Taming the Regulatory Beast: Role of Regulatory Trend Analysis in Successful FDA Approval

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The biggest risk in drug development is failure to convince the FDA that your product meets the requirements for marketing approval. By the time a company files a New Drug Application (NDA), it believes that sufficient evidence is available in support of the marketing approval, based on its understanding of the regulations and requirements. However, about 40% of the NDAs submitted to the FDA are rejected for one or another reason while more than half go through multiple cycles of review adding additional cost and delays to the ultimate approval to market a product. A recent independent survey of FDA review process found that most rejections or delays are due to one or two issues that, in the opinion of the FDA reviewers, could have been easily resolved with appropriate review of past information and consultation with the FDA.

The US FDA follows an elaborate, extensive, consultative and quite transparent process to approve or reject the products it regulates. All past approval decisions by the FDA are available in the public domain on its website for everyone to review and learn from. FDA also frequently releases guidance documents to help understand its current thinking on how various processes should be conducted. This wealth of information makes it hard to understand the reasons for such a high rate of failure. But there are some indicators. It was found, in the independent survey of FDA review processes, that companies with more experience of working with the FDA and a large regulatory workforce are twice as likely to get faster approval compared to companies that are not. Also companies that apparently were better prepared to address FDA concerns before submission and were more responsive to FDA's feedback were, obviously, much more successful at getting marketing approval than the average.

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The above information begs the questions: what can a company do to increase its success rate? The simple answer is to invest in understanding the regulatory processes way beyond the basic regulations and guidance documents to make the development process smarter, by proactively addressing the common issues and being responsive to changes in the trends throughout the development cycle. Here I discuss some ways to implement the above.

It Starts with Regulatory Education

Regulations and Guidance Documents published by the FDA and the International Conference on Harmonization (ICH) form the backbone of a development strategy. All processes must meet the basic requirements. Regulations are the laws which are written by Congress and implemented by the FDA. By definition these are core requirements and must be met. However, regulations mostly describe the core principles and do not go into extensive details. In the absence of additional information, regulations could be subject to interpretation. To help developers understand FDA's interpretation of the regulations, FDA releases "Guidance Documents." The guidance documents go into great details of what is expected from the sponsors

of applications. Most guidance documents are based on FDA's past experience with similar products submitted by other applicants for review and approval. Several of these documents are specific for product classes and highlight the key issues and ways to address the same. Guidance documents are not updated very frequently with some such documents being more than 10 years old and technology of course has may have changed significantly since the document was created. Occasionally guidance documents that are no longer helpful due to changes in regulatory processes are formally withdrawn.

The fact that guidance documents address an entire class of similar products and not individual products, and provide non-binding advice to developers, means they can at best assist a sponsor to list all the studies and tests that might be needed for their product but the sponsor still needs to customize their development pathway for a specific product in development. Despite the limitations, the guidance documents do provide excellent initial information required to strategize the development pathway for a given product. There is an inherent flexibility in the recommendations available in these documents with any changes from the norm permitted with appropriate scientific rationale.

Thorough review of applicable regulations and guidance documents is a great starting point for any development pathway. Over time, study of regulations and guidance documents has become an important training tool for regulatory experts.

Regulatory Precedence Fills the Gaps in Information

FDA reviews hundreds of new products every year. While the review process for clinical trials and all development steps is confidential, once a product is approved, detailed information about FDA's review of the marketing application and key elements leading to approval are posted on FDA's website. Information about review of various aspects of the product from clinical trials conducted in support of the NDA, the manufacturing issues, animal experiments conducted, etc are available for anyone to study. This information called the "Approval Package" or the "Summary Basis for Approval" (SBA) could run into hundreds of pages and provide critical information about review timelines, FDA suggestions to the sponsor and their response to the same, and the regulatory pathways explored during development, among other things. In addition, many times FDA invites its various Advisory Committees to provide an independent review of the critical information in a public setting. Advisory Committee discussions are open to the public and minutes of these meetings are also posted on the FDA website. While SBAs are only available for products that obtained approval from the FDA, Advisory Committee meeting minutes can provide information about other products that were not so fortunate. Together the two - SBAs and Advisory Committee minutes - form the basis of Regulatory Precedence.

