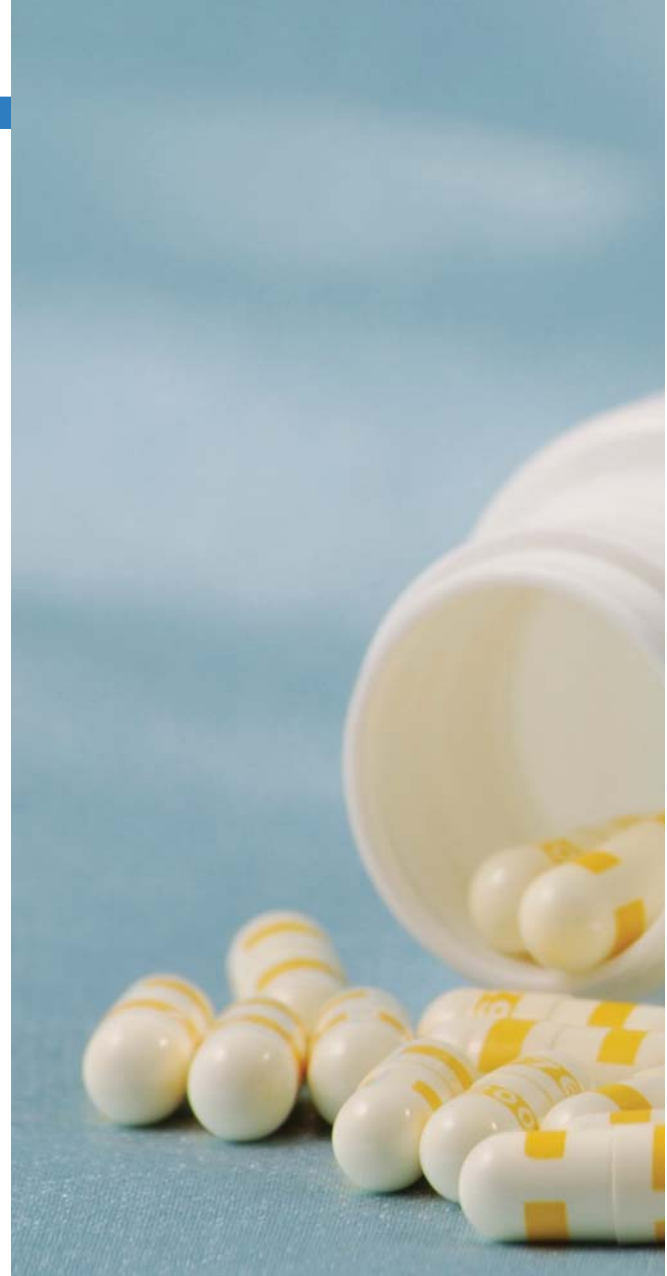




Designing a Global Product Development Strategy

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Pharmaceutical products are truly global in nature—not only in terms of usage but also in terms of the strategic location of different development activities. Clinical trials have been conducted at various locations around the world for years to meet recruitment goals and obtain approvals in multiple countries. However, with increasing worldwide harmonization of regulatory processes and intellectual property laws, and the highly interconnected global economic infrastructure, it makes good business sense to distribute the other steps in product development, such as discovery, early development and preclinical testing, as well. Almost every country accepts the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines for clinical and nonclinical pathways for biomedical product

development. This acceptance makes it easier not only to conduct multinational clinical trials but also to spread the front-end development steps, such as research and development and preclinical testing, around the globe. Companies use outsourcing and offshoring models to exploit the various regulatory and business incentives available in different countries. Overall, there is an increasing tendency for regulatory strategists and business leaders within a company to work together to create a product development strategy. Regulatory strategy identifies not only appropriate development pathways but also locations conducive to successful execution of the strategy. Company leadership identifies the feasibility of implementing these pathways. Together, these two approaches form what could be called a regulatory business strategy (RBS), where regulatory pathways are evaluated in the



context of overall business strategy. This article describes the various components of a product development strategy that utilizes multinational sites with a global market point of view.

