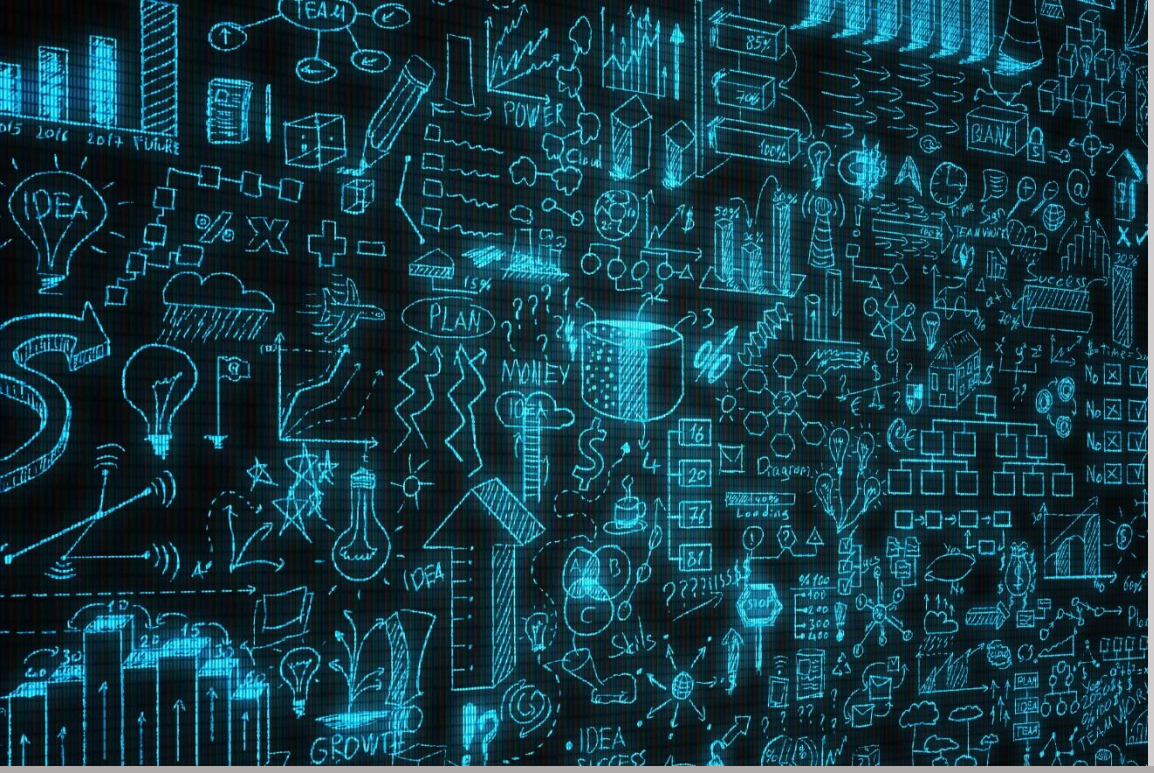


REGULATORY FOCUS

Regulatory Intelligence Communication for Business Impact

By Kirsten Messmer, PhD, RAC and Charity-Anne M. Schuller, PharmD, MS, RAC

This article focuses on maximizing Regulatory Intelligence (RI) in response to specific stakeholder requests and offers best practices recommendations for RI communication. The authors provide an overview of information delivery methods and their applicability and present general considerations for communicating RI information by spreadsheets, text documents, slide presentations, strategy reports and competitive intelligence reports. They also highlight the use of due diligence and carrying out gap analyses. The article concludes by noting future trends in RI.

