and keeping the product in the market.

As a common practice, tracking of registration activity may start as early as the planning phase for marketing authorization applications, or actual filing, and eventually approvals. Besides the necessity for permission to sell the product in a market, the registration serves several other purposes, again underscoring the importance of continuous monitoring and tracking of its status. Some considerations include:

- Registrations come with many regulatory obligations and commitments having stringent timelines (e.g., periodic safety update reports, annual reports, label updates, manufacturing updates, risk assessment updates).
- Registration status serves as a basis for regulatory and pharmacovigilance (PV) fees (PDUFA fees in US, PV fees in EU, etc.)
- Registrations require data entry and maintenance of certain product and approval information in regulatory and other databases, within certain timelines mandated by regulatory agencies. Examples include xEVMPD and SmPC in EU; final approved labels, establishment registrations, Labeler Codes, in SPL Drug Listings in US, and soon IDMP in EU and other ICH regions.
- Registrations also serve as an indicator of what products are approved in each market, which is also a major source of information and driver for Commercial and Supply Chain activities. Furthermore, this information is often requested by health authorities during inspections or via official requests, such as PSMF in EU.
- Registrations also serves as the basis for scheduling post-marketing updates such as PBRERs, PSURs, etc.
- Maintaining the exclusivity and awareness of patent expiration for a product in a market is critical and is yet another reason for closely tracking the approval dates.

- It is also important to track the launch date or when the product first becomes available to patients, for commercial and product supply chain and reimbursement reasons.

In some instances, the approval (registration) is temporary or conditional and therefore needs to be renewed after the initial approval period, or once the commitments and requirements are met. Therefore, tracking the approval date is very important to ensure follow-up and maintenance activities are performed and completed in a compliant and timely manner. In some cases, if the product is no longer serving its purpose or has a major safety or quality issue, the MAH may decide to withdraw the registration and pull the product off the market (temporarily or permanently). In other instances, the use of a product may be expanded through approval for use in other indications. In cases of mergers and acquisitions (M&A), which are commonplace and represent a growing trend in this industry, the MAH may transfer the ownership to other entities. Furthermore, co-development, partnership, and working with local distributors are also instances where the registration information may need updating.

Sponsors working on developing or marketing rare diseases will also be obligated to track the status of their orphan drug designation (approvals) which will help with maintaining exclusivity and other benefits that such designation grants to the sponsor.

Overall, tracking registration status and orphan designations are critical activities for successful business continuity and marketing of products. Tracking should be managed meticulously and in a compliant manner, as there are many interconnected activities and dependencies related to keeping a product in a market: change management, label updates, safety variations, supply chain, and M&A, among others.

11 Change Control and Variation Management

Pharmaceutical products undergo significant change over their lifetimes. These changes can be triggered by several events: registering a new supplier, a health authority requiring a change to a label, a new indication, or the manufacturer's desire to improve the production process to name a few. Whatever the cause or nature of the change, there is a potential impact to the product registration, and a potential corresponding need to file a Variation (referred to as a Supplement or Extension in some markets) with one or more health authorities. Some variations require prior approval, others serve to notify the authority of a change.

11.1 The Variation Process - Stakeholders

There are many stakeholders involved when a company wants to change an approved product. The change control review board usually works closely with the regulatory, manufacturing and supply chain teams to ensure requested changes are properly completed. Internal stakeholders can include:

- Clinical / medical Affairs
- CMC / manufacturing, supply chain
- Regulatory
- Change Review Board (cross-functional)
- Quality
- Marketing
- Commercial

- Safety / Pharmacovigilance
- Affiliates

External stakeholders can include:

- Suppliers
- Distributors
- Health authorities
- Joint venture partners

The first step is to determine the regulatory impact. Variation filing requirements depend upon the change type, product type, health authority and the original submission.

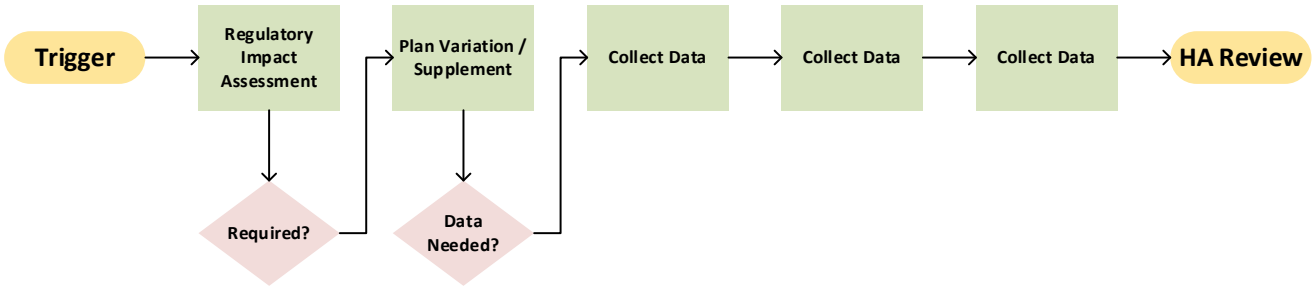


Figure 12. Variation Process

11.2 Impact Assessments

The regulatory impact assessment is where the challenges begin for the variation management process. Product changes may require prior approval in some markets, notification only in others and no action whatsoever in still other markets. As such, organizations must first determine what Variations will need to be filed as a result of the triggering event. The organization must assess the considerations to be made and the actions that need to be completed before the change will take effect. Key decisions they must consider include variation filing determination for each country, country filing requirements, as well as the number of variation filings that are permissible in a given year. In some cases, economic factors and regulatory requirements will influence the decision to move forward with the change.

11.3 Decision to Move Forward

Once the Change Review Board approves the change request, and Regulatory has determined that Variations are required, the team must also consider the impacted products, the required variation filings, the nature of the filings (prior approval, pre-change notification or annual reporting), and the time and resources needed to secure health authority approvals (if required). Other considerations include combining multiple changes under one variation (bundling) or filing multiple variations for one change (in cases of work-sharing or multiple licenses impacted by the change). The Regulatory team must also determine what information each agency will require and what submission documents need to be completed.

