

Understanding the RTF Letter

Practical guidance on what the FDA is looking for, and how to avoid receiving one

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Introduction

The development of new treatments, both drugs and biologics, is a long and arduous process, which can take many years. After the pre-clinical and clinical programs are successfully completed, the company makes a submission to the U.S. Food & Drug Administration (FDA). The subsequent FDA review, if everything has been done correctly, and the efficacy and safety data are supportive, can be completed within six to twelve months.

There are, however, two major obstacles to getting approval and market authorization. One is the Complete Response Letter, which comes at the end of the review and details the reasons why the submission does not support approval. These reasons typically relate to concerns that cannot be avoided due to safety issues or lack of efficacy. The other one is the Refuse-To-File (RTF) letter which comes at the beginning of the review process and is issued if the FDA reviewers deem that, upon initial review, the quality of the submission does not justify a detailed review. This paper focuses on the RTF process and describes how an RTF letter can be avoided.

Background

Once a submission for approval is made, the FDA does a preliminary review to determine if it would be a good use of its resources to perform an in-depth review of the submission or whether such a review could lead to multiple review cycles and to extended timelines and excessive and the unnecessary use of manpower on its part.

In the FDA Manual of Policies and Procedures document MAPP 6025.4, Good Review Practice: Refuse to File, in which the FDA describes the initial review process and, more importantly, the types of issues that can lead to an RTF letter, the FDA states that the upside for a company of this review is that an RTF letter can allow the applicant to begin repairs of critical deficiencies in the application far sooner, and therefore, it may lead to a more rapid approval.

That's the good news. The bad news, however, far outweighs it. It may lead to a more rapid approval, but the data suggests that it may lead to a much longer overall review process and may point to a high probability of ultimate rejection. Then there is the impact on the company's reputation. First, with the FDA: having got off to a bad start, the company has ground to make

up. It may cause the FDA to examine any current or future filings from the same company more closely. It also has a negative implication for any partnership or in-licensing discussions that are ongoing. Potential suitors are going to be put off by such a setback. Perhaps most dangerous of all, there is the impact on the street, which fears the unknown when an RTF announcement is made, particularly if no details are given and no remediation path is outlined, as is often the case. Or, the remediation path is a long and arduous one, such as performing another pivotal study, which, in the case of smaller companies, will not only delay revenues, but also drain precious resources. There are many companies that have suffered a large one-day stock price loss on the day of an RTF announcement. For example, Catalyst and their 37% decline on Day 1.

It is not just the small, inexperienced companies that suffer an RTF setback. Cases in point: Allergan and Celgene. In September 2017, Allergan announced that, upon its preliminary review, the FDA determined that the sNDA for Vraylar in the treatment of negative symptoms was not sufficiently complete to permit a substantive review, with no further details given. More recently, on Feb. 27, 2018 after the market closed, Celgene announced that it had received an RTF letter for ozanimod, its Multiple Sclerosis treatment, because the non-clinical and clinical pharmacology sections were “insufficient to perform a complete review.” Celgene’s stock price went down over 6% the next day.

So, the consequences of an RTF letter can be dire, and even the large companies can have missteps.

Understanding What the FDA is Looking For

In their MAPP 6025.4 referenced above, the FDA details the reasons for refusing to file a submission for detailed review. The appropriate code is CFR 314.101(d)(1)-(9). However, except for sub-section 3, the reasons given are reasonably self-explanatory, such as lack of a completed application form and lack of accurate and complete English translations. Section 314.101(d)(3) allows the FDA to refuse to file an NDA if the application is incomplete because, on preliminary review, it does not contain the specific required information. Importantly, the MAPP also states that CDER has interpreted the sub-section to permit it to refuse “an

application when required content is presented in a form that makes it inaccessible.” The document then describes the Policy used by CDER staff to determine the “reviewability” of the submission and, therefore, if the submission is suitable for in-depth review or if an RTF letter is required.

Of the five policy statements, the most significant and open to interpretation is that CDER staff will refuse to file “Materially incomplete or inadequately organized applications that would not permit timely, efficient, and complete review by all relevant disciplines...” To give more substance and therefore allow companies to anticipate the type of issues covered by the unclear terms “materially incomplete” and “inadequately organized,” further details, along with examples, are given of the types of filing issues that can arise. They are divided into Potentially Easily Correctable Deficiencies and Complex Significant Deficiencies that preclude correction before filing. It is very important to understand the difference between the two types of issues, as the FDA’s understanding of what constitutes a ‘complex significant issue’ may not be intuitive.

