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Regulatory

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Developing a Regulatory Strategy

By defining hurdles to registration, emerging companies benefit from early regulatory guidance.

Given their focus on discovering and rapidly building scientific evidence to support the safety and efficacy of their compounds, emerging pharma companies often direct their limited resources to near-term activities. In doing so, they are often unaware of or undervalue the importance of getting early regulatory guidance on long-range development strategies.

In early development, emerging companies often view regulatory affairs as a function that is primarily necessary to ensure compliance. They recognize the need to manage operational activities such as preparing, submitting, and maintaining an IND (Investigational New Drug Application), submitting adverse event reports, and coordinating other routine communications with the FDA. However, this approach potentially neglects a greater value-added contribution that these experts can provide: regulatory strategy.



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Benefits to realize

Starting well before clinical trials are initiated, companies need to understand both the regulatory landscape (i.e., guidelines, important stakeholders, emerging policies) and relevant precedents. Regulatory guidance in these areas can help build a crucial framework for the overall development plan and aid in determining the fastest and/or greatest value path to market for their product. Furthermore, it can facilitate assembly of a total picture of the scope of nonclinical, technical, and clinical testing that will be required for registration.

With a comprehensive regulatory strategy in hand, sponsors can fully understand the expectations, carefully evaluate potential hurdles, and create a plan to proactively address them early in development. Additionally, this plan can inform the entire development program. For example, elements from the regulatory strategic

documents drive the clinical plan, identifying issues that affect clinical trial design requirements and the associated budget.

Some emerging companies may believe that it is not important for them to prepare a thorough regulatory strategy since they intend only to develop their compound independently until proof-of-concept, and then they plan either to out-license the product or find a (typically larger) partner for codevelopment. While it is true that a partner or licensee is likely to develop their own regulatory strategy after joining the development program, it would be a lost opportunity to wait until this point to develop the first iteration.

Having a good understanding of the clinical, preclinical, and technical development requirements—as well as timelines, achievable commercial claims, risks, and regulatory mechanisms to enhance product value like exclusivity and accelerated approval pathways—can be extremely helpful in designing an efficient early development pathway, assessing the value of the product and knowing how far a company can proceed before needing additional financing or a partner.

Importance for novel approaches

Many emerging companies develop agents for niche markets where there remains a significant unmet medical need (i.e., orphan or other small indications that may not be commercially attractive to large pharmaceutical companies). Other emerging companies focus on novel indications or seek unprecedented labeling claims to differentiate their product from competitors.

While each of these circumstances presents a unique set of regulatory challenges and opportunities, companies pursuing these novel approaches have at least one thing in common: They are all venturing into uncharted regulatory territory. Indications that are less commonly pursued are unlikely to have development guidelines with fewer, if any, precedents. As such, these situations dictate that sponsors develop a thorough regulatory strategy early. This is based on several realities:

- Novel approaches often require development and validation of new endpoints.
- Registration programs are increasingly becoming reliant on physician- and patient-reported outcomes to measure clinical meaningfulness.
- It is not uncommon for health authorities to require utilization of multiple coprimary endpoints for registration studies when presented with a new endpoint.

These unique requirements can have a substantial impact on the size of the clinical development program as well as on the risk. As a specific example, coprimary endpoints will decrease the probability of success in comparison to the typical requirement for a single efficacy endpoint. An

early understanding of the registration requirements offers efficiencies that are realized throughout the development of a novel product. Emerging companies, focusing primarily on the next stage gate, may not realize these efficiencies without an early regulatory strategic plan.

Well-established approaches

Even companies developing products for established indications with well-understood chemical classes should take the time to understand the current regulatory environment. For many indications there are either no development guidelines available from health authorities or the directives are obsolete. In the absence of current official guidelines, information from the development program for precedents can provide extremely important direction. Even so although this information is very valuable, sponsors cannot blindly follow precedents. Health authority requirements continuously evolve as the scientific field advances. As such, even areas with multiple, consistent precedents may not represent the current requirements.

In fact, it is worth noting that the value of precedents generally declines over time as the scientific and political environment shifts. In circumstances where it is believed that policies and requirements may be “evolving,” it is important to monitor public presentations made by FDA representatives. Information communicated this way often precedes the formal distribution via a new regulation or guidance. While large companies often have regulatory resources dedicated to monitoring the external environment, emerging companies generally need external regulatory support for such information.

Role of the strategist

Increasingly complex registration requirements mandate a more sophisticated regulatory staff. As a result, today’s regulatory affairs professionals typically hold advanced science degrees and have extensive experience in one or more of the drug development disciplines. Armed with these credentials, they have the required depth to provide scientific and strategic guidance to development teams.

