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# how to compile a science-backed New Drug Application (NDA) submission like an expert

You're getting ready to begin the process of compiling and submitting your New Drug Application (NDA) dossier to the Food and Drug Administration (FDA). You've been working tirelessly for years to get to this point and all your efforts are paying off; you're finally here. However, after all of the long days (and nights) and all of the hours spent laying out your regulatory strategy, pouring over the data, preparing for and attending meetings with the FDA, and so much more, it would be tragic for all of your efforts to be derailed.

You're at one of the most critical junctures in the entire process of drug development. Doing the right thing in the right way is imperative to the success of your product and, in turn, your company at this point. Our experts are laying out six of our best kept secrets for compiling an NDA submission like a pro.

## 1. strategy is key: make sureyou start with a well-vetted regulatory strategy

Having a solid, yet adaptable, regulatory strategy as the foundation of your drug development efforts is the first step in setting yourself up for success when beginning the process of developing your NDA. The strategy provides the foundation for the entire submission and will act as the blueprint for your project team. This is a step that is commonly skipped at the start of development in an attempt to cut costs, but that is one of the biggest mistakes that a Sponsor can make. The regulatory strategy is the most leveraged part of the drug development process; when compared to other FDA milestones, strategy development has the lowest cost, but is often thought to make the most impact. On average, developing a well-vetted and complete regulatory strategy costs Sponsors the equivalent of three-to-five patients in a clinical trial. Although regulatory strategy development is becoming more and more common, it is not something that should ever be considered "*optional.*"

However, it is not just important to have a regulatory strategy, but it is also important to have a *great* regulatory strategy. What makes a regulatory strategy great, you're probably wondering? A great regulatory strategy is based on a full understanding of the current regulations coupled with the FDA's current thinking, applicable scientific topics, and balancing cost, speed, and probability of success. Great regulatory strategies take a holistic, cross-disciplinary approach to drug development and provide solid logic and rationale for the path that is selected and outlined in the document.

## 2. engage a strong, cross-functional team to lead the project

The second key to developing an award-winning NDA submission is to make sure your team is made up of the best and the brightest experts that you have access to. Your people are your biggest asset, and making sure you have industry-leading experts on your side of the playing field is imperative to achieving success with the FDA.

The process of NDA development, submission, and approval is milestone-driven. As such, you need to ensure your team consists of individuals that are equally as focused on the milestones, making sure they are focused at the task at hand, but also able to keep one eye on the upcoming tasks without compromising the current issues. It is important that the team members understand the FDA's current and relevant regulations and that the individuals have prior experience developing NDA submissions. The individuals on your team should be interacting with the FDA on a regular basis, so making sure they are comfortable with this type of communication is critical.

Perhaps the most important attribute for the individuals on your team to possess is a scientific mindset. Drug development, and thus the regulatory approval process, are both driven by science. If there is nothing else, this is the one thing your team should always have in common with the regulators. As such, to the extent possible, science and scientific data should be the driving force behind any and all decisions that are made throughout the entire drug development process.

In addition to having a strong team of highly intelligent and well-versed experts leading this effort, it is equally important that this be cross-functional, possessing both a deep breadth and depth of knowledge and experience. In order to ensure your submission is complete and of the highest quality possible, having experts from every specialty area (i.e., nonclinical and toxicology, clinical, biopharmaceutics and clinical pharmacology, chemistry, manufacturing, and controls (CMC), etc.) on your team is a must.

## 3. make full use of type b meetings with the FDA

Type B meetings are routine meetings between the FDA and a Sponsor that occur at various, pre-defined milestones, including:

- Pre-Investigational New Drug (Pre-IND) Application meetings
- Certain End-of-Phase 1 meetings
- End-of-Phase 2 (EOP2) and pre-Phase 3 meetings
- Pre-New Drug Application (Pre-NDA)/biologics license applications (Pre-BLA) meetings

These meetings are not required by the Agency but are ***strongly*** encouraged by both the FDA and ProPharma. Type B meetings are intended to engender the Agency's assistance and cooperation. These meetings allow the reviewers to fully understand the Sponsor's objectives and provide the Sponsor with an understanding of the Agency's expectations. During these meetings, Sponsors are able to seek clarification on specific points and questions they may have, thus decreasing the risks associated with submitting an application to FDA.

When conducting these meetings, it is important that Sponsors do everything in their power to make the meeting as successful as possible. How do you do that? A few points to keep in mind include:

- The meeting should build on an existing strategy.
- Prepare your questions in advance, and make sure they are worded in the appropriate format. The FDA will not answer open-ended questions, so anything a Sponsor asks should be posed as a yes or no question.
    - Correct format = "Is the current nonclinical data sufficient to support the NDA?"
    - Incorrect format = "What additional data do we need?"

