Developing an Effective Regulatory Strategy

By Mark D. Kramer, MS, RAC

As the global regulatory environment becomes increasingly complex, companies can no longer rely on assumptions or duplicating previously successful strategies for any but the most straightforward new products. Instead, they should develop and document a customized regulatory strategy that takes into account short- and long-term corporate objectives, the current and projected regulatory environment during the course of product development and the needs of multiple stakeholders within and outside the company. This article lays out an approach for building a comprehensive regulatory strategy. While the overall approach is written with device development in mind, the principles may be adapted for other types of regulated products.

Begin With Questions, Not Answers

As seasoned regulatory professionals know, when it comes to questions about regulatory strategy, the best answer is often "it depends." This catch-all response underscores the multitude of potential variables that must be considered to develop a definitive strategy.

Good regulatory strategy cannot not be created in a vacuum, and often requires balancing competing priorities, so, assemble a cross-functional project team represented by regulatory, marketing, medical/clinical, engineering, reimbursement, manufacturing, quality and/or other functions within the company. Don't forget about necessary expertise available from outside the company, such as from partner companies, key suppliers or consultants.

Below are the kinds of issues you and the team should consider to fully understand the product, its proposed marketing and the regulatory ramifications. Once you have the basics, "peel the onion" to make sure you understand any subtleties that may have regulatory impact.

- Device description—What versions are proposed for marketing? Which device characteristics could be significant from a regulatory perspective? Are there any device accessories, and will they require approval/clearance?
- Intended use—What are the proposed indications for use? What is the target patient population(s) and/or anatomical site(s)? What is the use environment (e.g., ICU, surgical suite, office setting, home)? Is the device proposed for prescription or over-the-counter use? Could the device qualify for expedited review or humanitarian use designation?
- Claims—Are there unique claims for which regulatory approval is required (or desirable)? You can often help secure a competitive advantage by carefully planning and obtaining the data necessary to support desired claims.
- Target markets—Where will marketing authorization be pursued? Which countries may require unique regulatory strategies due to differences in regulatory or reimbursement requirements? Do any of the countries require another country's prior approval, which could impact staging or timing of approvals? What national requirements will impact product development (e.g., requiring product display/software screens in local language)? What are the regulatory application fees? Is the potential revenue in a target market significant enough to justify the costs of pursuing regulatory approval?
- Compliance—Will the design and manufacturing sites require registration and/or inspection prior to regulatory approval? What are the key quality and Good Manufacturing Practice (GMP) issues for the product? If it is a combination product, how will drug GMP requirements be addressed?
- Lifecycle issues—What short- and long-term changes are anticipated? How might these changes impact the regulatory strategy, e.g., require a staged approach, with approval of one generation of device building off another?

Gather Data

With the added complexities of the global regulatory environment, evaluating all relevant sources of information that could impact your regulatory strategy has never been more important. On the other hand, in this web-enabled information age, obtaining regulatory intelligence has never been easier. Even if a product is truly unique, it is almost always beneficial to conduct a careful assessment of the regulatory history of related products or uses. Choose wisely and ensure the information has relevance before depending upon it too heavily. Information sources that may provide insight include:

- Regulatory agency websites—The databases on FDA's website, such as the 510(k), PMA, MDR and new "Total Product Lifecycle" and "CDRH Transparency" sites for medical devices, and the Drugs @ FDA, Orange Book and AERS sites for human drugs, provide a wealth of information related to the regulatory history, approval requirements and postmarket concerns for FDA-approved/cleared products.
    - Although FDA does not currently post letters requesting additional information on product applications, this might change under new FDA proposals to improve transparency of the review process. Even under FDA's current information disclosure policies, examining approval letters,

review documentation (including Summaries of Safety and Effectiveness for PMA products and the extensive reviewer documentation posted for NDAs), and postapproval requirements can provide considerable insight into approval requirements, reviewer concerns and approval timelines for related products.
    - If you think your product might not be regulated, research whether competitors have registered or listed similar products. If you think your device is 510(k) exempt, look to see if competitors have submitted 510(k)s for their products.
    - What kinds of issues surfaced at advisory panel meetings? Even if your product may not require a panel meeting, reviewing transcripts for meetings where related products or conditions were discussed, or for the kinds of issues the same review division has raised even for devices used for other conditions, can provide general insight into top-of-mind issues for that review specialty.
    - What kinds of clinical trials are in progress? The website at www.clinicaltrials.gov is an excellent source for basic information about clinical trial design and status.
- Competitor websites—These can sometimes be good sources of product information, including labeling, the product development pipeline, clinical trial protocols and press releases.
- Agency review staff—Informal conversations with agency reviewers or managers can be very helpful to obtain insight; however, these are busy people so use these interactions wisely. For novel technologies or indications, initial meetings with agency staff may provide necessary direction as a full strategy is being developed.
- Colleagues and consultants—Expand your network by seeking input from trusted colleagues, especially if they are working with the same review division/branch. Regulatory consultants are also good sources to help develop an effective strategy based on related experience.