Including Regulatory Strategy in Corporate Planning

Development of biomedical products—drugs, biologics, devices or any combination thereof—requires extensive planning, both short- and long-term. Biomedical product development starts with crafting a strategy. This strategy needs to address specific regulatory requirements for product approval as well as the company's financial goals and corporate mission. A new technology may have several potential applications. A targeted product type is defined based upon the most feasible use and the projected market size.

Market size estimates are no longer based solely upon one or a few countries, but rather on global projections and market access. A well-devised RBS could help define the product development steps in the context of investment and timelines for key milestones.

Several internal and external drivers influence the selection of a given product's development pathway. Internal factors including financial strength, management regulatory and scientific capabilities, intellectual property status, and regional versus international ambitions are important in a biomedical product developer's selection of a pathway for a particular product. External drivers, such as investor expectations, the political and economic environment in the area where key development steps will be conducted and business alliances required for corporate sustenance could also help determine a

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product's selected pathway. For example, political concerns make it difficult to conduct most types of stem cell research in the US, and regulations do not permit most phase 0/1 or first-in-man studies in India.¹ Regulatory intelligence, i.e., knowledge of regulatory processes in various parts of the world, and due diligence via partner/contractor capability assessment are critical for developing an optimal regulatory strategy.

It is important to recognize that the strategy may have to be revised based upon the results of various steps in development or changes in the regulatory processes that affect the product in question. As harmonization of regulatory processes increases, economic factors and recruitment issues seem to be major factors in strategy revision. In addition, special circumstances such as business mergers and acquisitions or changes in partnerships obviously affect the overall strategy due to changing business priorities.

Creating a Global Regulatory Strategy Document (GRSD)

A GRSD translates business objectives and regulatory strategy into a written plan. It is a combination of the business and project plans for the product's development. Based upon the factors described previously, a GRSD addresses the product's complete lifecycle, from the start of the project to potential marketing and postmarketing issues. A GRSD can be created for a family of similar products; however, best practice is to create a unique plan for each product.

The GRSD starts with defining key product development milestones (**Table 1**). The next step is to identify the tools and standards to be used. These include Standard Operating Procedures (SOPs), project management tools (e.g., Clinical Trial Management System), communication tools, risk assessment tools (safety reporting methods, etc.), applicable regulatory guidance documents (e.g., ICH guidance documents), and regulatory intelligence methods (e.g., monitoring FDA Advisory Committee meetings and conference presentations). For multinational projects, communication plans and tools are perhaps the most important determinants of the project's success or failure. Communications plans are discussed in the next section.

Personnel at all locations need to deal with not only different time zones and harmonizing training requirements but also cultural and business sensitivities. Hence, personnel recruited to the project need to be experienced in multinational projects.

Once all product development plan processes are identified, the next step is to determine what needs to be outsourced and what technologies/licenses should be acquired or insourced. Over the last decade, the contract research industry has grown exponentially and this trend is projected to continue in the near future. The main reasons are reduced risks due to contract research organization (CRO) experience, and reduced overall cost compared to establishing infrastructure and hiring experienced personnel, particularly for multinational projects. Further, with regulatory practices, considerable harmonization has occurred in business practices, making it easier to work in multinational environments. Practically all product development steps can be outsourced by hiring local and multinational CROs. CRO selection could be the most critical step in product development. Criteria for selecting a CROs need to be addressed in the GRSD. In addition, a GRSD should include plans for crisis management and trouble shooting.

Executing the Global Regulatory Strategy

Execution of the global regulatory strategy and its project plan has two main components: operations and personnel.

Operations

The operational component includes all of the physical aspects of application assembly: timeline management, assembly procedures and quality control procedures. Depending upon the extent of the effort, operational aspects might also include, extended work hours and the impact of that on company resources (e.g., air-conditioning/heat off-set times, janitorial services, security and safety, office supplies, and even restocking vending machines). The ex-US regulatory strategy may also include countries that still only accept paper (be sure to check on the paper size as most countries will only accept A4 size), which will influence the decision regarding the location of your assembly and copy production activities. The authors usually favor keeping these activities in the US (or wherever the regulatory department is located) so that consistency, quality and adequate physical space can be ensured.