11.4 Submission Planning

When planning for the variation, it is important to verify that documents are current, accurate and complete. Regulatory teams will need to confirm which version of documents were submitted in which country – for

example, and update to a specification or test method may only apply in certain markets, while the original may still be the governing document in other markets. Affiliates, who may be preparing their submission at a later time, must make sure that they re-confirm whether updates have been made since the initial filing. Submission planning for variations also includes resource planning. Also, some countries may limit the number of variations that can be filed, requiring companies to plan ahead and "bundle" changes into a single variation submission.

11.5 Submission Preparation

When filing a Variation, many types of supporting documents must be completed depending on the jurisdiction. The compiled documents must conform to the formats required by the respective health authority. To ensure compliance and quality, the RIM system should be used to manage regulatory requirements.

11.6 Approval Management

Once the variation filing is complete, it is submitted to the relevant health authority for approval. Post approval variations could potentially require simple changes requiring minor review or major changes which are often complex. Minor variations generally have minimal impact on the quality of the product and may not require significant time for approval. Major changes to product registration are needed when the updates involved generally have a potential impact on a product's quality, safety and/or efficacy and may require significant time for approval.

11.7 Post-implementation Notifications

Once approval by the relevant health authority is received, all stakeholders are notified and companies are then allowed to release the updated product to the market. This is often done through email communications. Of course, this would need to be tracked in RIM, as well as the corresponding notification from the HA.

11.8 Challenges

Managing change to products and manufacturing processes is one of the most complicated cross-functional capabilities. Regulatory Intelligence plays a critical role supporting:

- Variation filing determination for each country, as well as how many variation filings are permissible in a given year
- Change bundling and planning decisions
- Variation submission content decisions across all markets
- Implementation planning based upon expected approval times (leveraging upon previous approval experience)
- Implementation timing based upon expected approval times and remaining pre-change inventory
- Post-change implementation notification requirements

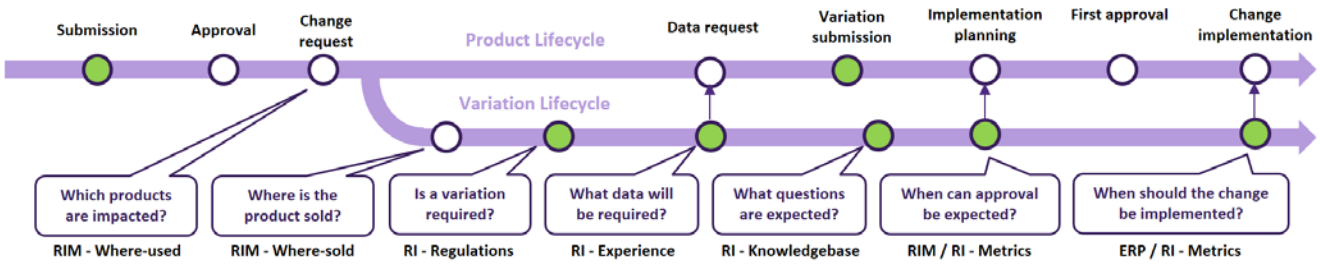


Figure 13. Importance of Regulatory Intelligence throughout the Change Lifecycle

11.9 The Regulatory Impact Assessment

The regulatory impact assessment is a multi-step process. Before assessing regulatory impact, companies need to understand the products and markets impacted by a change request, as well as regulations that apply to the change. A single ingredient or manufacturing change can impact multiple products. Companies need to use the system of record (ERP, RIM or PLM) to determine the extent of products impacted by the change.

The next step is to determine where the products are registered. Products may be registered in various countries, which can cause unique challenges to the variation lifecycle. Companies need to determine which regions will be affected by the change and how that may impact product licenses in that region.

From there, Regulatory can determine the submission requirements and related regulatory costs. Requirements will vary by each country in which the product is sold. The various requirements can leave room for interpretation on whether a submission for the change request is necessary.

11.10 Submission Planning

After understanding submission requirements by country for the product, companies should then begin Submission Planning to gather requirements for the change. Submission Planning includes the scope of the submission for each country, content requirements, the timelines and dependencies, and resources required. Companies may face challenges locating their original submission documents that may be spread across multiple functions, as well as gathering the most up-to-date information contained in the documents. Companies have learned the hard way that all submissions documents, whether coming from global HQ or a local affiliate, need to be captured and classified for future access through a global RIM system.

At the country level, regulatory teams need to be aware of local regulations that may limit the number of variations submitted in a year. Submission Planning will need to address “bundling” or combining changes for inclusion in a single submission for certain Health Authorities.

11.11 Implementation Planning

The manufacturing teams that are responsible for implementing a change rely on information from the RIM system to understand which Health Authorities have approved the change. Based upon that data, and understanding of past approval times, manufacturing can decide when to implement the change without fear of releasing unapproved lots or creating shortages of old stock in markets where the change has not been approved.

11.12 Best Practices

Regulatory Intelligence is critical to effective change control and variation management. Without a clear understanding of the requirements in each market, companies expose themselves to compliance issues and drug shortages. Companies need to know requirements related to content, the number of filings allowed (will bundling be required), submission timing, as well as the need to file at all (which varies form market to market depending upon the drug and type of change).

12 Cross Functional Touch Points

Few functions touch as many other stakeholder groups as Regulatory. Regulatory teams are involved early in a product's life, providing early assessments of probability of regulatory success and supporting development of product strategies. Engagement continues through the product lifecycle to end-of-life, addressing any residual activities with health authorities. Along the product journey, Regulatory interfaces with external stakeholders such as health authorities, industry policy groups, and outside legal and compliance teams. Inside the company, Regulatory works with Marketing, Research, Clinical, Quality, Manufacturing and Supply Chain, Pharmacovigilance, Commercial and other groups to optimize product safety, compliance, and profitability.

