

Regulatory Intelligence— A Key to Successful Submissions

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Glossary

AI	Artificial intelligence
CMC	Chemistry, Manufacturing & Control
COVID-19	Coronavirus disease 2019
EMA	European Medicines Agency
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
HA	Health authority
RAPS	Regulatory Affairs Professionals Society
RI	Regulatory intelligence

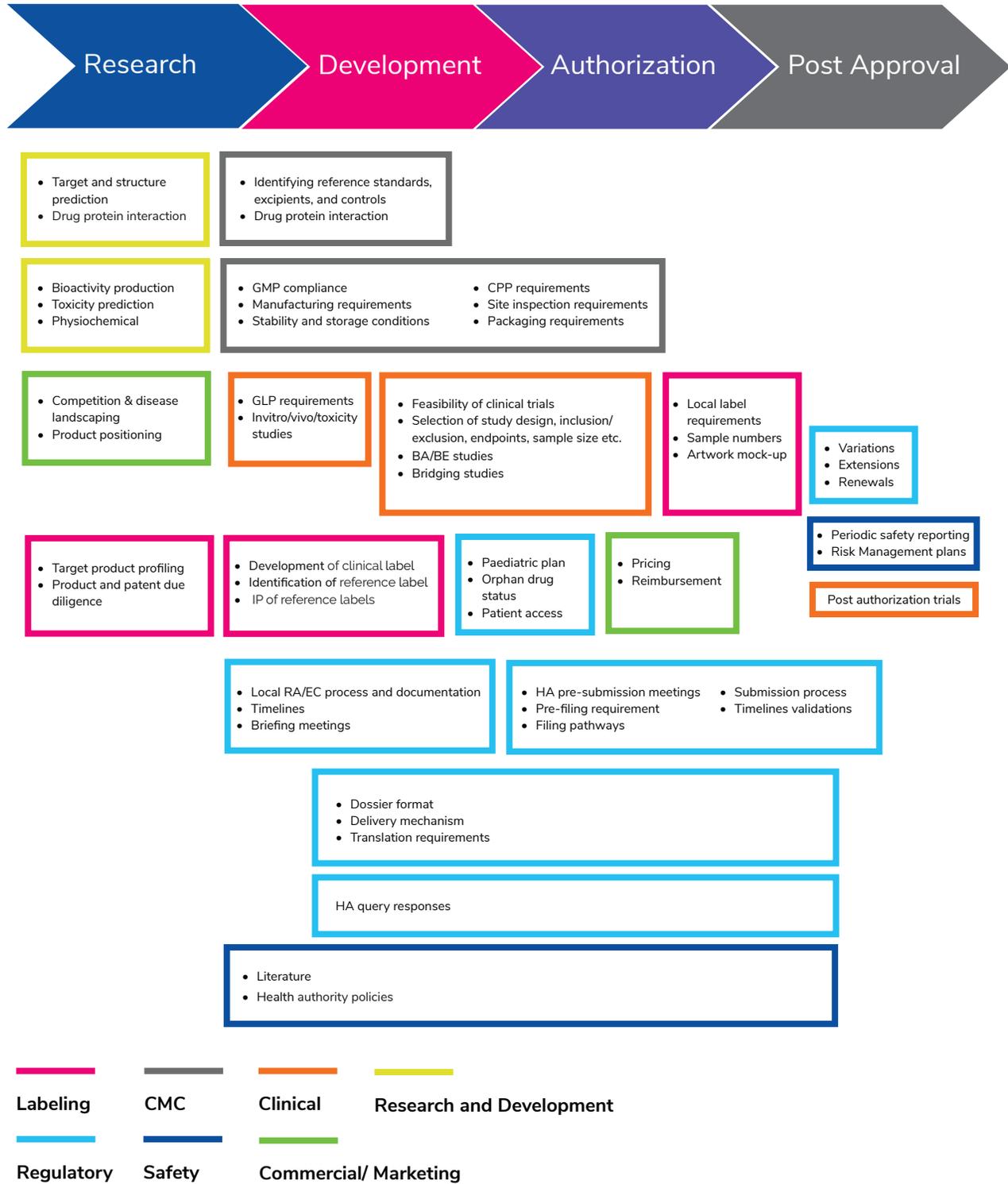
Background

The regulatory information on the advancements in healthcare and technology, insights on the approaches to support patients with unmet needs, and policy influences on the drug development processes keep on evolving constantly. Staying abreast of the continuous thread of this information requires careful consideration to the credence and the impact this information has for all pharmaceutical companies globally. Although this information is complex to organize and manage, it is critical in achieving successful product (drug/device) registrations and market authorization. The health authority (HA) guidelines, policies, and laws governing the product registration, manufacturing, or licensing processes vary across markets, based on that country's healthcare requirements. Leveraging precedence, insights, and continuous monitoring of the regulatory environment can benefit regulatory professionals to strategically plan and expedite the product approval processes as well as address HA queries. Establishing an effective regulatory intelligence (RI) data strategy, governance, and review procedures from early development through the launch of the products provides the best opportunity to increase confidence in the submission compliance for each product class and HA. Therefore, the RI lifecycle management practice is the backbone of any pharma submission strategy and submission plans.