Define and Document the Strategy

Once you fully understand the project's scope and subtleties and have conducted relevant regulatory intelligence, it is time to define and document the strategy. It might be helpful to prepare separate regulatory strategy documents for each major country where you plan to seek approval, especially if the strategies will vary significantly.

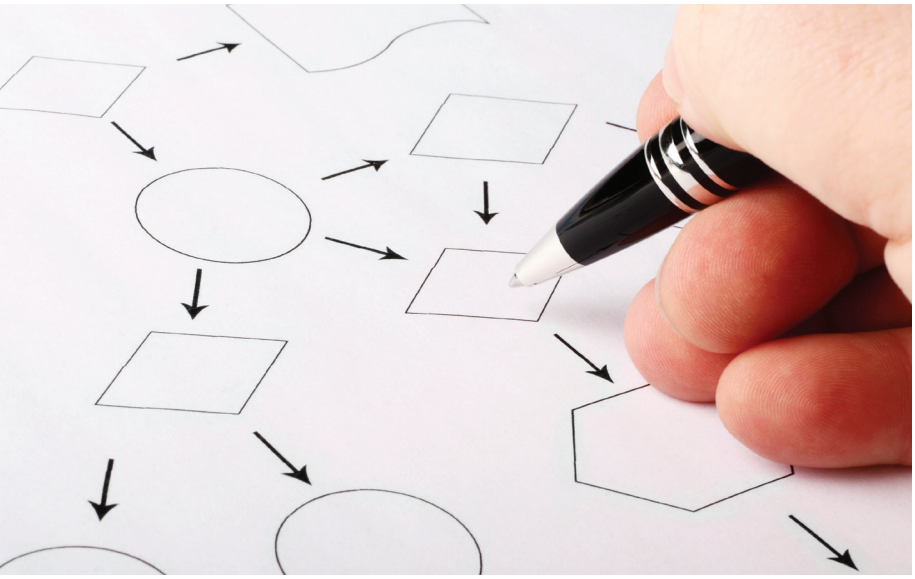
Below is a high-level outline for defining and documenting the strategy based on the issues that arise most often, but since "it depends," make sure you address all the issues with regulatory significance for your product that you identified during the "peel the onion" process described above.

Objectives

Depending upon the complexity of the program, initial objectives may focus on foundational elements, such as completion of proof of concept studies, preclinical and/or clinical study protocols or an initial agency meeting. For projects on a faster track, initial objectives could include clearance for easier-to-obtain indications, claims or country approvals, while longer-term objectives may involve approvals for future product generations or approval in secondary or more-complex markets.

Regulatory Pathway

Describe how the device will be regulated, relevant agency guidance and key data considerations based upon the regulatory intelligence gathered above. Describe any publicly available information about the regulatory strategies used for, and apparent successes and/or pitfalls of, competitive products. Identify the key risks or barriers and any critical assumptions, issues or questions that must be confirmed or resolved, and anticipate how prior or current requirements might evolve over the product development timeline. Some specific recommendations for key pathway issues to define and document:



- If there are several options for the regulatory pathway, identify them, along with the advantages and disadvantages of each for your company. Though it may often turn out to be the best choice, resist the temptation to automatically select the fastest route to market. For example, in the US, positioning the product as a PMA device might provide greater long-term gains in market exclusivity, claims or reimbursement despite the historically longer approval time required compared to a 510(k). With the current uncertainty in the 510(k) process, PMAs have never seemed more attractive, particularly if your device is one for which a 510(k) may be an uphill battle.
- If you have determined the device is on a 510(k) track, provide a detailed comparison of the proposed and predicate devices with respect to all key characteristics that are significant from a regulatory perspective. Identify any differences that may have regulatory significance and how these will be resolved. Be wary of reliance on so-called "split predicates," even if such a strategy has worked in the past.
- Describe specific approaches planned for regulatory submissions, such as filing a Request for Designation for a combination product, requests for expedited review, modular PMA review, paper vs. electronic submission, STED format, etc.
- Identify projected timelines for key regulatory milestones such as agency meetings and submissions, and the resources, such as new hires, contractors or consultants, that will be required to meet those milestones.