Introduction

RI professionals support the drug development process with strategic information, serve as liaisons with regulatory agencies and channel RI to the appropriate stakeholders. Typically, an RI professional is asked for an outline of the regulatory requirements and asked to identify existing precedent for regulatory actions and landscape opportunities for a certain product in a specific country, region or globally. Project-specific assimilation and analysis of the relevant information available through public sources, internal experience and/or subscription services to avoid regulatory pitfalls, requires the necessary skills for seeing “the big picture,” evaluating the details involved and developing

a specific and creative regulatory strategy to support a time- and cost-efficient product development program. However, strategy needs to be reviewed throughout the drug development process to update the strategy with regard to any changes in the development plan and/or regulatory requirements. This article concentrates on information provision approaches to maximize the use of RI in response to a specific stakeholder request (for proactive RI communication see Huddle and Messmer.[1])

RI Requests

Requests (both a*d hoc* and project-specific) for RI can vary widely in content and purpose. The purpose, requested content and teams involved determine, in part, the presentation method and level of detail provided. However, the RI professional also needs to include her/his own judgement on what level of content and information delivery method provides the best strategic support to the requestor. Knowing the information needs and presentation preferences of the customer is paramount, as noted in the previous article on proactive RI communication by Huddle and Messmer.[2] In *ad hoc* requests, the primary customer is the person requesting the information. However, the RI ultimately might be presented to a secondary customer, as would be the case if the internal business development (sales) department requests RI to support a proposal to a specific customer. In this case, the RI professional needs to cater to both the internal and external customer based on the request specifications and any prior experience with similar requests.

RI Communication: General Considerations

The RI provided should always be concise, complete, current and accurate. Independent of the presentation vehicle, the writing always should be of the highest quality and free of spelling and grammatical errors. The material should be presented in an easy-to-understand manner, yet without being overly simplified to suit the requestor's background understanding of the subject matter, perhaps for someone who is likely not as intimately familiar with the material as is the RI professional.

The most powerful reports combine text, tables and graphics to communicate the RI. Overly lengthy and text-dense reports are generally not helpful due to the significant time pressures of drug development. RI is an exciting, fast-moving field with a potentially high business impact. It is important to translate that 'buzz' into the key outputs needed by the customer.

Original sources need to be cited whenever possible as this will help avoid any potential issues regarding copyright infringement. Although one might consider the risk to be limited, it is always advisable to err on the side of caution and, when in doubt, seek input from the legal department. Second, and perhaps more importantly, citing original sources allows for easier updates and vetting of the information. While this practice might be less necessary for responses to specific questions and time-limited use information, such as the assessment of a clinical trial feasibility, citing original sources will become more important for regulatory strategy reports, competitive intelligence and due diligence. These

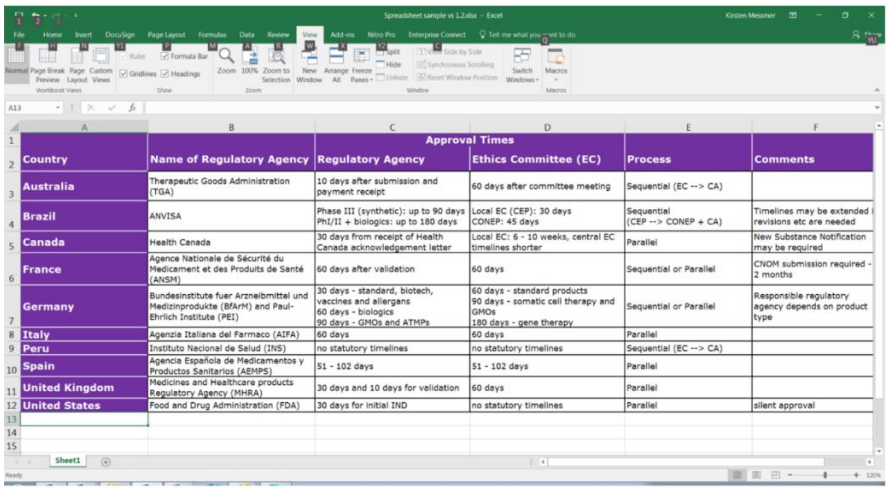
latter works will likely be used as “roadmaps” for extended periods of time. In an ever-changing regulatory environment, it is important to revisit the information provided in regular intervals or even more frequently because guidances can change swiftly. It is paramount for any updated assessments to have access to the original information sources to be able to accurately compare the new information to that provided in the initial report. The ability to time-efficiently update RI will add value for the customer. “Re-inventing the wheel” for every update of RI reports adds unnecessary cost.