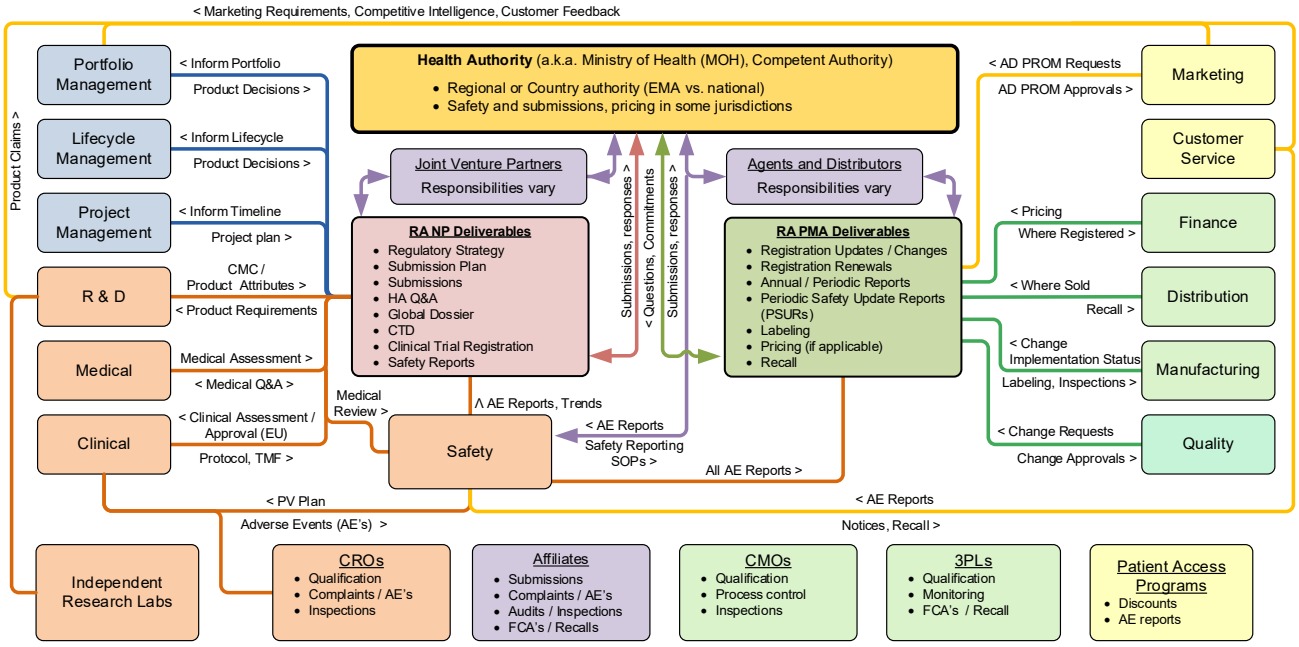


Figure 14. Example of Regulatory Interactions with Other Functions

12.1 External Stakeholders

Regulatory is the primary touchpoint with health authorities globally. However, the breadth of external stakeholder groups is far greater, with interfaces to local distributors, notified bodies and 3rd-party service providers. The interactions include but are not limited to:

Local and Regional Health Authorities – Regulatory is typically the primary company interface to the governing authority in each jurisdiction. The interaction includes formal submissions as well as innumerable types of correspondence and meetings such as pre-submission meetings, approval letters, warning letters, facility registrations, and inspections findings to name a few. Regulatory is also responsible for reviewing draft

regulations and specifications, informing the company's response, providing comments to the authorities, and ultimately interpreting and assessing impact of final regulations.

Notified Bodies – In some regions, notified bodies (NBs) perform the submission reviews for the local or regional health authority, typically for devices. Companies may have a choice of notified bodies depending upon the jurisdiction.

Accrediting and Certifying Bodies – In some cases, accrediting or certifying bodies may interact with regulatory teams as part of certification of a facility. Also, certain health authority programs such as the FDA's *Case for Quality*, involve such entities (e.g. CMMI) to certify participation and conformance within the programs.

Distributors – In many cases, distributors will work with global regulatory teams to collect documentation for submission and report local health authority interactions. Specific roles and information exchange will vary depending upon the operating model. Regardless of the distribution of responsibilities, effective communication and sharing of data is critical to compliance and operational efficiency.

3rd-party Service Providers – These relationships can be with Contract Research Organizations (CROs), Contract Manufacturing Organizations (CMOs), Regulatory Intelligence and other Regulatory Services Providers and other groups that provide data and documentation or perform outsourced services for regulatory teams. Information exchanged will depend upon the nature of the relationship.

Joint Venture or Licensing Partners – In many cases, companies will co-develop or license in or out their Intellectual Property. These relationships require effective exchange of information to support submissions and lifecycle maintenance. Safety and quality data exchange is often handled directly between respective departments, though Regulatory may sometimes be a conduit.

12.2 Internal Stakeholders

Marketing– Regulatory should provide early input into development and approval timelines as well as Probability of Regulatory Success (PRS). Also, Regulatory works with Marketing, in conjunction with Labelling, to review advertising and promotional material.

Product / Portfolio team – Also, planning and decisions from the Portfolio Team must be continuously communicated to Regulatory to allow for effective submission planning and resourcing. Regulatory will coordinate regulatory strategy and explore accelerated submissions and approval pathways with the Portfolio Teams.

Clinical – Clinical teams will provide Regulatory with content for submissions: for filings of the initial IND or CTA and their amendments, disclosure of information on health authority sites such as clinicaltrials.gov, and for product registrations including new product filings, variations, supplements and lifecycle maintenance submissions. Regulatory communicates regulations as well as health authority expectations and meeting outcomes to the Clinical teams to inform protocols and clinical programs.

Biostatistics and Data Management – While Clinical is typically the customer for statistical analyses, Biostatistics and Data Management teams are responsible for providing regulatory with datasets to be included with submissions. Regulatory will inform the Biostatistics teams with Regulatory Intelligence and insights to guide the

statistical analysis and reporting. Regulatory may also communicate requests by Health Authorities for additional analyses.

Labelling – Regulatory may provide input to the initial target label, sometimes referred to as the Target Product Profile (TPP). Labelling will provide proposed artwork for all packaging, package inserts and eLabels for inclusion in the product submission. Interactions also can include communicating changes mandated by Health Authorities.

Chemistry, Manufacturing and Controls (CMC) – The CMC team is responsible for developing and documenting the end-to-end manufacturing process and creates content for Module 3 of the CTD submission. CMC may initiate product changes and will typically create content supporting the change if a Supplement/Variation is required. CMC is responsible for maintaining all product and production documentation throughout the product lifecycle, as well as releasing appropriately qualified product for distribution to each jurisdiction (right-product / right-country).

Supply Chain – The end-to-end Supply Chain includes clinical development and supply, manufacturing, and the entire distribution ecosystem. Regulatory's responsibility is to maintain supply chain information for registrations and launch, as well as labelling and serialization.