Potentially Easily Correctable Deficiencies include electronic navigational problems, electronic incompatibility with the FDA’s systems, and small amounts of missing data (e.g. collected but not submitted). Although encouraging, this category should not be misinterpreted. There is no threshold as to what constitutes a “navigational problem” or a “small amount of data,” so these deficiencies can still lead to an RTF letter. At a minimum, they will cause delays in the filing and could lead to a negative impression of the company’s preparedness with the FDA.

The list of Examples of Complex and Significant Deficiencies that may provide support for an RTF action is much longer than the list of Potentially Easily Correctable Deficiencies.

The first category is missing sections; this is very straightforward.

The second broad category is related to incomplete sections or sections that are unable to be reviewed. This category has many entries, the first one being “Application is unreasonably disorganized,” which leaves a lot of room for interpretation. Among the more specific examples are data tabulations (line listings) and/or “graphical displays are not interpretable....”

problems with hypertext links (an example of the need for care when interpreting the FDA's two types of issues as this could be classified as a "potentially easily correctable deficiency"), and omission of critical statistical analyses without adequate justification and explanation, such as an analysis accounting for all clinical trial subjects (what does "critical" mean? Again, open to interpretation).

The third broad category is failure to include evidence of effectiveness compatible with statute and regulations. This can be the death knell for a submission, even for a company, or at least be the beginning of very lengthy and expensive delays. Examples are: lack of any adequate and well-controlled trials, use of a trial design that is inappropriate, reliance solely on trials that fail to achieve statistical significance without adequate justification, and use of a statistical analysis plan that was finalized after data unblinding. An issue in this category is almost certainly going to require extensive discussion and an additional trial or trials.

The fourth category is that, despite adequate and well-controlled trials having been submitted, the content is deficient in other aspects, resulting in the omission of critical data, information, or analyses required. This can be broadly split into two sub-categories: failure to collect the critical data required for safety and efficacy assessment and failure to perform all the necessary analysis and evaluation of the data collected. It is very unlikely that an RTF letter can be avoided in either case. It may be possible to minimize the cost by collecting data that is available but was not submitted, and by performing the required analyses and evaluations retrospectively, provided the FDA will allow the development of the required statistical analysis plans post-unblinding.

The last category relates to electronic datasets, technical issues, and quality issues. Datasets will be reviewed for appropriate organization, formatting, and general coding inaccuracies. Examples of issues given are: absence of important variables in the primary efficacy data file, lack of unique subject ID for each subject throughout the submission (this sounds straightforward but subjects can participate in more than one study), incompatible structures that prevent merging of datasets, missing datasets, datasets containing transcription, or other errors, preventing an independent data review, and reducing confidence in the accuracy of the captured.

Key components of datasets that must be present are:

- Define.pdf and define.xml
- List of codes used in a database
- Data source references for graphs and other displays
- Acronyms and abbreviations
- Concomitant drug dictionary usage
- Legible scanned CRFs where required.

This last category shows the importance of giving high priority to producing high quality and comprehensive electronic datasets and accompanying documentation. This is important to the FDA because the datasets and documentation are critical for their statisticians who use these datasets for their own statistical analysis to come to their own conclusions about the safety and efficacy of the treatment. Therefore, it is not surprising that issues in this category are considered “Complex and Significant Deficiencies.”

Examining the Impact

The FDA does not provide information publicly that can be used to analyze the actual reasons given for an RTF action. Such information is difficult to obtain as companies will not necessarily give the reason for the receipt of an RTF letter, and if they do, it is very unlikely that the full reason will be given.

Matthew Herper, in his Feb. 28, 2018 Forbes article about Celgene’s RTF letter for ozanimod, gives as much detail as is known for 45 examples of RTF letters for biologics since 2001. In some cases, no further detail is available. In others the reason is vague, such as ‘insufficient information in application’. Sometimes the RTF action is definitive and is the signal for a large amount of extra effort before the file can be resubmitted (examples being two-pooled studies not representing proof of efficacy, the trial did not establish efficacy, and a new clinical trial being needed). In these three cases, two approvals were obtained, but only after 1003 and 1240 days. In the third case, there has been no approval after seven years. In some cases, there are issues with the data (for example, manufacturing issues). In several cases, the reason given is related to format or data inclusion issues. Some examples are: software issues with

electronic application, inconsistencies and omissions in the drug's database, format issues with the electronic submission, data integrity issues, reformatting and reanalysis needed, the presentation of data sets needs modification, deficiencies in formatting, and formatting issues (x2).

Herper's analysis shows that, as of the end of February 2018, 21 of the 45 affected submissions had still not led to an approval. Of the 24 approvals, the median time to approval was 839 days, and only 14 were achieved after at least two years.