So, what roles are regulatory strategists expected to play? First, they evaluate development options, issues, and challenges based upon the needs of a key external customer: the health authorities (i.e., FDA and EMEA). In addition, they are now expected to monitor and understand all details of the regulatory “environment,” including guidelines, precedents, influence of politics, government resource challenges, priorities, and emerging policy issues.

These strategists must then communicate this information to the various disciplines within development teams and translate it to the programs under their direction. Ideally, beyond sharing their findings, they become integral members of these development teams so that as issues

arise, they are identified early and assessed regarding how best to address them with health authorities.

Beyond information sharing and problem-solving ability, regulatory strategists need effective presentation and negotiation skills because interpreting medical data is subjective. Moreover, they can help sponsors understand the needs of their FDA “customer,” as well as the political and resource-constrained environment in which the health authorities work. Because they understand the nuances of this complex relationship, highly experienced regulatory professionals can lead FDA interactions, successfully delivering the key messages. This is particularly important for emerging companies, since early identification and appropriate resolution of issues impact not only the speed and efficiency of the project but often the financial viability of the company.

Purpose and scope

A regulatory strategy should aggregate critical regulatory information and strategic plans in a single document. It should serve three primary functions:

- As a tracking tool that summarizes key agreements reached with health authorities
- As a planning tool that documents timelines and lists topics to address in future meetings with health authorities
- As a risk register to record key open issues that could impact timelines, cost, or commercial value for the project.

Specifically, the document should provide information on current project status, target timelines, target product labeling, key risks, and open issues relevant to the specific scientific discipline (e.g., safety, efficacy, quality, and commercial). Policy advancement should also be tracked by listing such events as upcoming health authority

Components of a Regulatory Strategy

COMPONENT	DESCRIPTION OF CONTENT
Summary of Guidelines and Precedents	Provides an overview of public domain information that is available through such sources as the Freedom of Information Office at FDA (FOI) and the European Medicines Evaluation Agency (EMA) Web site. [These sources provide access to development guidelines and summaries prepared by health authorities to document the basis for approval of precedents.] Also captures key aspects from these documents, such as pivotal efficacy and safety study designs (e.g., patient population, number enrolled, key endpoints); total number of patients to assess safety; and any concerns raised by health authorities during review.
Strategy to Optimize Product Label Claims	Describes the plan for substantiating key label claims and differentiating the product from competitors.
Lifecycle Management	Outlines the strategy for initial product launch (i.e., narrow versus broad initial indication), as well as how supplemental indications, claims, and formulations (if applicable) will be staged for the product.
Global Submission Strategy	Addresses relative commercial and strategic importance of key markets. Identifies timing of marketing applications around the world, inter-dependencies, and risk management.
Target Submission and Approval Dates	Documents the planned schedule of submissions and approvals across the major regions.
Special Populations and Special Safety Evaluations	Addresses how special populations (i.e., pediatrics, elderly, poor metabolizers, renal and hepatic impairment) and special safety evaluations (i.e., QT/QTc, abuse liability, suicidality) will be assessed in the development program. Explains whether studies to assess these populations and safety issues were required for precedents, and when they need to be conducted in the development program.
Implications of Licensing Agreements	Documents how product development is affected by licensing agreements (i.e., co-development, milestones for transfer of responsibilities, split of roles/responsibilities).
Regulatory Risks	Identifies known or theoretical risks associated with the development project, categorizing each risk by discipline (toxicology, PK, clinical, manufacturing, regulatory, etc.). For each risk, identifies the probability of the risk occurring, the impact to the program should it occur (cost, resources, timelines, product value), and the prospective mitigation plan.
Exclusivity	Lists the patent(s) that cover the product and their expiration date(s). Comments on the duration of “effective” patent protection relative to the anticipated approval date. Explains whether regulatory forms of exclusivity (Waxman-Hatch, pediatric exclusivity, orphan designation, etc.) are important to the commercial success of the product.
Accelerated Development and Approval Options	Describes whether accelerated development and approval options (i.e., “Subpart H,” “Fast Track,” priority review) may be relevant to the product, as well as implications on cost and timelines.

meetings, including public Advisory Committees and presentations by FDA at scientific congresses. In addition, the document should essentially outline the development pathway to market approval, relative to regulatory requirements. Generally, this is coupled with the clinical development plan, which provides details of the clinical trials program needed for the marketing application.

Since data from all scientific disciplines will ultimately be submitted as part of a marketing application, and the consequent labeling (i.e., package insert or summary of product characteristics) will dictate how the product is marketed, a regulatory strategy document must be comprehensive. It must address preclinical, clinical, chemistry/manufacturing, and commercial issues.

The first version of a regulatory strategy document should be created early, before clinical testing has begun.