Quality – Quality often has direct responsibility for managing inspections and audits, and typically owns the Change Control Process. Many changes require a regulatory impact assessment, and many of those proposed changes require some sort of filing in the form of a Variation where prior approval is required or Change Notification where change activity is merely communicated to appropriate Health Authorities. Quality is also a key content provider for product submission content and periodic product quality submissions. In some cases, the Quality organization may provide Regulatory with services such as Six Sigma and continuous improvement support.

Pharmacovigilance – For Pharmaceutical and Biologic companies, pharmacovigilance teams provide information related to drug safety to Regulatory for new product and expedited and periodic report submissions. Information regarding the Risk Management Plan may be maintained by Regulatory. Health Authority communications regarding safety issues may also pass through Regulatory.

Affiliates – Affiliates are local operating companies (LOCs) that may have Regulatory resources, or they may rely on the manufacturer's global or regional Regulatory resources to interface with local Health Authorities. The Affiliates will work with global regulatory teams to collect information and documentation for submission and report local health authority interactions. Specific roles and information exchange will vary depending upon the operating model. As with Distributors, effective communication and sharing of data is critical to compliance and operational efficiency.

12.3 A Lifecycle View of Interactions

Regulatory's involvement changes throughout the product lifecycle. The table below roughly follows the lifecycle from the decision to move into clinical trials, to commercialization, through to product end-of-life. It presents interactions with Regulatory typically seen in mature pharmaceutical and biotech companies.

A few caveats: the activities and deliverables are indicative and not exhaustive. They are representative of the more common interactions with Regulatory teams. The individual functions have much broader responsibilities

not reflected in this table. The table does not reflect other Regulatory responsibilities such as regulatory intelligence and policy-setting that impact all stakeholders. For Medical Device manufacturers, the roles of Quality and Regulatory are often combined. Finally, operating models vary from company to company, so roles and relationships are not universal.

Coming from	Regulatory Affairs' Role	Going to
	Pre-clinical & Clinical	
Development organization – decision to progress candidate	Provide probability of regulatory success	**Portfolio teams** – development plan
Portfolio teams – launch targets	Translate launch target, countries and timeline to submission plan	**All stakeholders** – submission plan
Pre-clinical – DMPK, toxicity, other testing	Assemble content for future submissions	**Health Authority(ies), NBs**
Bio-statistical teams – Clinical data strategy and plan	Assemble content for future submissions	**Health Authority(ies), NBs**
Clinical – Protocol, Investigator Brochure, clinical documentation	File IND/CTA submission	**Legal, Health Authority(ies), NBs** – IND/CTA
Drug Safety – PV insights, Risk Management Plan	Assemble content for future submissions	**Health Authority(ies), NBs**
CMC – product documentation	Assemble content for future submissions	**Health Authority(ies), NBs**
Quality – QMS documentation	Assemble content for future submissions	**Health Authority(ies), NBs**
Affiliates – local regulations and requirements	Provide regulatory intelligence, contextual requirements	**All stakeholders** – submission and operational requirements
	NDA/MAA	
All Stakeholders – subject matter expertise, content review, questions	Coordinate and facilitate pre-submission meeting(s)	**All Stakeholders** – meeting minutes, Responses-to-Questions
Bio-statistical teams – Raw data sets, statistical analysis, report	Assemble content for future submissions	**Legal, Health Authority(ies), NBs**
Clinical – Clinical reports, summary	File submission for approval	**Legal, Health Authority(ies), NBs** – NDA, BLA, MAA, PMA (device)
Drug Safety – Safety analysis, DSUR (filed prior to submission)	Assemble content for future submissions	**Legal, Health Authority(ies), NBs**
CMC – drug product and manufacturing process information	Assemble content for future submissions	**Legal, Health Authority(ies), NBs**
Supply Chain / Manufacturing - Package Data Carrier Identifiers (GTIN, etc.) and Marketing Status	Submit as part of product registration data e.g. IDMP	**Health Authority(ies)**
Labelling – label content, artwork	Approve, assemble content for submissions	**Legal, Health Authority(ies), NBs**
Marketing – advertising and promotional content	Approve, assemble content for submissions	**Legal, Health Authority(ies), Commercial, NBs**
Affiliates – local submission calendar	Factor local submissions calendars into global plan	**Development Team** – development calendar adjustments
Affiliates – local intelligence	Collect local-market insights, intelligence, curate, distribute	**All stakeholders**

Coming from	Regulatory Affairs' Role	Going to
(n/a)	Prepare HA-specific submissions or forward Global Dossier	**Affiliates and Distributors** – material for local submissions
	Post-marketing	
Clinical – Clinical reports (ongoing studies/Phase IV), safety signals	Assemble content for variations, supplements or notifications	**Legal, Health Authority(ies), Affiliates**
Investigator Initiated Studies – Clinical reports, safety signals	Assemble content for variations, supplements or notifications	**Legal, Health Authority(ies), Affiliates**
Drug Safety – Safety signals, ongoing safety analysis, PSUR	Submit periodic reports as required	**Legal, Health Authority(ies), Affiliates** – periodic safety reports
CMC – product and manufacturing process updates	Assemble content for variations and supplements	**Legal, Health Authority(ies), Affiliates** – variations
Supply Chain / Manufacturing - Package Data Carrier Identifiers (GTIN, etc.) and Marketing Status	Submit as part of product registration data e.g. IDMP	**Health Authority(ies)**
Labelling – label content, artwork	Approve, assemble content for submissions	**Legal, Health Authority(ies), Affiliates**
Marketing – advertising and promotional content	Approve, assemble content for submissions	**Legal, Health Authority(ies), Affiliates**
Affiliates – local submission calendar	Factor local submissions calendars into global plan	**Product teams** – product change calendar adjustments
Affiliates – input from local HAs (findings, questions, etc.)	Document / take action as appropriate	**All stakeholders** – as appropriate
Affiliates – local intelligence, regulatory impact assessment	Collect local-market insights, intelligence, curate, distribute	**All stakeholders** – as appropriate
(n/a)	Release of packaging/SKUs for sale	**Supply Chain / Manufacturing**

12.4 Challenges

Clearly the above intersections are complex, sometimes concurrent, and often urgent. And, they evolve over the course of the product lifecycle, especially when the product is in a pre-approval state in some markets and in lifecycle maintenance in other markets. There are multiple factors that exacerbate these challenges which are certainly, but not exclusively, aggravated in cases of merger and acquisition. Conditions that create inefficiency and increase risk include:

Unclear Process, Data Governance and Ownership – The processes described above all involve Regulatory teams, yet many are owned by other functional areas. Development of content for submissions is typically owned by the respective function, Regulatory simply coordinates and aggregates content. Change Control is owned by Quality, yet Regulatory is accountable for many of the process steps, and both functions rely on data and information from still other functions. Each group has different needs, so process steps and priorities can easily be misaligned.

