REGULATORY FOCUS

Regulatory Strategy 101

By Meredith Brown-Tuttle, RAC

What is regulatory strategy?

As a regulatory associate you hear the word "strategy" bandied about without any real definition. You know that is what you want to do some day—put together a strategy—but you do not know what it really is or how to do it. What you do not realize is that you are in a perfectly conducive environment to soak up all the knowledge you need about how to put together a strategy and this only gets stronger as you gain more experience as a regulatory professional.

Although you might not have known it, you have already created strategy if you have:

- put together a target product profile or a draft package insert
- conducted research on other products in your field and compiled it for comparison to your product
- researched endpoints for clinical trials and mapped out the required clinical trials for Phases 1-3
- conducted a gap analysis
- reviewed regulatory correspondence for commitments and outstanding action items due to a health authority and made recommendations on how to fulfill these requests

As shown by this list, regulatory strategy encompasses a wide range of activities and disciplines, so how strategy is defined and implemented by each regulatory professional varies across the profession.

Strategy Defined

The *Merriam-Webster Medical Dictionary* (2002) defines "strategy" as "an adaptation or complex of adaptations (as of behavior, metabolism, or structure) that serves or appears

to serve an important function in achieving evolutionary success." Therefore, regulatory strategy could be seen as the adaptations a company makes to move its product from development to marketing approval.

Regulatory strategy incorporates the drug development plan, outstanding issues or questions, background information, regulations and/or guidance documents, strategic advice, past precedents (if any) and recommendations on implementation. Additionally, strategy can take the form of:

- an individual question as it pertains to a development program or a change in regulations
- a review of the development plan (gap analysis)
- a drug development plan (US, EU or global)

This article explores the requirements for putting together a strategy for a US-centric drug development plan with some global considerations thrown in for good measure, as drug development is increasingly going global.

Why implement a strategy?

As the old adage says, "If you fail to plan, you can plan to fail." Implementing a strategy allows you to map your path forward and examine the pitfalls and mitigate any risks, challenges or issues the drug might face.

Small companies tend to plan to fail by not recognizing the value of strategic planning. They may claim to be "too busy" to put together an overall strategic plan. Putting together your Target Product Profile (TPP) or draft Package Insert (PI) at the end of Phase 2 or during NDA preparation, only to find you need to conduct additional nonclinical or clinical studies (such as QT prolongation) to support the filing or claims, is not a winning strategy; plan early and look at all your options before proceeding with the program.

In the long run, developing a strategy will save time and money and focus the development team. This article will cover an overview of the when, who, what and why of regulatory strategy (in the form of a drug development plan with some PI elements) and the US Food and Drug Administration's (FDA) perspective on your strategy or lack thereof.

When

The ideal time to construct a strategy is before you file an Investigational New Drug (IND) application, when it will get the team thinking about all the elements of the drug development plan. Pre-IND meeting requirements include submission of a development plan with the meeting package; this item can be used to drive the team to map out a plan.

Additionally, communicating the strategy to FDA via a TPP or by other means (typically in a meeting) will apprise the agency of your strategic thinking.

Who

Typically, the global development team works together to create the drug development plan. The effort is led by a regulatory director or vice president who drafts a plan for team discussion. Each team member brings perspective to the process and affects the ultimate outcome of the strategy negotiations, which in turn influences the drug development process.

The team members and their typical simplified questions and/or perspectives about any new compound are as follows:

Member	Perspective/Questions
Preclinical scientist	Is there a scientific basis or rationale for this drug? Does this rationale justify moving into humans? Do pharmacology studies demonstrate the mechanism of action? Are findings reproducible? Any specific toxicology signals of concern? What battery of nonclinical studies will need to be conducted for an approvable New Drug Application (NDA)?
Manufacturing department representative	Can the Active Pharmaceutical Ingredient (API) be made consistently and where will the source materials come from? Can the compound be manufactured consistently and at current facilities? Will outside vendors or contract manufacturers be needed? How much will it cost to make? Is the formulation correct? Is the drug stable? Will any methods have to be developed? What container closure method will be used?
Regulatory director	What is the regulatory status of the drug? Has it been approved before in the current form or another? Can a precedent be relied upon or is it too old? What regulations or guidance documents apply? What FDA division will review the drug? What pathway should be chosen based on the pathways laid by precedent drugs, or is there no precedent?
Legal department representative	Can we protect our intellectual property or is it infringing on others'? Is it patentable?
Medical director	Is there a medical need or therapeutic value for the drug? How is the disease currently diagnosed and treated? What is the standard of care for the disease and how will the new drug impact this? What drugs are used off-label to treat this disease? What are the concomitant medications? Can safety and efficacy be proven? What will the endpoints and design of the trial be? How many patients are in the target population? How many studies will be needed for an approvable NDA?
Finance representative/ business development	What is the return on investment? How much will it cost to develop? Can we afford it or do we need to raise capital to complete the development program or partner out?
Marketing representative	What is the new drug's potential market position? What are the other drugs on the market and what are their annual sales? How is the new drug different than other drugs and is there room for a new therapy on the market? What will someone be willing to pay for the drug?
Reimbursement specialist	What metrics need to be included in the studies so that the price of the drug can be justified? Will there be reimbursement issues with any payers?