Traditionally, RI lifecycle management has been implemented either by proactively acquiring a broad set of defined regulatory information from various sources, assessing their impacts, and generating contextual insights; or by tactically procuring information for a novel cause or requirement when required¹. Each approach has its merits and efficiency opportunities. When implementing either of these approaches, it is crucial for the RI governance to consider the needs of a broad set of roles across business functions including regulatory affairs, pharmacovigilance, clinical development (such as R&D, chemistry, manufacturing, and controls [CMC], clinical, nonclinical) and regulatory writers, so that information presented can enable these functions to work collectively through the product development lifecycle and strategically plan for HA briefings at each milestone and eventual submission.

Timelines to perform the product risk analysis could be accurately determined only if the regulatory submission strategist acquires all the necessary regulatory updates for that particular market in a timely manner through constant monitoring of the landscape and utilizing precedence where applicable to develop a strategy. For instance, over the past couple of years, amid the coronavirus disease 2019 (COVID-19) pandemic, several regulatory authorities have amended or updated their regulations with flexibility for accelerated pathways to approvals, more so concerning emergency use. There have also been many guidelines around clinical trials' conduct given the pandemic's impact on the various aspects of trial conduct, including trial participants, healthcare providers, infrastructure, and logistics. Proactive investment on expert regulatory guidance and strategies could help achieve timely and accurate regulatory filings for approvals, and reduce delays, noncompliance, or penalties.

Requirement for Intelligence Across the Product Lifecycle



Information Sources for Regulatory Intelligence

Curating relevant regulatory information from various authentic sources is an important step and crucial to generating an efficient RI report. However, no single source provides collated information across markets; therefore, urging regulatory professionals to perform robust research for identifying appropriate sources to gather relevant regulatory information either for an immediate requirement or routine monitoring. Broadly, the sources could be classified based on their origin as below:

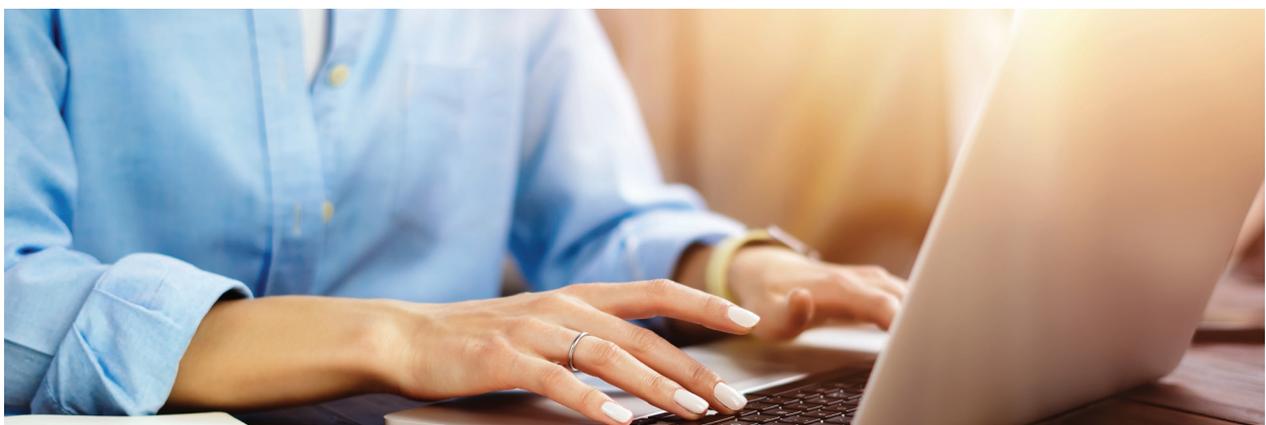
1. Internal sources

- a. **Precedence:** Leveraging past regulatory strategies, timelines for approvals, and internal interactions with local affiliates help in planning and defining filing strategies and optimal approval pathways that can lead to successful First-Time Right submissions.
- b. **Insights from prior HA interactions/advisory meetings/queries:** This is an invaluable source of information for companies as they steer through many such HA interactions across the globe for various products across therapeutic areas. A repository with the ability to pull out the needed information ensures efficient planning in line with RA expectations, and consistent responses for the product while also serving as a basis for subsequent reference and future planning.
- c. **Regional regulatory affiliates:** Another credible source of tribal regulatory information comes from regional and/or local regulatory affiliates and Regulatory Affairs Managers, who are the primary recipients of regulatory information from local HAs, where information is mostly available in the local languages, especially in the Asia Pacific or Latin America regions.