Spreadsheets and Text Documents

With a specific customer request or notification, probably the simplest presentation of large amounts of information is represented as a spreadsheet, or a briefing document, focused on key elements relevant to the request. Information topics, such as a set of specific regulatory questions, can be represented against target countries in tables. For spreadsheets, the topic covered in each column or line needs to be focused and precise. The breadth and depth of the information should be comparable for each data point for a given topic (e.g., country when assessing regulatory questions for various countries) while succinctly providing key information.

While a “yes” or a “no” answer might be preferable, in regulatory affairs such simple answers are not possible. Thus, it becomes paramount to fully understand the question in relation to the general context and to subsequently formulate the response as precisely, and as to the point, as possible. The shorter the presented information can be for each country (and overall) the better; additional information always can be provided in further commentary.
The main advantage of spreadsheets is that they can present large amounts of information in a concise and consistent format (**Figure 1**). However, this type of presentation requires further data analysis to draw the pertinent conclusion. The RI professional should analyze the collected data and provide the main findings, including conclusions drawn based on that information, as well as the RI professional’s experience to the ‘customer’ as an analytical overview.

Figure 1. A spreadsheet can provide a lot of information, but often requires further data analysis to draw the pertinent conclusion.



	Approval Times				
Country	Name of Regulatory Agency	Regulatory Agency	Ethics Committee (EC)	Process	Comments
Australia	Therapeutic Goods Administration (TGA)	10 days after submission and payment receipt	60 days after committee meeting	Sequential (EC --> CA)	
Brazil	ANVISA	Phase III (synthetic): up to 90 days PhI/II + biologics: up to 180 days	Local EC (CEP): 30 days CONEP: 45 days	Sequential (CEP --> CONEP + CA)	Timelines may be extended i revisions etc are needed
Canada	Health Canada	30 days from receipt of Health Canada acknowledgement letter	Local EC: 6 - 10 weeks, central EC timelines shorter	Parallel	New Substance Notification may be required
France	Agence Nationale de Sécurité du Medicament et des Produits de Santé (ANSM)	60 days after validation	60 days	Sequential or Parallel	CNOM submission required - 2 months
Germany	Bundesinstitute fuer Arzneibmittel und Medizinprodukte (BfArM) and Paul-Ehrlich Institute (PEI)	30 days - standard, biotech, vaccines and allergans 60 days - biologics 90 days - GMOs and ATMPs	60 days - standard products 90 days - somatic cell therapy and GMOs 180 days - gene therapy	Sequential or Parallel	Responsible regulatory agency depends on product type
Italy	Agenzia Italiana del Farmaco (AIFA)	60 days	60 days	Parallel	
Peru	Instituto Nacional de Salud (INS)	no statutory timelines	no statutory timelines	Sequential (EC --> CA)	
Spain	Agencia Española de Medicamentos y Productos Sanitarios (AEMPS)	51 - 102 days	51 - 102 days	Parallel	
United Kingdom	Medicines and Healthcare products Regulatory Agency (MHRA)	30 days and 10 days for validation	60 days	Parallel	
United States	Food and Drug Administration (FDA)	30 days for initial IND	no statutory timelines	Parallel	silent approval

Slide Presentations

Generally, most of us can take in and understand large amounts of information much faster if conveyed in a visual medium, such as a slide presentation. However, there are typically two manners in which slide presentations are provided - summaries of information without commentary for each single slide sent to the customer, and slides presented to the customer in a meeting. Slides presented during a customer-facing meeting should contain enough text to summarize main messages. It is the speaker's responsibility to provide the context and crux of the slide's message by verbally capturing the attention of the audience. It is equally important to create the slides so they tell 'the story' by guiding the listener and, at the same time, conveying critical information. Wherever possible, pictures and graphics should replace text to convey complex concepts.

While an Internet search for "slide presentation rules" generates an abundance of articles, all results provide suggestions that lead to the same general principles - slides presented verbally should not contain full sentences unless they are direct quotes. Large amounts of text on slides – particularly in complete sentences – entices the audience to read the slides rather than listen to the information provided by the speaker. **Figure 2** and **Figure 3** show two presentations of the same information. While **Figure 2** is crowded with text, **Figure 3** represents the same information graphically.