Putting together a drug development plan in which all team members need to be aligned toward the same goal that still addresses everyone's needs can be difficult since there can be competing perspectives.

What does a strategy document look like?

The strategy document's format depends upon the company, its culture, the past experience of regulatory professionals who are leading the effort and the amount of detail to be included in the final document.

Ultimately, a strategy document is an organized meld of all the facets of drug development from pre-IND through NDA and into commercialization that have been agreed upon by multiple stakeholders. Whether the document is an Excel spreadsheet or a working "book," it must capture and document any changes to the drug development process so the whole team understands them and their impact on the strategy.

Please see **Figure 1** for an example table of contents from a drug development plan (high-level strategy).

Where to Start

Typically, teams start with the draft label or the TPP and build on this to create a playbook since these represent the first attempt at combining information from all disciplines; if these have not been developed yet, they can be pulled together after the playbook is drafted. The following content needs to be covered, but the compound and indication will drive the strategy document's ultimate format:

- medical and commercial requirements (usually include key marketing messages that need to be woven into the NDA modules)
- patient requirements
- research and development requirements
- desired marketing messages
- adverse event profile

Following is a breakdown of the specific items usually researched and evaluated and the decisions made about each topic that affect drug development for the US or globally.

Indications and claims	• Target indications ○ Requirements for clinical trials, by indication, which might differ by country • Label format, content (organization) and language requirements by country
Disease or condition	• Prevalence • Prognosis • Treatment options • Diagnosis • Standard of care • Adverse events expected for disease, expected for other drugs in class and used for disease • Off-label use • In what countries/population does this disease typically occur?
Unmet medical need?	• Market demographics of disease • Description of current management of disease • Proposed therapies • Description of market segments • Market projections – each segment • Overhead costs to reach market • Risk assessment for each market segment
Approval strategy (for each country)	• Health authority (reviewing division) • Classification • Approval route • Regulatory hurdles • Regulatory submissions needed • Supporting documentation • Approval options (fast track, priority, accelerated approval, orphan) • Meetings with regulatory authorities/scientific advice • Regulatory risks and mitigations • Marketing exclusivity expected • In what countries should marketing applications be submitted for the product and what are the documentation requirements?

Preclinical testing program	• Relevant regulations and guidance • Pharmacology • Safety testing • Mechanism of action/mechanistic studies • Pharmacokinetics • Toxicology • Anticipated outcomes or testing that can be conducted at Phase 2, Phase 3 or postapproval • Biocompatibility • Risks and mitigations
Clinical	• Clinical strategy that encompasses: o Phase 1, 2 and 3 studies o Location of clinical trials ▪ Ethics Committee approval ▪ Regulatory authority approval ▪ Core documents needed for trials ▪ Trial start-up times o Country-by-country diagnosis, treatment and standard of care for disease o Required safety database for a marketing application • Anticipated outcomes • Risk mitigation • Key opinion leaders in the field • Key publications for the disease • Publication planning
Manufacturing	• Components/ingredients of drug substance and product • GMP status of all starting materials and final finished product compendial ingredients (by country) • Excipients and regulatory status • Master/site files needed • Contract manufacturing needed or on-site manufacturing • Sterilization • Stability requirements (by country) • Packaging/labeling • Import/export issues • Clinical trial supplies and materials
Commercial strategy	• Other products on the market and their market share • Clinical trials needed to establish non-inferiority • Market need for new product and estimated annual earnings • Potential countries to market compound
Competitive information	• Other companies with products for this indication • Stage of development • Clinical study details • Competitor claims (label) • Indications • Recent launches, by country
Reimbursement	• By country, determine requirements such as: o Patient reported outcomes o Pharmacoeconomics information o Reimbursement of similar drugs in a variety of countries (helps develop price points)
Intellectual property	• Applicable patents and expiration • Patent law interpretation by country or whether patent protection exists in certain countries

Miscellaneous	• Resources needed • Milestones in project • Translations needed • Timelines • Lifecycle management strategy • Assumptions about compound

Why document a strategy?

