Drug Information Journal, Vol. 34, pp. 703–707, 2000
Printed in the USA.
0092-8615/2000

SIX ENDURING PRINCIPLES FOR PREPARING NDAS

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Six enduring principles for preparing New Drug Applications (NDAs) are advanced: Principle Number 1: An NDA is the document that supports the labeling of a drug, Principle Number 2: An NDA is the only "form" of a drug that most regulators will ever see. A firm should look at its NDA as an example of its finest work, Principle Number 3: NDAs are organized to facilitate review by the authorities, Principle Number 4: Group studies in a logical order, Principle Number 5: Standardization of format and consistency of content make for high quality applications, and Principle Number 6: Getting it submitted on time is important; but getting it right is more important if your goal is an approved application.

Key Words: New Drug Applications; Principles; Labeling

INTRODUCTION

SWEEPING CHANGES CONTINUE to reshape the pharmaceutical workplace: mergers, competition, pricing pressure, evolving health care systems, new regulatory requirements, International Conference on Harmonisation initiatives, new technologies, increased dependence on outsourcing, and new work processes are but a few. The new millennium promises many more. In the context of these sweeping changes, it is comforting that there are some principles which have stood the test of time. This article offers six enduring principles for preparing New Drug Applications. (The term NDA is used in this article to denote a marketing application in any country, eg, a New Drug Application in the United States, a New Drug Submission in Canada, or a Marketing Authorization Application [MAA] in the European Union.) These principles are based on the personal experiences of the author over the last three decades, working on scores of NDAs with large, midsize, and small pharmaceutical companies, and listening to feedback from thousands of participants in tutorials on NDA preparation at DIA Annual Meetings. While the principles focus for the most part on United States NDAs, they apply universally.

PRINCIPLE NUMBER 1: AN NDA IS THE DOCUMENT THAT SUPPORTS THE LABELING OF A DRUG

This principle is so important that it has been the "take home message" of the DIA NDA preparation tutorial for almost two decades. Why? Because approval of a drug requires that the labeling (ie, the package insert in the United States or the Summary of Product Characteristics in Europe) of a drug be truthful as evidenced by data in the NDA. If NDA preparers do not keep this principle in mind, they risk a nonapproval decision.

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The Food and Drug Administration (FDA) expressed the importance of the package insert in its staff manual (1):

> "The package insert and other labeling represents the final distillation of the substantial evidence and supportive data in the NDA translated into clinical meaning upon which the sponsor, FDA, and their advisors can agree. It is the product of the scientific data submitted in the NDA and should accurately reflect the essence of the NDA."

It is not surprising, therefore, that United States regulations require that every statement in the package insert of a drug be annotated to where the documentation supporting the statement may be found in the New Drug Application (1).

Keeping the labeling in mind from the beginning of drug development can not only improve the quality and overall focus of the NDA documents, it can also improve efficiency of drug development and communication both within a sponsor firm and between a sponsor firm and the regulatory authorities. To this end, in March, 1999, the United States FDA began the "Targeted Product Information" (TPI) pilot program in the Office of Drug Evaluation (ODE) IV. The TPI is an evolving version of the annotated, proposed package labeling that may be used during all phases of drug development. The sponsor writes the TPI to guide the design, conduct, analysis, and reporting of clinical trials so that at the end of the development program, the sponsor will have gathered the necessary data and written the appropriate documents to support the sponsor's desired outcome—the approval and appropriate labeling of the drug under development. The TPI can also serve as the basis for an ongoing dialogue between FDA and the sponsor to facilitate a shared understanding of the goals of the drug development program, as well as the specific studies designed to achieve those goals. This tool could be especially useful at key meetings with the FDA during drug development: pre-Investigational New Drug (IND), end of Phase I, end of Phase II, and pre-NDA, as well as discussions about efficacy supplements.

PRINCIPLE NUMBER 2: AN NDA IS THE ONLY "FORM" OF A DRUG THAT MOST REGULATORS WILL EVER SEE. A FIRM SHOULD LOOK AT ITS NDA AS AN EXAMPLE OF ITS FINEST WORK

NDA preparers work with their drug daily, often for many years. They know their drug very well. Many will have seen the manufacturing plant in operation, witnessed patients being administered drug, and written reports which constitute the very essence of the NDA. It is easy for NDA preparers to get so comfortable with the drug and the associated data that they write the NDA documents assuming that "the drug will speak for itself." Nothing could be further from the truth.