Figure 2. Sample Text-Rich Slide That Appears Crowded

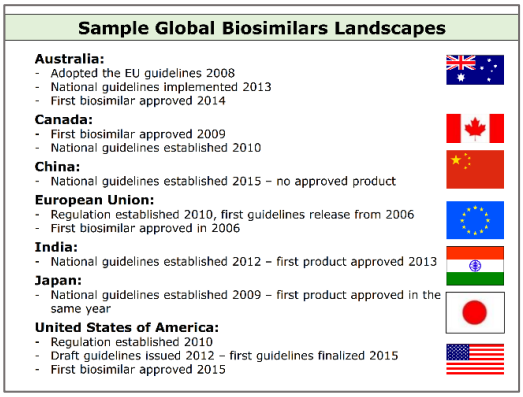
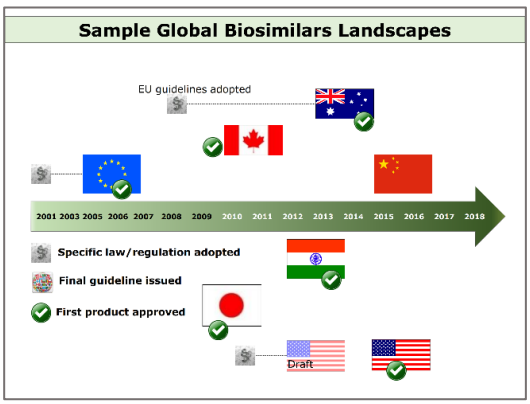


Figure 3. Sample Slide Representing the Same Information as in Figure 2 Graphically.



Other things to consider when designing the slides include font size, font color, and background color. Although presentation of RI to a specific requestor is likely to be conducted in a smaller room, there might be an opportunity for follow-up with a larger audience. Choosing the largest font size possible for the text will ensure readability from the back rows in large conference rooms. When choosing colors, it is important to use high-contrast differences and test the chosen colors for any colorblindness impediments. Although slide deck presentations provide the opportunity for visualizing complex information, any images, graphics, and infographics used should all support key points, not detract from them.

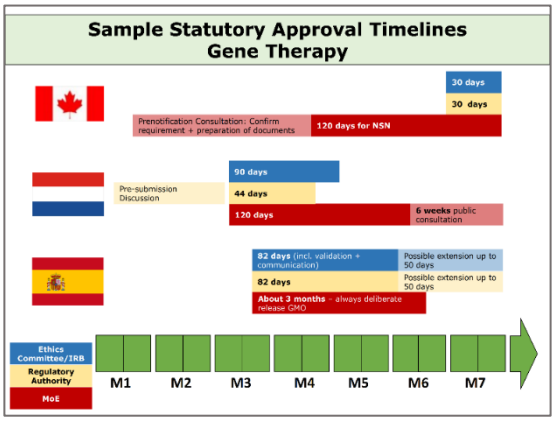
Strategy Reports

Strategy reports are probably one of the most valuable presentations of RI because they often combine the information, knowledge and experience of various experts. A good strategy report begins with an executive summary outlining a "roadmap" for tackling the project at-hand. The summary frames the discussion for the audience and, if possible, includes a high level SWOT analysis (Strengths, Weaknesses, Opportunities and Threats) outlining strategies for taking advantage of opportunities and to address the threats. The summary will conclude with a succinct outline of the strategy and suggested actions.

The main text of the strategy report depends on the question(s) asked, so it is important to ensure a complete understanding of the question(s) and the purpose of the report. For example, if the aim of the report is to propose a strategy for developing a medicinal product in a select group of countries, the presentation of information will differ from a strategy report aimed at filling in gaps for a specific product identified during due diligence. Considering the first issue for developing a gene therapy and gaining approval for the first clinical trial (**Figure 4**) could suggest the submission sequence needed to obtain clinical trial approvals at approximately the same time.

In the select country example, the executive summary likely will be followed by a side-by-side overview of information for all countries considered, before addressing each country in more detail. The concluding section will then provide the proposed strategy to ensure smooth execution of the development program in as many suggested countries as possible, or for a core group of priority countries.