"If it isn't documented, it doesn't exist." There are many reasons to document a strategy in a sort of "playbook" for the team:

You are asking the team to think critically about all the factors that go into drug development, not just their small segment of the process. By seeing the whole picture, people understand how their small portion affects the strategy.

Constructing a formal written analysis of the regulatory strategy for personal use or presentation to the team provides a reference to why a decision was made at a particular juncture in the development timeline so new team members understand the whole picture. In addition, it can serve as the foundation document for any future updates.

When an assumption or some component in the strategy changes, its effect on all the other facets of the drug development program can be evaluated.

A playbook also:

- drives identification and management of prospectively defined regulatory issues
- mitigates risk in the development program by getting team members to plan out the whole development process and obtaining management buy-in (which helps with project initiation and budget justification)
- ensures efficient utilization of project resources
- can create credibility with regulatory agencies
- can result in a timely approval for a product meeting business objectives
- expedites patient access to new and improved product and therapies

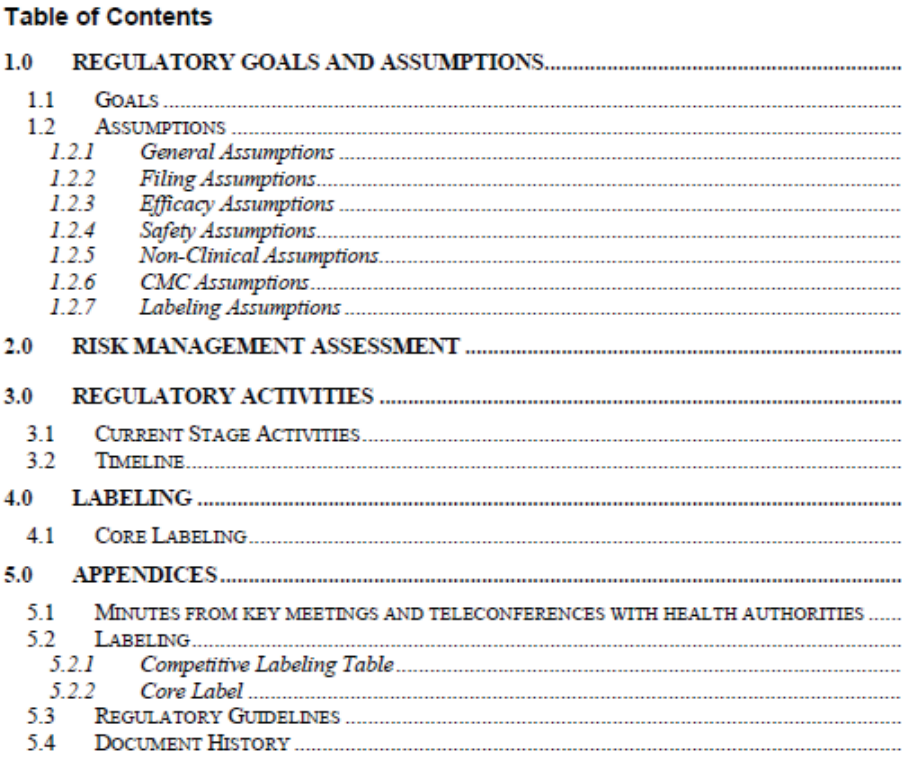
The process of putting together a regulatory strategy does not need to take months or a year to complete. Regulatory can provide the research, information and intelligence and come to the table with a reasonable working draft for team discussion (which might take a month or two) but once the initial draft is done, this process requires the team to sit down and focus on the task at hand and leave competing interests outside the room to develop the first team draft of the strategy. Participating in strategy development also requires the team to act and agree, so everyone can stand behind the decisions made.

FDA's Perspective

FDA, when reviewing your marketing application, will reverse engineer the application, looking at all facets of the strategy described herein to see whether you addressed the necessary components of a successful drug development program, incorporating the regulations, guidance documents and past precedents. If your team does not take the time to put together a strategy, FDA will—which could result in a refuse to file or complete response letter—and your company might not be happy with the results, especially if the strategy is not clearly laid out.

Planning for success can occur when the team sits down and discusses drug development issues that will need to be addressed at all stages of drug development. It is better, and ultimately cheaper, to prospectively examine and mitigate these issues than react to them as they arise or when the agency brings them to your attention.

Figure 1: Example Table of Contents for Regulatory Strategy Document



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