Do not assume that regulators charged with reviewing your NDA know your drug as well as you do. Most regulators have a limited time to complete their review, often without the benefit of being involved with the drug during its investigational phases. Most will never see the drug itself and will never come in contact with a patient who received it. Rather, most regulators only see the reports written by the applicant's NDA writers and designated experts. It is important, therefore, to describe what you did and why you did it, to present your data clearly, and to explain the basis of your conclusions. Use regulatory jargon and show how your data and your studies meet the criteria for approval and support your proposed labeling.

Each NDA must be judged on its own merit, but each application also contributes to an impression about the applicant. Does the firm understand the regulations? Does it endeavor to fully characterize its drugs and write adequate instructions for their use? Is the firm honest? Are its reports well written, accurately reflecting the data? Are the firm's conclusions valid? Are its NDAs well-organized and easy to review? Does the firm live up to its commitments?

"A firm should look at an NDA as an example of its finest work." This statement, attributed to FDA staffers G. Meyer and J. Yorke, speaks volumes. For a firm steeped in history, with many approved NDAs in its portfolio, its work product is well known to the regulators. A level of credibility and trust has presumably been established. For a new firm, the first application is particularly important. Not only does its success rely heavily on an approval action, but the firm's credibility with the authorities is being established.

PRINCIPLE NUMBER 3: NDAS ARE ORGANIZED TO FACILITATE REVIEW BY THE AUTHORITIES

Every major country has its own rules, regulations, and guidelines governing the marketing of pharmaceuticals. The rules (also known as laws or directives) put forth the requirements for marketing a product. In most countries the rules are aimed at assuring that pharmaceuticals licensed for marketing are effective and safe for their intended uses, are properly manufactured, and are labeled truthfully. The authorities in each region are charged with assuring that the rules are met. How authorities accomplish their charge varies from country to country, in part due to the varying budgets allocated to drug approval around the world.

Regulations and guidelines tell industry what information the local authority requires to make its assessment, and how to organize the required information to best fit the local authority's way of conducting its review. Since in many countries, a satisfactory review requires the assessor to both understand the data and write a comprehensive review document, it is in the applicant's interest that the NDA be organized to facilitate these efforts.

Consider, for example, the applicable rules, regulations, and guidelines in the United States. The rules are put forth in the Federal Food Drug and Cosmetic Act, Section 505 of which mandates that: "No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application . . . is effective with respect to such drug" (2). Among other things, Section 505 states that the application shall contain:

> (A) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use; (B) a full list of the articles used as components of such drug; (C) a full statement of the composition of such drug; (D) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; (E) such samples of such drug and of the articles used as components thereof as the Secretary may require; and (F) specimens of the labeling proposed to be used for such drug (2).

The regulations and guidelines describe how the application should be organized. The organization required for a United States New Drug Application is put forth in 21 CFR 314.50, which specifies the need for an archival copy of the entire application which, for a new chemical entity, will generally contain an application form, an index, a summary, five or six technical sections, case report tabulations, case report forms, drug samples, and labeling (3). The technical sections comprise:

1. Chemistry, manufacturing, and controls (CMC),
2. Nonclinical pharmacology and toxicology information,
3. Human pharmacokinetics and bioavailability,
4. Microbiology,
5. Clinical data, and
6. Statistical information.

In addition to the archival copy, a review copy and a field copy are also required.

The organization of the NDA into technical sections and the provisions for review and field copies was fashioned to match the review process and organizational structure at FDA. Prior to 1985, it was not uncommon for applicants to provide "desk copies" of selected NDA documents to individual regu-

lators so that parallel reviews could take place. The "NDA Re-Write of 1985" gave rise to most of the current NDA regulations, and provided for standalone review copies for each technical section to enable reviews by each discipline to proceed in parallel rather than in sequence. The additional requirement for a field copy was added in the early 1990s to further enable parallel reviews. Prior to the addition of the requirement for a separate field copy, the FDA staff responsible for preapproval inspections and methods validation depended on the chemists at FDA "headquarters" to send them copies of the parts of the application needed to accomplish their review.

The documents required by regulation are intended to provide assessors what they need to accomplish their reviews. Consider the documents required in the clinical section of an NDA as elaborated in FDA's *Guideline for the Format and Content of the Clinical and Statistical Sections of an Application*: the background/overview of clinical investigations, an overall summary of clinical pharmacology, a report of each clinical investigation, an integrated summary of effectiveness data, an integrated summary of safety information, and an integrated summary of benefits and risks of the drug. All are well-matched to the information typically included in the medical officer's review.

Electronic NDAs have become increasingly important and are also aimed at facilitating review. A major goal of electronic submissions is to make the NDA documents and the underlying data more accessible to regulators to speed their review of the data and their writing of their summary documents, and to enable them to make faster, better-informed decisions.