Lack of Systems / System Integration – Systems maturity varies from company to company. Where systems do exist, lack of smooth data flow among systems compounds the issue of process ownership. Latency and data quality issues related to the manual transfer of data and documentation often generate compliance risk. These issues can also result in delay of approval and product release. Speed and compliance translate directly to profitability as well as timely patient access to therapies.

Immature Master Data Management – Regulatory has traditionally been document-based. Focus is on the submissions and correspondence among parties. Documents become lost in local drives or inaccessible due to ineffective search capabilities. Using documents to drive business process is burdensome. For these reasons, as well as regulations such as the upcoming Identification of Medicinal Product (IDMP) requirements, the industry is slowly moving to data-based activity. Working at the data level requires competencies seen more frequently in finance and aerospace. Lack of ability to define effective taxonomies and data structures translates to continued reliance on reading volumes of documentation to drive processes and stay in compliance.

12.5 Organizational Considerations

Often challenges relating to the effectiveness of regulatory processes can be attributed to traditional corporate organizational structures. A hierarchical organizational structure attempts to break critical functions into separate groups that can specialize on a set of specific tasks, add resources, manage group/department budgets, etc. This structure has been the dominant organization type and yielded enormous benefit throughout modern corporate history, but the advent of technology has made cross-departmental data information flow as much, and perhaps due to the never-ending pressure of competitive markets, more important than whatever benefit is gained by rigidly siloed functional areas. Nowhere is this more evident than in CMC (Chemistry, Manufacturing and Control), where, to name just a few examples:

- Most decisions have a long cascade of impact throughout the rest of the organization, crossing the barriers between R&D and Commercial Manufacturing
- Changes can happen with little or no notice, such as a sudden and unanticipated issue with a supplier or raw material
- Governing regulations proliferate in variety and complexity as the product is sold to more markets, which is also amplified by the number of products carried by a sponsor.

Although accountability for considering and implementing changes lies firmly within the CMC silo, the information about the change is not, at least not to the extent it can impact other line functions such as Regulatory. It is not uncommon for Regulatory to find out about a change that happened five months ago, with the results that depending on the market, the submission may be three months late, due in yet another month, or no submission being required at all. These examples are representative of a broader set of challenges for Regulatory.

There are many issues to consider: Who owns what data? If there are multiple systems containing the same information, which data takes priority? Which organization is accountable? How can the authoritative source be established? At present no system or technology has definitively answered these questions, because at present they are designed for the silo they serve first and make whatever data available to other silos second. In such situations, it makes sense to establish owners for each business process, data and system to ensure appropriate accountability and governance across functional silos.

12.6 Best Practices

Not surprisingly, the industry best practices align to the challenges. The first, Transparency, is more of a guiding principle than a practice. The others, process and system integration, are achievable activities, likely on any company's capability roadmap.

Transparency – Transparency as an ideal is generally embraced. Who wouldn't want clear visibility to upcoming product and regulatory activity, the ability to anticipate and plan so that all the parts fall into place, the ability to rapidly locate information critical to any given process? Legal concerns and competitive fears all attenuate the ability to freely share information, both internally and externally. Leading companies have implemented effective controls, policies, and stakeholder communications to address the issues, and have successfully achieved breakthrough levels of transparency, improving speed, quality and compliance.

Process Integration – A primary target is Change Control and Variation Management. Triggers come from Manufacturing, Marketing, Safety and Health Authorities, among others. Quality typically owns the process, and Regulatory coordinates a significant portion of the activity, especially if Variations need to be filed. Process hand-offs are typically bottlenecks and cause for error. Leading companies execute process design as a cross-functional effort, with all parties involved form beginning to end: from project initiation to approval of the final, negotiated outcome.

Systems Integration and Access – Systems integration enables process integration. Moving data from one system to another with minimal or no human intervention increases speed, reduces error. Effective Master Data management is a prerequisite. Tools include direct system-to-system integration, integration with a common data-bus or data-lake or use of automation tools such as Robotic Process Automation to move data.

Leading companies are exploring overarching workflow tools to provide simplified user interfaces to all users, automatically retrieving and sending data to all impacted systems, moving the process along its prescribed path, alerting participants when intervention is needed. The workflow tools accommodate all process participants regardless of their function.

Another approach, Intelligent content management, enables the use and reuse of content within the documents to perform automated metadata mapping and migration of content or documents.

13 Regulatory Analytics and Dashboards

13.1 Background

Measurement has long been the province of Quality. After World War II Joseph Juran[13] and Edward Deming[14] raised consciousness of the value of measurement and driven concepts such as continuous improvement across industries and across the globe. Some industries, such as automotive and aerospace, have embraced measurement and continuous improvement, while the life sciences industries have been more focused on compliance. Regulatory Affairs has been particularly slow on the uptake. The introduction of workflow within

[13] Juran.com
[14] Deming.org

regulatory information management (RIM) and electronic document management (EDMS) systems has provided the foundation for measurement and opens new opportunities for improving regulatory performance.

Companies have realized that Regulatory is on the critical path to product launch. A private 2017 study revealed that the submission process alone can take anywhere between 4 weeks and over 36 weeks. Companies that can reduce the time from data lock of the pivotal study to submission are able to start serving patients and generating revenue by an equal amount of time. For pharmaceutical companies with large pipelines, shaving 10 to 12 weeks off submission time can translate to hundreds of millions of dollars Net Present Value.

Measuring speed alone will not necessarily translate to increased revenues. Regulatory teams must measure other factors such as submission quality, resource competency and balance, or workforce satisfaction to achieve and sustain benefits. Regulatory leadership must first decide what they are trying to achieve (the why of measurement) before determining what to measure. Metrics should support strategic and tactical objectives at the level of focus (corporate, function, or team).