2. External sources

- a. **Health authority websites:** HA websites can provide critical information for defining the overall regulatory strategy for the product, its development, marketing approval/authorization, and further life cycle management. These websites provide access to the most recent guidance documents, policies, regulations, and drug approval summaries/assessment reports.
- b. **Competitive intelligence:** Company website press releases, annual reports from competitors, newsletters, and competitor labels are other sources of intelligence providing insights on the unmet areas and opportunities, safety issues, recalls, and competitive positioning of products. In addition, public access to clinical trial registries, EPARs - European public assessment reports, and evaluation reports available via health agency websites provides a warehouse of competitive intelligence.
- c. **News releases:** Press releases, news updates, bulletins, and newsletters on initiatives, directives, guidance documents, regulations, warning letters, decrees, and published in the public domain.
- d. **Industry events:** Industry events including conferences, seminars, and workshops the regulatory landscape, organized by healthcare companies.
- e. **Regulatory platforms:** Network of regulatory professionals through various platforms and paid subscriptions such as Drug Information Association (DIA), Regulatory Affairs Professional Society (RAPS), Canadian Association of Professionals in Regulatory Affairs (CAPRA), The Organisation for Professionals in Regulatory Affairs (TOPRA), CenterWatch, and so on.
- f. **Published papers:** Insights from published white papers, literatures, podcasts, blogs, webinars, presentations, etc.
- g. **Clinical trial registries:** Country-level intelligence on clinical trials and their endpoints can be availed from registries such as the World Health Organization (WHO) – International Clinical Trials Registry Platform (ICTR), EU-CTR, US National Institutes of Health, Japan Primary Registries Network (JPRN), Clinical Trials Registry – India (CTRI), German Clinical Trials Register (DRKS), and so on.



Criticality of Regulatory Intelligence

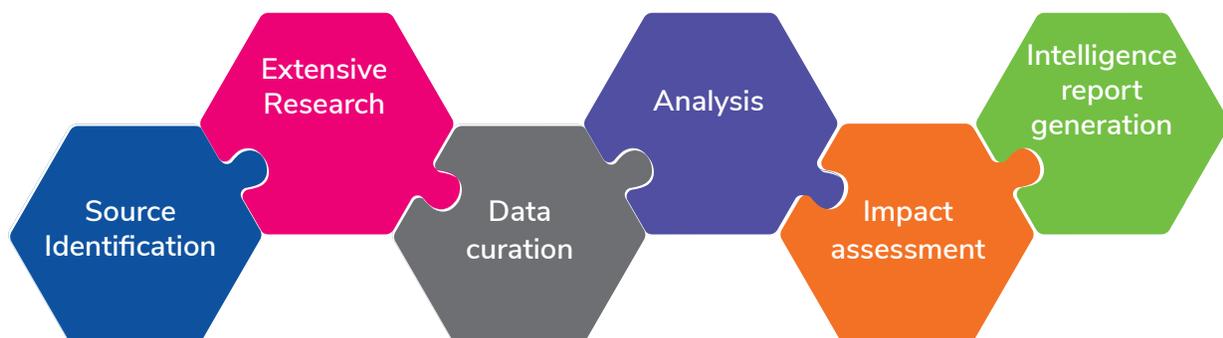
Regulatory Intelligence plays a critical role in regulatory strategy and operations, product due diligence, target product identification, clinical development, feasibility assessment for global/local clinical trials, manufacturing requirements, regulatory submissions, and further modifications that may be planned post-approval. The key uses of RI include:

