Creating Positive Communications *with* the FDA

Denise Myshko

A critical success factor in the regulatory review process is clear and frequent communications to ensure a smooth and efficient review of an application.

Navigating the regulatory review process can be challenging. Industry experts say creating an efficient development process depends on engaging regulatory officials and proactively communicating.

Companies need to treat FDA communications as a formal end-to-end process, says John Cassimatis, co-founder and president, of TayganPoint Consulting Group.

"This means creating a process owner, creating key metrics, and making sure everyone's roles are clear."

A recent survey by Cutting Edge Information found that taking the initiative in communications with the FDA is key.

"Companies have to make the effort to communicate the science behind the product and the advantages that the product has," says says Jacob Presson, research analyst, at Cutting Edge Information. "It's important that companies keep regulators informed and aware of the latest science and how their potential product fits into the therapeutic pathway."

The Communications Process

There is a formal process for communicating with the FDA, and the agency offers milestone meetings intended to enhance the development process for drug developers, says Eugene McNally, Ph.D., executive director, at PPD Consulting.

"Early development discussions include the pre-IND meeting to resolve aspects that might prevent first-in-man exposure and an end of Phase I meeting to understand initial clinical findings and to agree on plans for a meaningful Phase II effectiveness proof-of-concept study," he says. "As the program matures, an end of Phase II meeting informs plans that will maximize the likelihood of success in registration Phase III investigations. As the development program approaches conclusion, a pre-NDA/BLA meeting allows for agreements leading to a complete, fully reviewable NDA/BLA."

The regulatory agency will often stage the importance of meetings, says Susan Stewart, head of regulatory affairs, quality and compliance, at Tokai Pharmaceuticals.

"Pre-IND and end of Phase II meetings, for example, are Type B meetings, which means regulators will schedule those meeting six to eight weeks ahead of time," she says. "Documents are required to be submitted before these meetings."

Companies get a chance to meet more immediately when there is a safety issue or the product is in the NDA review stage where the communication is more fluid, Ms. Stewart says.

When INDs or NDAs are under regulatory review, communications between pharma companies and members of the FDA review team routinely are managed by a divisional regulatory project manager (RPM).

"Ongoing dialogues are optimally sustained through email exchanges between the client and specific discipline reviewers," Dr. McNally. "The client or the reviewer may request a telephone discussion to offer further clarity and understanding. Agreements achieved during these dialogues require subsequent written memorialization to the IND/NDA review file."

Special product-related aspects, such as orphan drug, fast-track, and breakthrough therapy designations, also require specific FDA-defined written documentation processes formally submitted as part of an IND for review consideration.

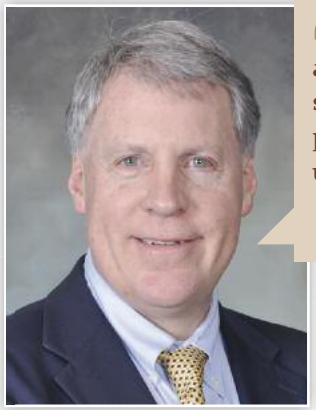
"Complete, comprehensive, and compelling written justifications that satisfy FDA's expec-

Communicating with the FDA

Formal meetings provide an important forum to present information, and for the FDA to provide specific and targeted advice. These meetings fall into one of three types — Type A, Type B, or Type C. The FDA determines the meeting type based on the nature of the request and the information in the meeting request.

- **A Type A meeting** is a meeting that is necessary for an otherwise stalled product development program to proceed. Examples include dispute resolution meetings, certain meetings to discuss clinical holds, certain special protocol assessment (SPA) meetings, and a post-action meeting requested within three months after an FDA regulatory action other than approval.
- **Type B meetings** include the following meetings: pre-IND, pre-emergency use authorization, pre-Phase III, pre-NDA/BLA, and post-action meetings requested three months or more after an FDA regulatory action other than an approval. These meetings also include meetings regarding risk evaluation and mitigation strategies or post-marketing requirements that occur outside the context of the review of a marketing application, and meetings to discuss the overall development program for products granted Breakthrough Therapy designation status.
- **A Type C meeting** is any meeting other than a Type A or Type B meeting regarding the development and review of a product.

Source: Food and Drug Administration



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tations for structure, format, and content are essential to successful designation requests,” Dr. McNally says. “Successful designations allow for more frequent company-initiated access to multi-disciplinary FDA reviewers to assess the significance of findings uncovered during conduct of the clinical program.”

Creating Positive Communication

Dr. McNally says the key to working with the FDA is to funnel all communications through the RPM, from general review matters to specific questions seeking information on timeline expectations.

“Initial telephone conversations and written follow-up communications should be as detailed as possible to provide sufficient clarity and understanding,” he says. “The FDA only should be asked to provide guidance on clinical, nonclinical, or manufacturing proposals offered by the client, and should not be asked to advise on conducting drug development programs.”

Ms. Stewart says one of the biggest don’ts in communicating with the FDA is to view the process in an adversarial way.

“Mutual respect on both sides is critical,” she says. “The first line of people you are working with is medical reviewers, chemistry reviewers, and statisticians. They are asking the questions about the protocol and the product. Having a battle with these reviewers isn’t going to resolve an issue because they may not be authorized to change the agency’s position.”

Ms. Stewart says a mistake companies make is bringing an attorney to resolve a conflict.

“With an attorney present, the conversation goes to a different level for something that could have been worked out,” she says. “Now the conflict is a legal issue, and a debate about a protocol shouldn’t be a legal issue. This will only delay the process.”

Ms. Stewart says it’s important to address any FDA concerns early on.

“The best thing to do is to discuss with the agency any open questions or commitments,” she says.

She stresses it’s important to submit high-quality documents to the agency before any meetings with regulators.

“Many people think the meeting with the FDA is the show,” she says. “But the actual work and regulatory decisions have already been made before you walk in the door. The quality of the information presented in your briefing documents is critical. This should be a fairly comprehensive document and focus on areas where you need to reach an agreement with the agency. They’ve developed their response before you walk into the meeting. It’s rare that you are going to change their minds in that room. You will get that opportunity in another meeting.”

Dr. McNally says clear articulation of background information and specific questions in written communications supporting open discussions with FDA is key to promoting transparency and understanding communications with FDA reviewers.

Mr. Cassimatis says it’s also important to develop relationships with regulatory authorities as a way to create opportunities for more informal communications.

“One best practice is to use these relationships to help gather insights,” he says. “It’s about relationships and the ability to leverage those relationships to help inform the FDA and vice versa. It becomes more of a partnership than a one-way dialogue.”

He says one mistake companies make is not being clear about who within the organization is communicating with the FDA.

“There are many different touchpoints with the FDA,” he says. “What makes it particularly challenging for the FDA is receiving inconsistent answers.”

He says companies need to think of their interactions with the FDA as a business process and have SOPs around those communications.

“Information systems can be used to track any interaction anyone has with the FDA,” he says. “In this way, there can be a history of all the interactions and anyone would be able see if there were any commitments or any actions that need to be addressed.” PV