Precedence information is very important in filling critical gaps in information not evident from regulations and guidance documents. If a product that is similar to yours has gone through an FDA review, its review information could provide crucial details about the potential development steps - pre clinical and clinical trials, safety reporting requirements, manufacturing limitations - for your product. Not only similar products but products targeting similar indications, similar structure, similar population, and even other reviews conducted by the same division of the FDA as yours could provide valuable pointers about potential issues and possible resolutions. Unlike the regulations and guidance documents, precedence information is much more specific about a product under development and forms a critical basis for understanding regulatory and scientific trends for product approvals. However, precedence information needs to be applied appropriately. FDA reviewers routinely insist that each product is unique and should be reviewed on its own merits. Precedence can be best used to understand what to expect in most cases.

The review information for a given product gives the snapshot in time for the extent of review process, state of available science and the risk to benefit assessment at the time of review. Reviews are done depending on

the laws, science and requirements at the time of the review. The relevance of precedent information to the current strategy diminishes with time due to rate of progression in knowledge. As a general rule of thumb, it is generally accepted that precedent information loses most of its importance in about 10 years from the date of release.

Regulatory Intelligence = Regulatory Education + Precedence Analysis

Regulatory education and precedence information go together to provide complete information about a given product, its potential competition, most acceptable development strategy and smarter product development that requires fewer clinical and non-clinical trials and take lesser time to market. Ideally, one should start collecting regulatory intelligence at the very beginning of the product development process and make it the basis for all planned development steps, discussions with the FDA, and design response measures to adapt as new information emerges.

Regulatory intelligence usually goes beyond the US FDA, whereby regulatory reviews in other key regulatory agencies are also collected and analyzed. Just like the FDA, EMEA and Health Canada publish policy papers, guidance documents and summaries of product reviews. Although the precedent information available from these regulatory bodies is not as comprehensive as that from FDA, it does provide some insight into regulatory processes and trends on a global scale. The first place to start is the approval packages. EMEA labels such product reviews “Summary of Opinion” or “European Public Assessment Reports” (EPAR), while Health Canada refers to these as “Notice of Decision” or “Summary Basis of Decision.” Of all three, FDA releases the most comprehensive packages which include great details and run to as much as 700 or 800 pages. The EMEA review documents are shorter, usually between 50-70 pages, while the one from Health Canada is even shorter. Most of the information is available on the websites of the respective organizations and are fully searchable using search engines such a Google and Bing.

Although the regulatory websites are the primary and most trustworthy source of information, regulatory intelligence also involves collection and analysis of alternate sources of information such as press releases, product labels, publications in journals and magazines, clinical trial registries, and filings to Securities and Exchange Commission (SEC) for publicly traded companies. These alternate sources of information usually give information about the strategies in the works, the summary of information not released by FDA due to confidentiality issues, and the business issues affecting the development pathway of a given company.

Regulatory Trend Analysis is a Multi-Dimensional Process

The ultimate aim of any trend analysis is its ability to predict potential pitfalls, identify shortcuts, and avoid surprises during discussions with the FDA. Regulatory strategy is a living process that should start with comprehensive analysis of the several alternative pathways for development, identifying the most feasible and acceptable pathway, getting regulatory concurrence from the FDA, and then proactively adapt when any critical new information surfaces. This does not mean that one needs to change the core design frequently, but that one should be aware of and have a logical explanation about how to address the new information.

Some times the wealth of information could lead to information overload and make it hard to identify the information most relevant to a given product, and its appropriate interpretation. Also not all information should carry similar weight in terms of importance. The most important and relevant element of regulatory trend analysis is the SBA. It not only provides scientific information but also about regulatory timelines, intellectual property, and business strategy-related information. Next, in terms of importance of drug development strategy are the guidance documents, followed by advisory committee discussions, publications, FDA presentations, and finally information from the alternate sources. Other places to look for important information could be public

comments to FDA's announcements, warning letters issued by the FDA, FDA's standard procedure manuals and staff training materials, all of which can also be found on FDA's website. While designing a development strategy, one should be able to distinguish between scientific and credible information from anecdotal and business-centric information, both of which could be important for different aspects of trend analysis. While documents from the regulatory agencies could help provide critical information about FDA's acceptance, the one from alternate sources might be crucial to gauge business interest and investment advice.

A comprehensive review of information and effective regulatory trend analysis could be a critical element of getting successful marketing approval from the FDA. It involves allocation of resources and time. But it could pay dividends over time and should be the backbone of all product development strategies. Experience pays dividends: the more you research, the more you learn. Your product is unique—your plan should be, too.

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