This will allow data gathered from guidelines, precedents, and desired labeling to drive the development program and serve as the basis for early interactions with health authorities.

The regulatory strategy should also be seen as a “living document” that is regularly revised based on scientific results, as well as on changes in the regulatory environment. Given that many compounds do not survive early development, it may be prudent to “stage” preparation of regulatory strategy components. For example, it may not be worthwhile to prepare a comprehensive Target Product Label or to evaluate the merits of the centralized procedure for European registration early in development. Instead, the focus in early development should be on providing guidance that is critical for early stage decision making.

COMPONENT	DESCRIPTION OF CONTENT
Trademark	Documents the timeline and strategy for trademark review by health authorities to minimize chances of rejection late during review of the marketing application. Addresses whether the sponsor intends to conduct research to substantiate that the trademark is not confused with existing products to ensure safe prescribing; also evaluates the probability that FDA will believe the trademark inappropriately promotes the product by overstating efficacy or downplaying the risks.
Plan for Future Interactions with Regulatory Authorities	Outlines the plan for engaging regulatory authorities during development, describing timing and issues to be addressed at standard interactions, such as pre-IND, End-of-Phase II and pre-NDA meetings, as well as other anticipated important submissions and meetings. Identifies, for example, whether European advice will be sought centrally via EMEA or from individual EU health authorities. If individual countries will be involved, which ones will be selected?
Key Product Label Attributes	Documents key elements of the labeling (e.g., US package insert and EU summary of product characteristics), through a collaboration of regulatory professionals, scientific disciplines, and the sponsor’s commercial representatives. In early development, when not much data exist, the target labeling will largely be a “wish list.” Over time, proposed statements should be substantiated by data from the development program or revised. Early development versions can address only core elements of the labeling. Once the product nears completion of Phase II, this document should be converted into a verbatim draft package insert. It is usually valuable to submit such a document to FDA in the briefing book for the End-of-Phase II meeting. This allows FDA to review the Phase III program in the context of the labeling you ultimately want to support.
External Influencing	Describes the actions that will be taken to influence key opinion leaders, regulatory agencies, guidelines, etc. to support registration and maximize the commercial value of the product. This is especially important for novel products and/or novel indications where consensus on study design and the magnitude of changes in endpoints that would be clinically meaningful are not established, or in areas where there are significant changes in scientific knowledge.
Table of Advice from Regulatory Authorities and Outstanding Commitments	Summarizes key input received from health authorities either specific to the compound or general to the class, while denoting any outstanding requests that need to be fulfilled by the sponsor.

Source: Mark Ammann 2008

Table 1. This table shows the key components to be addressed when establishing a regulatory strategy.

Pivotal questions

When it comes to a regulatory strategy, a number of questions need to be addressed, including:

- What are the key differentiating characteristics of this product vs. competitor products in terms of target labeling?
- Is there a precedent for the indication and for the key claims being sought? If not, what incremental activities (i.e., unique studies, endpoint validation, opinion leader consensus) are needed to substantiate this new approach?
- Which currently available guidelines might impact the development program?
- When should meetings with health authorities occur and which key issues should be addressed at each meeting?
- What is the range of options available for registration (e.g., fast-to-market with small initial indication followed by supplemental applications vs. broad claim up front)?
- Are any accelerated development or approval pathways applicable, such as Subpart H approval, Fast Track designation, or priority review?
- Are there opportunities for expanded market exclusivity via such regulatory mechanisms as pediatric exclusivity, orphan drug protection, and/or Waxman-Hatch exclusivity?
- Is there a need to influence health authorities and/or key opinion leaders to accept proposed study designs, endpoints, key claims, etc.? If so, what is the plan (who, when, how, desired outcome)?
- What are the known regulatory risks in the program?
- What is the plan for global registration, if applicable? Simultaneous EU and U.S. submission? Or key market first? For a listing and description of the elements of a

comprehensive regulatory strategy, see Table 1 (also available online at www.appliedclinicaltrialsonline.com).

Conclusion

While creation of a solid regulatory strategy is a critical enabling factor in the efficient development of a product for both emerging and established companies, there is particular importance for emerging companies, since they typically have fewer available resources than larger companies. For smaller organizations, an external regulatory strategist can serve as a bridge between scientific and commercial disciplines, integrating their respective needs, forming a cohesive internal strategy, and developing an external communication approach for the health authorities.

In this way, the strategist can provide efficiencies to development teams, informing the sponsor of requirements and options while outlining a pathway and defining the hurdles to registration.

As pointed out, the key to gaining the greatest efficiencies, however, is to launch development of the regulatory strategy early in development, ideally before starting clinical trials. In that way, the regulatory expert is an integral part of the team for all the subsequent critical steps, including implementation and negotiation with health authorities.

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