Another decision that will impact operational activities is the type of European submission (Centralised Procedure or Decentralised Procedure). The Centralised

Table 1. Key Pharmaceutical Product Development Milestones

Process	Description
Selection of the indication and need for special status	The most suitable indication is selected based upon corporate mission and status of development; available incentives identified, e.g., orphan or pediatric indication, tropical disease treatment, etc.
Preclinical design	Description of required in vitro and animal studies.
CMC design and manufacturing plans	Manufacturing process and analytical testing needed per Good Manufacturing Practices.
Clinical plan	Description of clinical studies required per current regulations for the indication selected.
Identifying the key regulatory agency	Even if planning to file approval applications concurrently in multiple countries, it is best to start with one regulatory agency, e.g., US FDA, where approval will be sought first to establish a regulatory history for the product to be used in subsequent filings in other countries.
Marketing plan	It is best to consider product marketing issues as early in the lifecycle as possible for periodic product viability assessment.
Postmarketing plan	Understanding postmarketing issues for similar approved products is critical to strategic planning.
Tactical regulatory submissions	For multinational studies, regulatory submissions should be filed in a manner that places them in the most favorable condition, for example, filing an IND with US FDA first helps get expedited approval of the same IND in India. ¹

Procedure generally reduces the number of specific submissions, but the Decentralised Procedure is more flexible, allowing the sponsor to choose the submission countries. For example, in 1996, Atorvastatin was submitted via the Decentralised Procedure to about 16 countries. Each country had specific copy requirements and one even required that the application be glue-bound. It is, therefore, essential that the submissions manager obtain and understand specific country requirements.

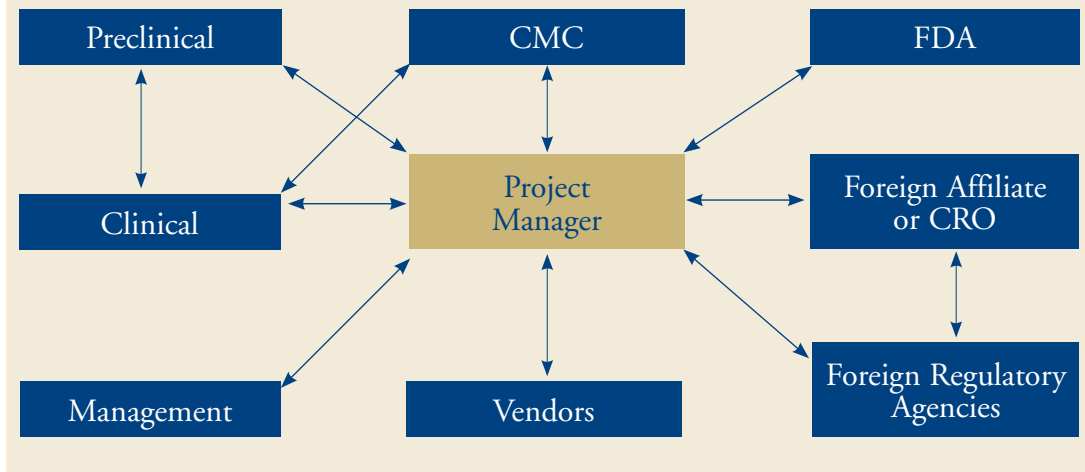
The final operational aspect can be summed up as good project management practices comprising the following five key components: budgeting and advanced planning; specific project planning; developing a communications plan; risk identification and mitigation; and proper use of project management software. Advanced planning should begin during the budget cycle prior to the expected date of application submission. This allows the company to anticipate cost and resource issues (e.g., user fees, additional personnel, shipping and supply cost, etc.). Do not underestimate. An axiom of building construction that holds true for a product submission as well is that a project will usually cost three times more than first thought and will take twice the estimated time.

