ChemWerth

A NEW LOOK AT ANDA APPROVALS

Exploring how inadequate U.S. FDA Type II Drug Master Files are one of the leading causes of delayed ANDA approvals.

Missed commercial product launch schedules. Project delays. Drains on both human and capital resources. The impacts of inadequate initial Drug Master File (DMF) submissions for Abbreviated New Drug Applications (ANDAs) are clear. But with an understanding of why these submissions are often returned on first pass and some of the most common mistakes, strategies for avoiding these issues can be even clearer.

INADEQUATE FILINGS FOR ANDA ARE NOT THE EXCEPTION. THEY'RE THE NORM.

While all organizations strive for a successful FDA approval of their ANDA on first pass, it's a lot less common than you might think. In fact, while DMFs supporting new drug applications enjoy a first review adequacy rate of better than 80%, the first review adequacy rate for DMFs supporting ANDAs is only 12%. Ultimately, ANDA approvals are delayed and commercial product launch schedules are missed. At best, market share is surrendered and operating profit targets fall short. At worst, entire projects are shelved and ROI is negative.

In many cases, inadequate filings also generate additional questions from the FDA that never would have been raised had the original DMF been completed correctly the first time around. This means the filer needs to deal with even more difficult deficiencies. Responding to DMF deficiencies is onerous, labor-intensive and time-consuming. On average, DMF deficiencies take the DMF holder 90 days to respond. This can take a toll on both human and capital resources. Having to deal with the deficiency could lead to the next scheduled project being delayed as well.

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WHAT GOES WRONG?

Inadequate DMF filings can happen for any number of reasons.
Still, the issues can typically be categorized under FIVE major root causes:

1. FAILURE TO STAY CURRENT WITH FDA PRACTICES AND GUIDELINES

The FDA is the most rigorous, bureaucratic, heavily regulated and process-intensive agency of the federal government. And for good reasons — the health and safety of people. Adding to the complexity, the FDA's practices, procedures and protocols evolve and change continuously. This puts pressure on ANDA filers to stay current on DMF requirements or risk filing an inadequate DMF. Companies that file without a regulatory expert reviewing their DMF prior to an FDA submission run the inevitable risk of getting a DMF deficiency simply because they did not follow the latest FDA guidelines and protocols.

2. **INEXPERIENCED STAFF UNDERESTIMATES THE RESPONSIBILITY**

Virtual companies tend to undervalue the technical regulatory expertise required to file an adequate DMF. Often these companies assign the DMF filing task as a special project to an employee who lacks the requisite experience necessary to complete this mission-critical assignment. More than likely, the inexperienced employee will miss essential preemptive data needed to satisfy the FDA.

3. **POOR COORDINATION BETWEEN THE DMF HOLDER AND ANDA SPONSOR**

Many ANDA sponsors receive DMF deficiencies because the Active Pharmaceutical Ingredient (API) information in the DMF holder's submission is inconsistent with the API-related information found in the ANDA. Open and transparent communication between these parties should begin prior to the initial submission, and continue after the deficiency is issued. Without continual dialogue between the DMF holder and the ANDA sponsor, it is likely that the initial deficiency response will be uncoordinated — thus, making the likelihood of a second rejection almost certain.

4. **ADOPTING A "DEAL WITH IT IF WE GET A DEFICIENCY" MENTALITY**

Too many companies fail to generate the data necessary in advance of the DMF submission deadline to ensure it can stand up to an FDA scientific review. Shareholders would cringe if they knew the number of DMF deficiencies generated by the FDA because the ANDA sponsor failed to apply a "stress test" prior to their FDA submission and instead had adopted a "deal with it later" attitude. Companies fail to conduct proper gap analysis with special attention to justification for specifications, impurities and starting material. Be assured that the FDA will perform the gap analysis, and they'll find what you missed.

5. **FAILURE TO RECOGNIZE AND PREPARE FOR FDA RED FLAGS**

DMF holders who don't address the two most common FDA deficiencies with sufficient supporting detail will often find themselves responding to their deficiencies in even greater detail the second time around. Take note that starting material selection and genotoxic impurity issues are two of the FDA's high-value deficiency targets. Extensive justification for API starting material must be robust in the DMF, and appropriate methods must be developed and explained for genotoxic impurity evaluation to be credible.

EXPERTISE AND EXPERIENCE

So what does make for a successful ANDA? What do the fraction of companies that keep their ANDAs on schedule have that others don't? The answer is simple. They have API suppliers with two essential characteristics: expertise and experience.

Full-service API suppliers, such as ChemWerth, employ teams of regulatory and compliance experts with years of experience working with the FDA. ChemWerth routinely gains DMF approval on the first pass and is among the best-in-class companies that are in the 12% approval group.

Having filed more than 500 DMFs in 38 countries, ChemWerth actively stays current on changing global regulatory guidance, on all GDUFA requirements and how those requirements tie into the ANDA sponsor's approval. Knowledge gained from previous DMF filings is continuously applied to each new DMF. Updated and standardized templates help prepare and organize each DMF section, and a thorough stress test is applied from administrative and scientific viewpoints.

ChemWerth's regulatory experts proactively work with the company's manufacturing partners to track and document the manufacturing process from starting material acquisition to exhibit batch production. As a full-service supplier, ChemWerth stays in constant contact with its finished dosage partners to ensure consistency and accuracy in all communications. Prior to the ANDA being filed, ChemWerth ensures the DMF has been fully vetted and is in sync with the ANDA filing.

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There is simply no substitute for experience.

Trust your ANDA to an expert.

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