Figure 4. Sample Regulatory Strategy to Accompany a Strategy Report for Obtaining Gene Therapy Approval in Several Jurisdictions at the



Same Time

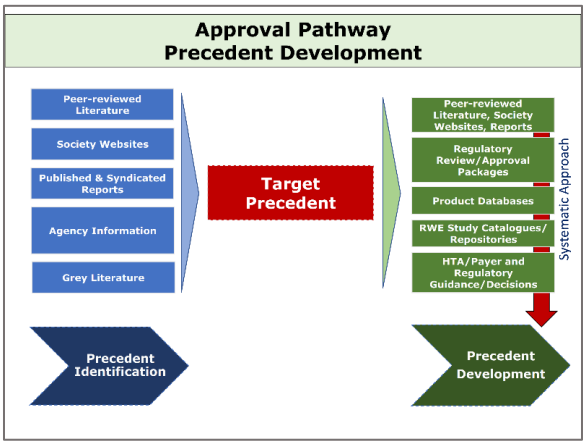
In the specific product example, due diligence may have identified gaps in a submission package that need to be addressed before the submission can proceed. The executive summary should include a brief overview of the product, the product's development status, and a listing of the issues identified. The report should then address each issue in detail and provide steps to achieve resolution. The summary will outline steps to be taken in order of priority.

Competitive Intelligence

The RI professional as a strategist provides internal and external customers with competitive intelligence to guide successful product development and commercialization. Competitive intelligence may include information on:

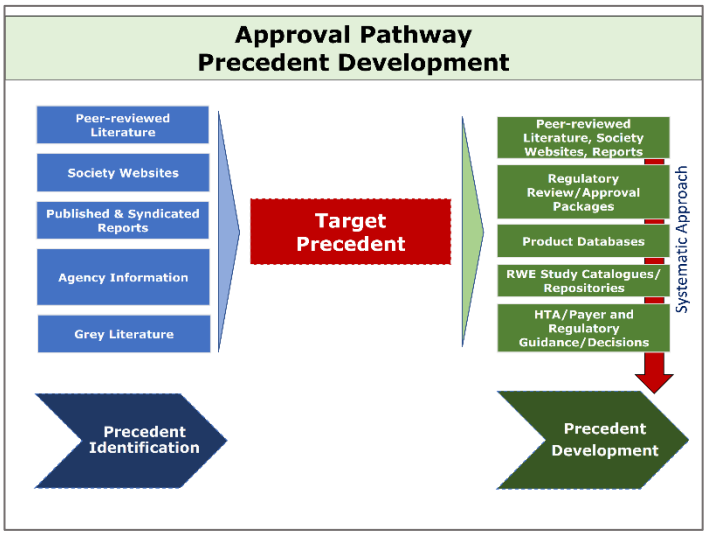
- Commercialized products for the same indication and/or mechanism of action,
- Revenues for these products,
- Products under development for a specific indication including the development stage,
- Product availability in various markets, indication prevalence and
- Clinical trial information and precedents (case studies).
- The type of information obtained during intelligence gathering depends on the questions asked. Common questions include, but are not limited to:
- How many other products are at the same development stage and how do they compare? (e.g., mechanism of action, expedited program designation)
- How many clinical trials are conducted in countries A, B, C, etc., that would directly compete with a trial the requestor may be considering (e.g., prevalence of indication, number of trials and patient enrollment target number, available marketed treatments)?
- Requestor wants to use a specific approval pathway – Has this been done before; if so, how was it done and was it successful? (e.g., precedent, publicly available agency interactions for similar product/pathway; **Figure 5** would support the report by illustrating the search strategy employed to develop the precedent)?

Figure 5. Sample Search Strategy For Development of a Regulatory Precedent



Spreadsheets and slide deck presentations may be suitable for some of the smaller requests, such as showing products under development against development phase. **Figure 6** provides a mock-up of a development landscape. However, most competitive intelligence-informing product development questions will require a formal report, one illustrated by graphics summarizing the information obtained from all available information sources, and provides a clear analysis and shows the conclusions drawn in respect to the specific questions asked. Key information, processes, and data should be highlighted by appropriate illustrations throughout the report.