Once advance planning is completed, a specific product application plan can be

developed. This plan should comprise the list of documents required for the application. Most countries now accept the ICH Common Technical Document (CTD) for submission. CTD Modules 2-5 are common to all countries while Module 1 contains country-specific document requirements. While major regulatory bodies (e.g., FDA and EMEA) allow electronic submission of almost all documents, most other countries will require a paper submission. However, all regulatory bodies are expected to start accepting electronic documents in the near future. Some regulatory agencies permit presubmission meetings, e.g., pre-IND and pre-NDA meetings with FDA, to review and discuss documentation requirements. Communication with the regulatory bodies about the submission is perhaps one of the most important aspects of product development and subsequent approval of an application submission.

One of the most difficult aspects of project management—regional or global—is the development of effective, efficient communication routes. **Figure 1** presents a sample communications diagram that illustrates the complexity of, and underscores the necessity for, developing a detailed communications plan. The plan should not only identify who is involved but also the best method (e.g., phone, email, text message etc) of communicating

Figure 1. Illustration of Communication Pathways



with each person who is responsible for the communication, and even their time zone. At minimum, the plan should consist of a list of contacts, the organization they represent and their contact information.

Another aspect of a project plan is risk identification and the development of mitigation strategies. There are three major components to risk assessment: identifying an unexpected event; determining the event's impact on project completion; and calculating the likelihood it will occur again. The GRSD lists potential events; however, actual events need to be assessed and logged throughout the project and appropriate changes made to the overall plan. Some delays arising from risk can be avoided by preliminary testing of tools, e.g., FDA allows a sponsor to test electronic document submission via its Electronic Submissions Gateway (ESG) prior to actual submission to verify system adequacy and logistical issues. Each identified event should be rated in terms of its importance *vis-à-vis* the overall project so mitigation strategies can be devised to address the event should it occur again.

Project management software can eliminate a lot of the guesswork. It can be created in-house or purchased "off the shelf." Appropriate project management software is identified in the GRSD, but actual testing of the software is required for user-friendliness, ability to create progress reports, and any necessary transition of responsibilities. However, remember that software is not a substitute for good project management techniques.

Personnel

Personnel, including selection and development of team members and, possibly, temporary workers, is the second major component, often described as the "soft side" of project management. An experienced team with good synergy is critical for timely execution of the GRSD. A project manager needs to understand not only the strengths and weaknesses of individual team members but also how to make the most of this information. Most of those holding business degrees are familiar with Tuckman's 1965 model, which describes the team development process as having four stages: forming, storming, norming and performing. A more recent model, developed by Mealiea and Baltazar,² offers a variety of ways to improve a team's effectiveness. Some of these include goal setting, leadership modeling of desired team behaviors, changing reporting relationships, promoting group problem-solving discussions, team member coaching, behavior modification strategies (rewarding desired behaviors) and formal training (e.g., communication, leadership, negotiation, etc.). A major challenge for the project manager is to be aware of cultural differences presented by team members from other countries. For example, in contrast to US workers, lower-level employees from Asian or Eastern European countries do not expect to be included in the decision-making process. They also identify with group membership and achievements instead of individual accomplishments. At the same time, US workers accept a greater degree of uncertainty than those in France, Japan and Russia.

International project managers, therefore, need to expend more effort in explaining complex issues, developing and maintaining consensus about objectives, developing trust among team members, defending the project team members, and obtaining the necessary resources required by the project.

Conclusions

Drug products are universal; they can be both developed and used at any location and by anyone. This fact, coupled with the warp speed of information and the interconnectedness of global economies—more so than at anytime in the history of mankind—makes it logical for regulatory agencies all over the world to increasingly share information and establish harmonized processes to avoid repetitive testing before approving medicinal products. This trend has not yet resulted in faster product approvals, but global filing of CTD applications is becoming more common for both large corporations and small to medium-sized businesses. As the pharmaceutical industry becomes more familiar with the universal nature of most regulatory processes and takes advantage of business incentives offered by different locations, a corresponding reduction is expected in the time from bench to market for most products. **F**

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