13.2 The Metrics Hierarchical Framework

Many companies have developed regulatory metrics frameworks. Key Performance Indicators (KPIs) are at the top of the hierarchy. The KPIs typically represent key objectives and may cover a variety of topics: speed to market, cost, workforce culture, product quality, and customer (patient) satisfaction to name a few. Senior management (and investors) look to periodic reporting of these KPIs to confirm strategic direction and drive strategic initiatives.

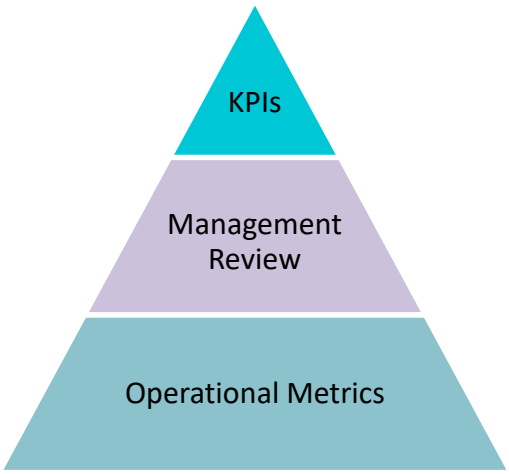


Figure 15. Metrics Hierarchy

Management Review metrics cascade from the KPIs. They typically are part of a periodic management review, and provide a more granular insight into divisional performance, trends, progress on key projects, etc. They are also used to identify and launch continuous improvement projects or initiate Corrective Action – Preventive action (CAPA) activities.

Operational Metrics then cascade from Management Review metrics into even greater detail. While KPI's and Management Review metrics often focus on past performance and trends, operational metrics represent a more

real-time view of performance. Ideally, data is collected automatically from the source systems so managers can quickly spot process constraints or milestone delays and proactively take action. A regulatory operational dashboard will often show all three levels of metrics across a range of key topics. Dashboards can also be developed to send alerts if a value is outside control limits, illustrate trends, or even support root cause analysis through functions such as data visualization, filtering, and pivot tables.

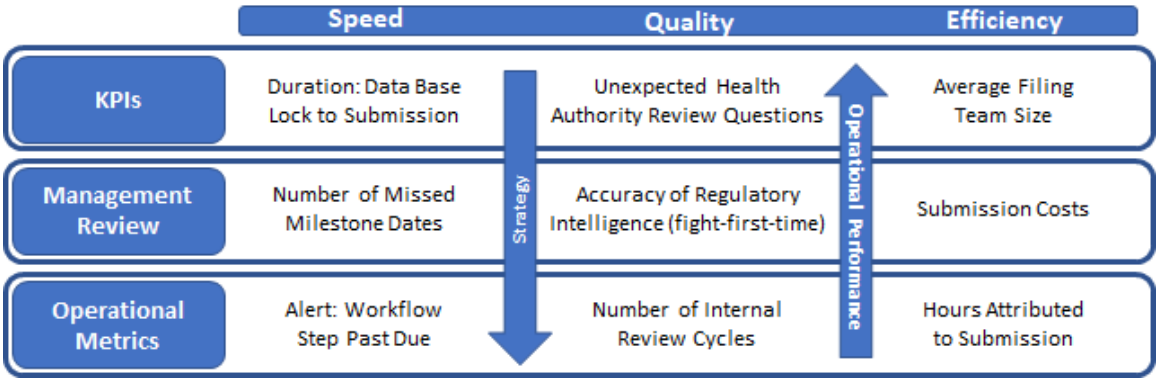


Figure 16. Sample Dashboard Framework

13.3 What to Measure, How to Measure

The decision on what to measure should be driven by the "why". First determine objectives: speed-to-market, balancing workload, reducing cost, etc. Once the objectives are determined, then identify the metrics that will support the objectives, as well as the sensors that will provide the data.

13.4 Metrics Maturity

In general, organizations tend to focus on easy-to-measure metrics and ignore those that are difficult to collect. Also, many organizations measure and report at the end of work cycle (historic metrics) when it is too late to do anything to improve performance. Measuring early and throughout the process will identify opportunities to avoid or rapidly correct issues.

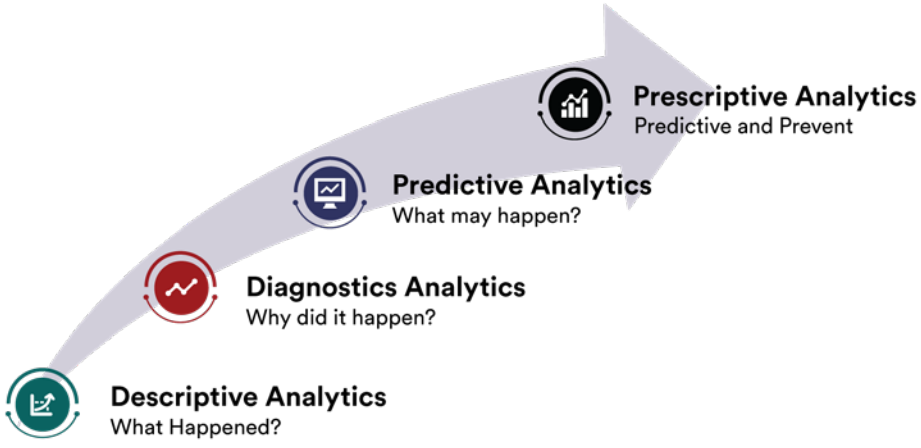


Figure 17. Metrics Maturity Model

As metrics maturity grows, organizations move from Descriptive Analytics (what happened) to Predictive Analytics (understanding what may happen) and even Prescriptive Analytics (driving results). Prescriptive Analytics sometimes leverages AI or Machine Learning to improve outcomes.

Type of Analytics	Regulatory Examples
Descriptive Analytics (What happened?)	• What is the total duration taken to make a submission from the time of initial planning? • What is the total number of submissions, by country, by product, etc.? • How did we perform in our submissions over the past five submissions? • How many re-works per submission?
Diagnostic Analytics (Why did it happen?)	• Why were there delays in making a submission to a HA? • Why were there re-works on a submission?
Predictive Analytics (What may happen?)	• What is the probability of achieving our target submissions dates? • What are the potential questions to be expected from HA? • What is the dossier submission plan for the ROW based on baseline market plans?
Prescriptive Analytics (Predict and Prevent)	• What are the best regulatory pathways for an oncology drug to get regulatory approval in Japan, for example? • Given past immunology drug approvals, what is the best strategy to apply for our current immunology submission? • What impacts may occur due to geo-political changes on approvals?