Figure 6. Sample Product Development Landscape Showing Development Stage for Various Products



Like the strategy reports, competitive intelligence reports will provide a regulatory strategy of product development based on RI analysis but also will add an operational and/or commercial strategy for product development and positioning.

Due Diligence and Gap Analysis

Although due diligence and gap analysis have slightly different meanings, they require similar thought processes to generate a high-quality RI output, one providing actionable recommendations.

Due diligence is defined as "action that is considered reasonable for people to be expected to take in order to keep themselves or others and their property safe."[3] This term might be best known from the business and real estate world where due diligence is performed to ensure that a purchase (acquisition, merger) provides the desired return on investment with no potential loss. In RI or regulatory affairs, due diligence may be called upon to lead or contribute to product and/or entity. In the case of a medicinal product, this entails ensuring that the product development pathway is adequate, including assuring that regulatory requirements have been met and all necessary documentation is available.

Gap analysis is defined as "a system that compares how a company works now with how it would like to work, and then calculates how the company can use time, money, etc. to achieve the success it would like."[4] Paraphrased: how does it look now and what does it need to look like to be successful? In the regulatory world, a gap analysis is generally performed on an individual product to determine whether all regulatory requirements have been met and to identify any 'gaps' needing to be addressed before the product can be successfully developed, approved and commercialized.

Gap analysis likely will form a vital part of the overall due diligence process. For due diligence/gap analysis during product development, it is paramount to understand the product itself to be able to accurately assess the current product status and any actions (and potential costs) needed to move the product through development to approval and commercialization.

The pharmaceutical market necessitates accurate and precise product assessment and regulatory outcome predictions to support corporate goals. The RI professional must ensure regulatory precedents have been correctly interpreted and applied, that all regulatory requirements are noted, and any opportunities to use expedited pathways are highlighted to maximize benefits for the requestor. The most appropriate format is a detailed and concise report supplemented by well-designed graphics and summary tables with pertinent information.

What does the future hold?

The ever-increasing pace of pharmaceutical product development and subsequent regulatory updates necessitates engaging new tools to support effectiveness and efficiency in the delivery to clients. Also, quick access to key points supports faster decision-making and process adjustments.

The use of Artificial Intelligence (AI) has dramatically increased over the recent years. AI applications in RI include "trend spotting" and identification of differentiators for a customer's product against competitors. AI can support many process of gathering, assimilating and reporting of information. This activity includes looking for gaps, identifying trends and testing new ideas. However, responsibility for the interpretation will still fall to the RI professional. Because innovation is guided by novelty and not existing regulations and laws, RI delivered to the customer needs to go beyond the regulations, pathways and guidelines, many of which are set retrospectively. For example, as a result of a novel efficacy endpoint created during the development of a gene therapy product for the treatment of a hereditary retinal disorder, FDA specifically began encouraging sponsors to develop and propose novel endpoints in the guidance addressing gene therapies for retinal disorders.[5] Regulators are generally open for early discussions of innovative products and product development processes in order to understand the drug developers' rational since there is no comparable benchmark. It becomes the RI professional's responsibility to 'read between the lines,' link trends across multiple disciplines, and assimilate the information available for fast and accurate communication. The RI professional must also possess the skill to separate fact from fiction and

the practical from publicity headlines to be able to create RI communications beneficial for clients, regulators and colleagues.

Conclusion

RI is an important, ever-evolving, always changing science. The pace of information release by regulatory agencies and other stakeholders continues to accelerate, reflecting the increase in experience with medicinal product development and approval. Additionally, the complexity of products has been increasing significantly in recent years (e.g., advanced therapy approvals). Information acceleration and complexity necessitates gaining an intimate understanding of the product at-issue and the regulatory requirements to guide product development and approval at every step. Also, taking advantage of innovative pathways regulatory agencies are implementing to support faster product approval is important. While RI delivery can take on many formats, support multiple objectives, and be developed using a variety of tools, the skillsets and methods for obtaining, providing and maintaining information remain the same. It will always be important to know the intended customers, utilize the most appropriate resources, carrying out thorough searches, and obtain an attentive secondary review. All of these processes go into ensuring successful RI provision and strategic support for drug development.

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