Thus, each country's guidelines provide considerable insights about how to present information to facilitate reviews. In addition to local guidelines, there are international guidelines originating from the International Conference of Harmonisation (ICH). The push at the ICH level to achieve a Common Technical Document (CTD) as a universally acceptable format for an NDA is a laudable goal. When achieved, it will mean that a single set of documents can be prepared for worldwide registration of a drug. Hopefully, the CTD formats will be well matched to the applicable rules, regulations, guidelines, and most importantly, the ways in which the local authorities work.

PRINCIPLE NUMBER 4: GROUP THE STUDIES IN A LOGICAL ORDER

Within every technical section, studies should be grouped in a logical order, with studies of a particular type grouped together. The order of studies reflected in the table of contents of an application is generally mirrored within the summary documents of that application. Many NDA summary documents include one or more overview tables, with each individual study represented in a row. The overview tables are typically followed by a brief synopsis of each study, in the order the studies are listed in the overview tables.

When deciding upon an order of studies, factors to consider include regulatory guidelines, scientific strength of the studies, poolability of data across studies, and desired labeling claims. Particularly in the clinical section, the ability to pool data from multiple studies may be impacted by database compatibility, geographical location of studies, and differences among treatment regimens, study designs, study duration, dosage forms, and formulations. Before finalizing the order of studies for a particular application, it is advisable to consider how each possible grouping will "play out" against each of these various factors. Generally, the earlier the study groupings are determined for a particular NDA, the more efficient the NDA preparation effort.

PRINCIPLE NUMBER 5: STANDARDIZATION OF FORMAT AND CONSISTENCY OF CONTENT MAKE FOR HIGH QUALITY APPLICATIONS

Standardization of formats across documents helps give an application a consistent look

and feel, and helps regulators navigate an application. Tools to achieve standardization include document templates, word processing styles, and authoring software. Following standard operating procedures and providing uniform training of authors also helps.

Consistency of content makes for an application that "speaks with one voice," and helps instill the regulators with confidence that the applicant has given attention to details and reviewed the NDA thoughtfully and thoroughly. Thus, make a conscious effort to be consistent throughout the NDA in terms of nomenclature, data, conclusions, key messages, and identification of unanswered questions. Pay particular attention to subjects addressed in more than one technical section of an application. For example, clinical pharmacology information is often included in multiple sections/documents of an application: nonclinical pharmacology, human pharmacokinetics and bioavailability, clinical pharmacology summary, integrated summary of effectiveness data, integrated summary of safety information, and labeling. To ensure consistency across sections/documents, work to optimize communication among team members. Take a big picture view of an application. Set up interdisciplinary reviews of key documents. Consistent with Principle Number 1, focus on the labeling.

When describing an individual study, be consistent across study documents: the protocol, the statistical analysis plan, and the study report. Also be consistent across studies of similar designs in terms of nomenclature, approaches to analysis, report format, and layouts of tabular and graphical displays. To achieve consistency, it is helpful to write components that can be reused across multiple documents and adopt a systematic approach to authoring, including the use of authoring software for NDA writers. Adopting standardized formats and using systems and procedures to ensure consistency of content will generate higher quality documents, make the process of NDA preparation more efficient, result in quicker reviews, and reduce cycle times.

PRINCIPLE NUMBER 6: GETTING IT SUBMITTED ON TIME IS IMPORTANT; BUT GETTING IT RIGHT IS MORE IMPORTANT IF YOUR GOAL IS AN APPROVED APPLICATION

Balancing quality, time, and cost is a challenge. High quality means getting it right. Getting it right does not necessarily mean getting it perfect. Rather, getting it right means making sure that the NDA data are reliable for regulatory decision making, that the proposed labeling is well supported, that the NDA is well organized, and that the various documents in the application are consistent.

Without a doubt, time is important. After all, the faster the time to market, the more rapidly returns on investments can be realized and the more quickly the new drug will become available to patients. Every day approval is delayed can cost millions or even tens of millions of dollars. Cutting corners on data quality, particularly data that are important for regulatory decision making, however, can be expected to result in longer approval times. Submitting an application before completion of reports of adequate and well-controlled studies demonstrating that the drug has the effects claimed in the labeling will certainly lead to delays and possibly refusal by the authorities to file the application. A poorly organized, poorly written NDA, full of inconsistencies, will not only be perceived as sloppy and impair the applicant's credibility, it can also lead to a refusal to file. Reworking a poorly done application is costly, so get it right, the first time. Remember, the costs of preparing an NDA are largely inconsequential compared with the cost of lost revenues from delays in approval.

REFERENCES

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