13.5 Challenges

Metrics programs face many challenges. First and foremost is lack of data or poor data quality. RIM systems (including associated EDMS) have the capability to capture and produce rich data and metadata to inform dashboards and reports. However, data quality cannot be assured simply by using the system, as the issues can arise from different sources including people, process, and technology.

Workflow is one source of data. For example, if the workflow is not used, fields are left blank, or quality is not controlled, the information is either missing or worse, deceptive. One company ran a detailed workflow report only to find that users routinely bypassed the workflow and entered only data they felt favorable to their careers.

Manually collecting the data introduces significant effort, time, and risk of inconsistency and error. Systems should be configured, where possible, to automatically capture data related to cost of filing, compliance, quality, speed, resource availability, and forecasting. Mature organizations typically automate metrics capture and enjoy lower costs and greater data integrity. When issues do come up, manual input may still be necessary to understand root causes and take corrective action.

Metrics definitions are another challenge. Terminology is often confused. Different divisions may have different performance definitions, different metrics calculations and different reporting approaches. Lack of standard definitions and calculations undermines efforts to drive performance and can lead to decisions based upon incorrect assumptions.

There is a tendency to measure what's easy, not necessarily what's useful. This does not drive performance. The goal must be in mind when identifying what to track. Rigor is required to identify the key decisions that will be supported by the metrics. Companies should also consider standard reports to drive compliance and

performance, as well as reports required for regulatory submission. Starting with the end in mind will generally address the issue of useless measurement.

Perhaps the most significant challenge to an effective measurement program is culture. Providing a window into performance brings new levels of transparency, something that is not always welcomed. Transparency requires clear communication of expectations and the basis and rationale for measurement. Cultures that punish underperforming teams or individuals may lead to altered or missing data. Once data is missing or altered, it is impossible to recover and achieve an accurate representation. Companies that have implemented metrics have found that an accompanying cultural change effort is needed. A culture of collaboration, communication, mutual support, and incentives should be promoted.

13.6 Leading Practices

Leading practices often come from other parts of the organization, or outside the industry altogether. Some that apply to Regulatory Affairs and Operations:

Standardize – Common definitions, calculations and process flows are essential to effective performance measurement. Valid comparisons can be made only where definitions, calculations, and algorithms have commonality. Stakeholders rely on comparative metrics to achieve continuous improvement in their regulatory program. Defining a common data model is one of the primary objectives of the DIA RIM Reference Model.

Workflows – Effective process maps will enable optimal workflows. This is the foundation for automation, which will in turn provide accurate metrics. Companies should take care to fully develop and pressure test workflows before embodying them in their RIM system configurations and incorporate organizational change management to drive full adoption. Many companies allow workarounds to system-based workflows. While flexibility is sometimes appreciated, it typically undermines efforts to track progress and enforce policies. True understanding of process efficiency and effectiveness is impossible.

Visualization – Dashboards and visualization tools can provide deep insights to operational performance at-a-glance. Common formats such as pie charts, bar charts, scatter diagrams, summary tiles, bubble charts and even word clouds can highlight issues and opportunities that can be buried within the narrative. More advanced dashboards also allow for data mining, pivot tables and other analytical tools to identify trends, correlations, causality, and even new metrics.

Culture – Develop a culture that supports metrics. New levels of transparency require acceptance on the part of all stakeholders that insights will be used to drive continuous improvement (e.g. Lean Six Sigma) and not be used to punish.

Center of Excellence – Managing analytics capabilities is a multi-dimensional effort requiring a balance of governance, data management and systems integration (in addition to the cultural efforts mentioned above). Many leading companies have independent centers of excellence, driving tools and practices across all functions. The result is a higher level of capability at reduced costs to individual functional teams.

Reports – Reports are critical for decision-making. A well-designed dashboard with a spectrum of common, referenceable snapshots, as well as real-time performance metrics, enables effective decision support.

Automation – Automation, in addition to reducing effort and risk of error, is essential to achieving real-time visibility, and predictive and prescriptive analytics capabilities.

13.7 RIM's Role in Enabling Effective Regulatory Analytics

The RIM system is at the center of regulatory metrics. Every interaction with the system generates metadata in addition to the documents and other artifacts that are held within the system. This metadata (time stamps, data sources, status flags, etc.) informs metrics such as process and sub-process durations, progress against targets, process deviations, and submission counts, among others. As machine learning and regulatory analytics mature, the content within the documentation will be used to inform future analytics. The RIM Reference Model highlights possible metrics related to many of the processes and objects within the model.

Many software vendors offer dashboards as part of their solutions. It will be up to each company to identify what to measure, how to present the metrics, and how to put the data and information to work.

14 Data Quality and Data Governance

As regulatory information becomes strategic to the business operations of Life Sciences companies, it becomes important to focus on data quality and data governance as an integral part of regulatory affairs and regulatory operations functions. This can be ensured by defining and adopting Good Regulatory Information Management Principles (Palm-Principe 2017). High-level principles include the following:

1. Treat data or information as a strategic asset
2. Embed data quality across RIM processes
3. Encourage data quality culture
4. Build data quality monitoring and reporting into all processes/systems

Data quality and governance can be enabled in three different ways, which are closely interlinked and perhaps may even seem, overlapping:

People:

- Support end users with entering RIM data right the first time by minimizing entry of duplicate data or free-text data and consistent use of controlled vocabularies or industry standard dictionaries.
- Develop a data quality mindset and culture as part of the training and change management efforts.
- Define data stewards and/or owners for various data elements and train them regarding data quality principles, approaches, tools, etc.
- Define and manage performance objectives around data quality metrics with incentives and/or negative impact.

Process:

- Ensure data entry and management processes are not too onerous, requesting only for information that is relevant to a particular aspect of the process at hand, etc.
- Establish a data governance program leveraging existing data governance methodologies and approaches.
- Define processes for data standards management, data quality reviews, data remediation and verification.

- Conduct process and information audits.