1. **Product development:** Assessing new business requirements for due diligence, target product profile, potential risks, impact on supply chain, competitive analysis, and tracking progress are critical starting from discovery to approval of the product and post-approval compliance and life cycle management.
2. **Global filing strategy:** Regulatory strategy is integral to any new product submission, product, geographic expansion, or life cycle management. Each strategy must consider information that includes external data sources (HA websites, policies, regulations, publications, etc.) and internal data sources (precedence information/lessons learned). The filing strategy should incorporate key milestones and decision points; regulatory objectives, obstacles, and regulatory landscape, and characterize risks to potential success in delivering a specific regulatory outcome. A global regulatory strategist must consult with the regional regulatory affiliates to provide regional regulatory requirements and experience, and cross-functional experts such as CMC, nonclinical, and clinical, to enable the contribution of relevant documents for submissions.
3. **Risk Mitigation:** RI can be applied for early identification of risks to effectively plan mitigation strategies for further development at product launch and during post-approval based on current requirements and precedents.
4. **Preparation for regulatory meetings and briefings:** Prior knowledge and a clear interpretation of the regulatory requirements help develop a precise, well-organized briefing document presenting a clear company position with a targeted set of questions that goes a long way in eliciting detailed responses/discussion with the HA.
5. **HA Query Management:** A repository of experience from past HA queries allows the user to predict possible HA queries based on submission type/therapeutic area/similar markets and propose the best suitable resolutions. Further, a consistent approach to common queries can be standardized.
6. **Shaping future policies and regulations:** A continuous monitoring of the regulatory landscape as well as interpreting and evaluating the implications create opportunities for pharma organizations to collaborate with health agencies in shaping the future regulations, guidance, policy, and legislations.

A Blueprint for Efficient Regulatory Intelligence

Regulatory intelligence activities require data mining, aggregation, analysis, and validation to generate intelligence reports in a desired format, thereby reducing resource burden and ensuring compliance to regulatory standards and requirements. Some of the key steps involved in the RI process include:

1. **Source identification:** As each market is different, it is essential to identify the right sources to gather relevant information. Additionally, not all sources provide comprehensive information for all areas. For instance, HAs of the United States, Europe, and Japan promote transparency, and the most recent updates would likely be accessible. At the same time, there could be inadequate or non-credible information available in developing markets for specific countries across the Asia Pacific or Latin America. Knowing these differences can ensure an effective process to collect regulatory information from public websites supplemented with information received from local regulatory professionals who engage with the local health authorities.
2. **Extensive research:** The use of keywords applied through search strings is significant for setting alerts or mining relevant and latest data.
3. **Data curation:** Upon collating relevant information, structuring and grouping the data help in screening, removing redundant information while retaining only the newest and most appropriate content in the context of the requirement.
4. **Analysis:** The compiled regulatory information is further analyzed to highlight regulatory rules and obligations and identify trends and patterns.
5. **Impact assessment:** Once regulatory intelligence data are analyzed, the impact of new or updated regulations on a particular market is assessed, and an impact assessment grade (high, medium, or low) may be assigned based on the market or product of interest.
6. **Intelligence report generation:** A well-organized RI report can be established to meet business requirements and preparedness for regulatory changes across geographies. Such reports contain the latest update and their impact around the targeted products, therapy areas, product lines, geographies, and so on. This helps the regulatory professionals to frame an appropriate regulatory strategy as per the company's requirements.





Dissemination of Regulatory Intelligence

A well-formulated report must present appropriate information in an easy readable format. The RI report may be generated in an agreed template to meet the requirements. Some of the ways to disseminate RI include:

1. **Regulatory surveillance reports:** Periodic (daily, weekly, bi-weekly, quarterly, monthly, bi-annual) survey on the current regulatory requirements and trends in the form of newsletters, bulletins, or emailers.
2. **Regulatory strategy report:** To prepare a filing strategy and roadmap for the product development starting from preclinical phase (as applicable), clinical trials, submissions, approvals, market analysis, and licensing in a particular geography.
3. **Regulatory database:** Regular monitoring and updating information on the database or SharePoint to keep stakeholders apprised of the latest updates, and meet the business needs or unmet areas.
4. **White papers:** Publishing white papers on new regulations and requisites as per industry standards to benefit a wider audience and facilitate strategic decision-making².

Outcomes of Effective Regulatory Intelligence

1. **Efficient strategic planning:** to cover target regions/countries influences product development, submissions, authorization, launch, and post-approval life cycle management – and end to the view of the entire journey.
2. **Improved compliance:** An efficient RI team can proactively identify any global or regional market risks by continuous monitoring, identifying information gaps, adhering to current regulatory requirements, preparing a robust regulatory strategy, and ensuring better operational compliance, thereby resulting in successful submissions.
3. **Faster time to approvals:** Acquaintance with proper resources and up-to-date knowledge of local, regional, or global regulations can help prepare appropriate first-time-right submission dossiers, thereby resulting in faster approvals.
4. **Reduced pitfalls and cost to company:** Performing risk analysis and generating a well-designed strategy can further reduce the product development costs and efforts.