Preclinical Testing
Describe the bench, animal, biocompatibility, software, electromagnetic compatibility or other studies that may be necessary to support the investigational and/or marketing applications for the device. Describe what existing data can be leveraged, and identify any new studies required. Be sure to determine whether new test methodologies must be developed due to any unusual design or nature of the device. Document the voluntary or mandatory standards the product will be designed to meet and how conformance to those standards will be demonstrated.

Clinical Investigation
Describe the types and phases of clinical investigations anticipated, and key aspects such as study endpoints and duration of follow-up. Provide an overview of the intended timeline for the clinical investigations.

Agency Contacts
Identify the division/branch in the regulatory agency expected to be responsible for leading the product review, as well as the types of agency consulting reviewers expected to be required, such as human factors, manufacturing, software and biocompatibility, or those with expertise in a drug or biologic component for combination products. Where known, identify typical areas of focus or concern for the review staff, as these may point to areas you will need to address.

Regulator Communication Strategy
Identify what presubmission meetings are necessary (or desirable) to gain regulator understanding of and/or agreement with significant preclinical or clinical testing plans and the regulatory strategy as a whole. Identify milestones for preparing for, requesting and conducting these meetings. In addition, note any key topical conferences or agency-sponsored meetings likely to include discussions impacting the regulatory strategy. These may include FDA panel meetings or medical society meetings where key results on related or competitive products may be presented.

Additional Considerations
If the product represents a sea change in medical practice, consider steps the company can take to help ensure physician adoption or payor reimbursement. Document whether the device raises any unique regulatory considerations for the company, such as device tracking for a life supporting device being moved to the home environment, more adverse event reporting expected given the type of device compared to previous company devices, direct-to-consumer promotion or the company's first foray into combination or human tissue products.

Combination Products
Describe the strategy for confirming product jurisdiction. Identify the jurisdiction of similar products and your position on the combination product's primary mode of action. If the jurisdiction for this type of product is unclear or in dispute, describe the strategy for positioning the product in a Request for Designation. Anticipate the possibility that FDA may assign the product to a center other than your preference or determine that the product will be subject to a different regulatory pathway or to separate marketing applications for the product's constituents. For devices used with a separately available drug or used to deliver a drug, describe whether regulatory approval may be needed for a change to the drug labeling. Describe the company's plans for modifying the quality system to encompass the proposed GMP and adverse event reporting requirements for combination products.

Confirm the Strategy

It is almost always prudent to confirm that the proposed strategy is sound (likely to be effective), practical (reasonable and efficient) and addresses company objectives. Circulate your draft strategy for review by the cross-functional team you initially assembled. Despite care taken up front to fully understand the program, it is possible you missed a key point, or perhaps more likely, a change has emerged since your initial meetings. Seek the feedback of others in the company, trusted colleagues or advisors to further vet your strategy. Finally, for many programs, particularly if the product is novel or the data required are expected to be extensive, contact regulatory authorities to refine and/or redirect the strategy as appropriate. In general, agency contact is desirable as soon as there is enough information available for a meaningful discussion but before you move too far ahead or commit significant resources.

Be Prepared for Changes

Even the most diligently developed strategy is almost certain to change in at least some respect during the course of product and regulatory development. Set a schedule to periodically review and update the strategy document with your team. If your product development cycle is short but intense, perhaps even weekly checks might be needed, but for most products, a quarterly review will probably be about right. Keep a keen eye out for new information that may influence the regulatory strategy, which may include:

- internally driven changes, such as company plans for new or revised indications or claims, device modifications or new markets
- externally driven changes, such as new regulatory requirements or guidance or agency action on similar products

Summary

A solid regulatory strategy is one of the foundations upon which successful medical product development is based. Start by asking a broad range of questions to ensure you have a solid understanding of the product and marketing plans, especially any subtleties that may have regulatory impact. Conduct regulatory intelligence to obtain as much information as possible about the regulation of similar or related products. Be practical and realistic when it comes to developing the strategy to attain the "must haves," but include strategies to stretch for the "nice to haves," too. Validate your strategy with internal and external stakeholders, and where appropriate, with agency personnel. Finally, closely watch product development and the regulatory environment, and be ready to revise the strategy as necessary.

Author
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