Technology:

- Eliminate duplicate data entry where possible by integrating with other sources of truth, such as product master data.
- Leverage standard reference data dictionaries such as MedDRA, WHO, ISO, etc.
- Improve the overall user experience by enforcing data entry rules, constraints, automatic naming conventions, etc.
- System-driven routines for data quality checks, reports for proactive data quality monitoring, alerts and notifications, etc.

15 Opportunities for Artificial Intelligence

The DIA RIM Reference Model Working group identified Artificial Intelligence (AI) as an emerging technology that holds the promise of improved speed to market, reduced resource requirements and improved probability of regulatory success. Exponential complexity with multiple markets and product variations is driving the need for AI to replace what has historically been a manual activity. Regulatory has traditionally been late to the party. The focus on compliance has distracted Regulatory from adopting new technologies.

Traditionally when groups talk about Artificial Intelligence, they are usually referring to some form of process automation or rules-based engine that provides efficiencies over manually demanding tasks. The true realization of AI would be having machine learning systems embedded in the routines that we undertake so that the work previously handled by manual and programmatic efforts would be undertaken by intelligent routines.

Initial applications of AI include using intelligent search to identify adverse events within a broad base of literature or identify relevant Health Authority correspondence to inform future submissions content. Natural Language Generation (NLG) has been used to develop case reports from clinical data. Natural Language Process (NLP) has been used for intake of content to parse into structured formats. Other applications include using NLP to support classification and adjudication of Adverse Events, as well as classification of documents.

As part of the AI Subcommittee, team members contributed ideas and application in a Problem – Solution format. Some AI use cases that our group has identified include:

Problem	Potential AI solution
Gaining institutional insight from global health authority interactions for patterns and previous answers/submissions	AI-powered search/content analytics to identify specific references and patterns/trends in interactions
Identifying commitments, questions and follow up from correspondence	Identify and extract commitments and other required responses embedded in documents into RIM and create and send alerts to ensure completion
Translating document content into structure (and vice versa)	Natural Language Processing (NLP) algorithm detecting content automatically and providing suggested structured format

Problem	Potential AI solution
Translating narrative content (language to language and scientific to laymen's terms)	Translation engines (using Natural Language Processing)
Giving the same and standardized response every time, so we seem as an integrated Regulatory Affairs (RA) team, rather than delivering several different/varying answers to the same question (similar to Medical Response Letters (MRLs) for Medical Information)	Assess responses for reuse and build an inventory of standard template responses that can be tailored. Tag responses to find and reuse them more readily. Can use NLP and ML to mine queries and responses to see where we have answered similar questions and provide similar responses
Content used in multiple submissions gets out of sync and can be non-compliant	Application of Structured Content Authoring allows repeated data and narrative to stay in synchronization
Automate management of requests coming into Regulatory Operations	NLP and RPA to read and classify the request then appropriately triage it to the correct group.
Reporting KPIs	Leverage analytics for reporting on KPIs. RPA can automate periodic running of reports and sending to leadership.
How does a delay in clinical activities affect a commitment	Workflow management tools can automatically identify and update the critical path as elements are updated
Purchasing a compound from a different sponsor and ensuring that you have all referenced documents throughout. Unless you read every document and identify every source you won't know you are missing anything until you go back to the original sponsor.	Intelligently identify document references within documents and correlate over all the received documents. A Learning Management System (LMS) can identify which documents are referenced but not available in the existing compound library.
Automated impact analysis e.g. change of supplier	Use of AI to identify multiple variables and predict impact to cost and timeline

The examples above illustrate the challenges that can be addressed with various forms of AI solutions. Vendors are currently tacking these and many other issues such as how do we effectively validate a system based on artificial intelligence.

Effectiveness is based upon large sample sizes. One company's body of knowledge may not be enough to achieve critical mass. Vendors and industry consortia with access to large bodies of data will need to be tapped in order to make progress.

Many contend that there will always have to be human oversight, with a goal to minimize that over time. There is evidence that in many cases, machines are already outperforming their human counterparts.

16 Conclusion

16.1 RIM's Role in Enabling Effective Interactions within the Ecosystem

Companies have taken widely varying approaches to implementing RIM, electing to carve out some functionality due to overriding considerations, such as constraints around giving up existing legacy systems and data ownership, complex legacy integrations, conflicting strategic and financial priorities and a host of other reasons. Resource constraints, competing priorities and workload can also influence decisions on implementation scope and timing. Regardless of how regulatory capabilities are divided among systems, information should flow freely and accurately in ways that no process is constrained, and no data is compromised. RIM should play its part in supporting transparency, speed to market and regulatory compliance.

RIM has evolved significantly over the past decade into end-to-end capabilities supporting the needs of the regulatory value chain and beyond. A key driver includes providing a single source of truth around regulatory information, not only for regulatory activities but also other functional areas, which require regulatory information as part of their business processes. In addition, significant M&A activities in the industry require ease of interoperability of data across systems and organizations. These drivers require a more integrated approach to managing regulatory information and working with a set of common business processes, data definitions and relationships. This Whitepaper has outlined an integrated approach to Regulatory Information Management along with the companion work around the definition of a RIM Reference Model.

16.2 Looking Beyond Traditional Definitions of RIM

As the slow growth and evolution of global standards such as IDMP, EUMDR and others marches on, companies have realized that waiting for them just won't work in a highly competitive marketplace. Effective management of content and data is critical to speed, quality, and compliance. Standard definitions will go a long way to enabling effective information management. Many companies are rushing to apply new technologies such as AI and RPA to understand health authority expectations and anticipate their actions. Failure to do so results in delays and rework at a minimum, failure to achieve application approval in many cases. These technologies can be effective only if common terms and definitions are applied.

Leading companies are looking beyond the traditional definition of RIM as a record-keeping tool, leveraging data and RIM-created metadata to drive continuous improvement in an effort to get safe and effective therapies to patients faster and at greater profit.

16.3 Next Steps

As the RIMWG continues to evolve, both the Whitepaper and the Reference Model will be updated. Just as this paper was reviewed prior to publication, the EMA delivered the IDMP Implementation Guide Version 2.0. Industry will need to evaluate how RIM can support IDMP requirements, and this will certainly be a focus for the group. Both the Reference Model and the Whitepaper were developed as a service to all stakeholders for the reasons stated in the Abstract. Please reach out to any member of the group with comments or suggestions.

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