## 3. make full use of type b meetings with the FDA *(cont.)*

- The briefing document that is submitted in advance of the meeting should support the questions the Sponsor intends to ask the Agency.
- Ensure the right meeting attendees have been selected.
- Preparation is key to conducting a successful meeting; thorough preparation includes pre-meeting teleconferences and face-to-face rehearsals.
- Do your research on the individuals you are meeting with. Make sure all the Sponsor attendees understand the background of the FDA's attendees.
- When you receive the FDA's Preliminary Comments, an immediate and thorough analysis should be completed.
- It is extremely important that you listen to and respond to any and all advice that the Agency provides.
- Prepare and submit Sponsor Responses in advance of the meeting, narrowing the talking points and focusing the meeting agenda.
- During the meeting:
    - Make sure you keep your overall regulatory strategy in mind.
    - Follow the script that you prepared in advance and rehearsed.
    - Be confident in the case you are making.
    - Understand your flaws and don't try to gloss over them or minimize them – *the Agency will notice!*
    - Keep the meeting as collaborative as possible.
    - Be direct and serious in any comments that you make.
- After the meeting, all attendees from the Sponsor should immediately conduct a debriefing and the Sponsor's meeting minutes should be prepared and submitted right away.

## 4. create and maintain a risk map

A risk analysis is a structured list of all possible future events that could result in a disruption to the overall project plan. Conducting a risk analysis allows Sponsors to minimize or eliminate known risks, resulting in accomplishing project milestones according to the pre-planned timeline.

When completing this task, you should start by listing all major risks that you know of. After all risks have been documented, you will rate each item as high, medium, or low risk regarding impact and probability. For certain risks, you will determine the steps you will follow to mitigate these risks from occurring, which will then be added to the overall action plan.
As you complete the risk analysis, you should be working to compile a risk matrix (example below) that comprises all risks as well as the impact, probability, and mitigation plan for each.

| description of risk | impact H, M, L | probability H, M, L | how to mitigate risk |
|---|---|---|---|
| **CMO has difficulty making the product** | High | High | Engage a manufacturing specialist to solve the problem |
| **FDA may require clinical trial to validate efficacy** | High | Medium | Locate existing literature to validate efficacy |
| **There may be quality issues with clinical data** | High | Medium | We will implement a GCP audit program |

## 5. communicate effectively

As with most things in life and drug development, communication is key. As such, planning how you intend to keep various groups of stakeholders informed, both internal and external to your organization, is essential to the success of your drug development program. Your communication plan should include a schedule that defines the actions you will take to communicate team activities to the rest of the organization. The purpose of having a plan of this nature is to:

- Minimize project roadblocks
- Encourage participation outside of the team
- Enable future teams to get started quickly
- Allow senior leadership to make rapid decisions

When developing a communication plan, the first step is to identify the key stakeholders that are involved. From there, you will need to define the message(s) for each group, select media for each stakeholder, and schedule events. When complete, the final product should be a matrix (as shown below), which defines the message, media, and schedule for each stakeholder.

| stakeholder | message | media | schedule |
|---|---|---|---|
| **Investors** | Regulatory Strategy is Sound | PowerPoint, Face to Face | One Meeting |
| **CEO** | Project Status,<br>Milestone Update | Milestone Report | Quarterly |
| **FDA** | We are Scientifically Sound and Responsive | Approval Process | Responding to FDA |

## 6. begin with the end in mind

Perhaps the most important topic of all, in our opinion, is beginning with the end in mind. At the initial outset of your project, you have a goal in mind. You can almost see exactly what you think accomplishing that goal will look like. Beginning with that end goal, and working backward to figure out how you will accomplish that goal – using science, of course – is the best way to successfully achieve that goal.

In order to do this when preparing and submitting your NDA, the best way to start is to use the Common Technical Document (CTD) table of contents. For each item listed, the first step is to determine and document the current status. This will help you define exactly what needs to be developed. From there, you can then determine who will be writing the content that is needed and identify any dependencies that exist; for example, the drug product specifications must be completed before nonclinical.

It is absolutely critical to ensure that each label claim **must** be supported by scientific evidence. Also, all team members must clearly understand the critical path in order for the project to be successful.

Developing an NDA submission is the most challenging and time- and labor-intensive aspect of drug development. Everything must be exactly right in order to obtain FDA approval. This can cause a large amount of stress and anxiety for your team, which can end up resulting in errors. Working with a team of science-minded

# 6. begin with the end in mind *(cont.)*

regulatory experts is the surest way to avoid trivial mistakes and ensure the highest quality application is submitted to the regulators. Our team works with the FDA and its regulators on a daily basis. We are scientists above all else, and we know the FDA's regulations and expectations like the back of our hands. Regardless of where you are in the development process or what your geographic location is, we can help with all FDA and EMA-related regulatory needs.

## FDA submission expertise

ProPharma has a proven track record of helping our clients obtain NDA approval by determining the appropriate regulatory pathway and assisting with developing and submitting the application to the FDA.

We will work with you, guiding you through the entire process of preparing and submitting your NDA using our vast knowledge of and extensive experience working with the FDA to create a seamless filing process.

### improve the health and safety of patients.

From early concept development through each clinical phase, product launch, and commercialization, we partner with pharmaceutical, biotechnology, and medical device clients to tackle complex challenges. We help to ensure regulatory goals are met, business objectives are achieved, and patient health and safety is improved.

Contact us to learn how our experienced team can help ensure successful outcomes throughout the product lifecycle


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