Importance of Regulatory Intelligence during the COVID-19 Pandemic

The COVID-19 pandemic has impacted product development and availability, including delays in clinical trials, the schedule of onsite inspections, workshops, submissions, subsequent approvals, and so on. Many HAs have proactively engaged with patient groups, therapeutic area/disease experts, and leading scientific bodies/experts toward minimizing the impact on trial subjects, patients, and healthcare in general, providing constant updates on the regulations and guidelines. On the other hand, the development of products, including biologics and vaccines, has been fast-tracked, ensuring the availability of the treatment or therapies for patients with Covid-19 worldwide. Health authorities across the globe have identified approaches to expedite product availability (fast-track reviews/approvals, rolling submissions, Emergency Use Authorization, to name a few). FDA's "Fast Track" designation program allows for the opportunity of a "rolling review" of New Drug Applications and Biologics License Applications that can be requested early in the product development process at the time of Investigational New Drug (IND) filing or after completion of Phase I studies. There is a strong emphasis on the importance of continuous communication with the FDA so that questions can be resolved quickly for fast-track submissions.

Therefore, understanding the regulatory HA, continuous tracking, consulting with appropriate forums, workshops, and surveillance are essential in ensuring that the most current information is made available to stay abreast with the current information.

Challenges in Developing a Robust Regulatory Intelligence Framework

Some of the potential challenges in tracking, reconciliation, and reviewing RI are listed below.

- a. Adaptation to rapidly changing and complex regulations
- b. Uncertainty of regulations in emerging markets
- c. Pooling information from multiple functions requires effort to contact and secure inputs
- d. Unforeseen delays or setbacks in contributions from stakeholders
- e. Unstructured information residing in silos rendering intelligence un-actionable
- f. Knowledge management: knowledge of regulatory requirements, access to precedence, and actual personal experience with the relevant authority that help the regulatory strategist collectively provide advice on what is “required” versus what is “expected” to deliver a positive outcome|
- g. Knowledge codification and dissemination to upstream and downstream systems
- h. Lack of a centralized mechanism of intelligence capture
- i. Proactive tracking of regulatory key performance indicators



Overcoming These Challenges – Emerging Role of Artificial Intelligence in Regulatory Intelligence

Several pharmaceutical companies are leveraging artificial intelligence (AI) technology for data processing and improved healthcare outcomes. Over the recent years, AI applications have been developed in the field of RI for strategic data wrangling by applying Natural Language Processing models to aggregate insights from public data sources, evaluate confidence in knowledge gathered to determine the risk for a submission, apply predictive analytics to determine the optimal filing strategy, gather and leverage precedence intelligence, translations (local language to English), timely monitoring of roles activities, and creating alerts. These initiatives have optimized a pharma company's capabilities, improved efficiency, and decreased human intervention. An AI-enabled RI system can ensure current information through a single repository for relevant information and real-time updates on changing regulations.

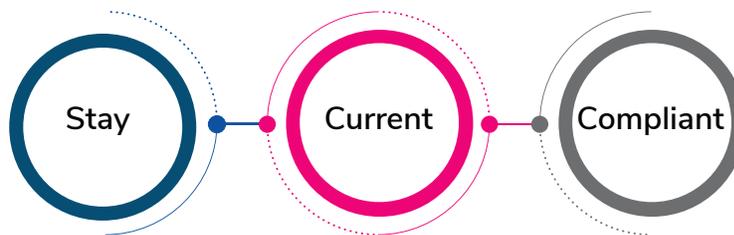
According to a survey by Mayer et al.³, 22 pharmaceutical companies and 3 companies leading in RI and AI technologies were interviewed for their value proposition, barriers, and risks. The companies considered that AI offered significant opportunities for RI activities on data processing involving mining, searching, monitoring, and alerting. The study results also showed that 32% of companies envisage the use of AI in data synthesis (combining different types of information across formats), 36% in data analysis (trends, predictive analysis), and 23% in decision-making. Overall, the assessment revealed a paucity of fully developed AI tools, although the demand from the RI community is gaining recognition. Studies on the application of AI technology in RI landscape claim that now is the time to advance the technology more than ever. There are various opportunities to enhance the quality, speed, and efficiency of RI activities³. Indeed, the significant contribution of AI toward the RI activities delivers greater agility in terms of saving time and costs.



Conclusion

The dynamic and advancing approaches for RI lifecycle management have been critical in accelerating the pharmaceutical product development and approval. The development of strategic data sourcing, aggregation, and application of regulatory intelligence can be the key to success for any drug or device development.

With their respective expertise and knowledge, Regulatory and technology professionals play a pivotal role in the success of the entire process. An efficient RI team enables seamless strategic planning and execution toward achieving the overall goal of making safe and efficacious medicines available, in a timely and regulated manner to patients across the globe.



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