Avoiding the Refuse-To-File (RTF) Letter

As can be seen, there are many reasons for an FDA RTF action, both hypothetical and real. There are a lot of parallel activities that a company can undertake to reduce the likelihood of receiving an RTF letter: planning, FDA communication, focusing on core competencies, partnering, constant vigilance and course adjustment, quality and standardization.

The regulations (although not crystal clear), together with the MAPP (which is open to some interpretation), give a very good checklist of what is required in all sections of the file, both in terms of content and structure. Use them as a solid framework for the overall development plan. Map everything out in detail from the beginning. Get an independent review of the plan to verify that, if all parts of the plan are performed correctly and the results are as expected, then not only will the file be accepted, but also the overall review process should be a smooth one.

Partnering with the FDA may be too strong a term, but it is not in the FDA's interest to delay a review or waste their time doing a preliminary review when an RTF letter is inevitable. Close communication is extremely beneficial to both parties throughout the process. Discuss all aspects of the plan as much as possible, at a minimum at critical milestones. One of these is the End of Phase II meeting, where the Phase III program is discussed and agreements on the key elements of the Phase III program can be made and documented, particularly any deviations from normal practice (e.g. the agreement that only one pivotal study is needed). Another is the pre-NDA/BLA meeting where the full content of the submission is usually presented; clarification on the format and presentation of the data can be obtained here to facilitate a

smooth review. Agree the statistical analysis plan, including any contingent analyses in case the results are not as expected, with the FDA as early as possible, especially before database lock for the pivotal studies or before the first interim analysis (if at least one interim analysis is being performed). Discuss the electronic submission with the reviewers and demonstrate the navigation of the files and the datasets well ahead of time to allow for changes to be made before filing.

Focus on building the right competencies in-house. Focusing on the wrong things wastes money, consumes time, and distracts attention. Have people in-house who are experts in the overall regulatory process and in the specific requirements for each of the required functions, including Clinical, Biostatistics, Data Management, and IT. The FDA is going to prefer dealing directly with members of the sponsor company rather than with representatives of a third party. However, there is no need to build the required infrastructure in-house, and for smaller companies, building large operational and technical capabilities should not be considered due to the very large investment and the inevitable shortcomings of any in-house developed technologies.

Partnership could take two forms: co-development with a larger, more experienced, company or partnering with a reputable, experienced CRO.

The former has the benefit of an infusion of cash and expertise. Also, it could mean the availability of the required technical capabilities without investment. Although, it usually means giving up control of the development, or at least needing to reach time-consuming compromises, which is difficult for the smaller partner. Also, it means giving up revenue in the future. As seen in the Allergan and Celgene examples, working with a larger company is not a guarantee of success.

Working with a well-established CRO allows the company to maintain control while benefiting from the input of individuals with considerable expertise in drug development and regulatory submissions. Such CROs have already developed the capabilities, both in terms of staff at all levels and the technology required, to run global clinical trials and assemble large regulatory submissions. The downside is the regular outflow of cash, but this has to be weighed against the loss of control and the loss of potential future income. Also, there is a

feeling that there will be conflicting priorities, meaning either a lack of assigned resources or lack of the right resources, but this can be handled in the contracting process, ensuring dedicated resourcing and company input on the selection of key individuals.

Constant vigilance is required at all levels. There need to be regular in-depth checks that the plans are being executed correctly and the inevitable issues are being anticipated before they occur through robust risk management. Do not accept a verbal “everything is fine.” Probe deeply, and perform Quality Audit (QA) and Quality Control (QC) inspections of the in-progress submission assembly to identify RTF risks, using independent reviewers. Be prepared to make hard decisions. If the data does not support a filing or is borderline at best, discuss with the FDA as soon as possible. Do not make a submission if it is almost certain that the FDA will issue a material RTF letter. It may be tempting to take the positive recognition for having made a submission, but the negative reaction to the inevitable RTF letter, and the subsequent delay in the approval process, is likely to be stronger and will certainly last longer. The positive recognition may enable smaller companies to get further investment, but the legal implications of knowingly making a doomed submission are considerable.

Quality is key. Build it in at the outset and maintain it throughout. Minimize missing data on an ongoing basis; obtaining missing data after the study is a very time-consuming and expensive process, which usually results in poor quality, even if it can be obtained. Test everything; better to have zero failed hyperlinks than getting into a discussion with the FDA about how many failed hyperlinks constitute a significant deficiency. Perform independent quality checks but hold individuals and your partners accountable for first time quality. A key component of quality, and of efficiency, is standardization. Use the Clinical Data Interchange Standards Consortium (CDISC) data standards, use standard analyses, and use the FDA’s standard formats. If possible, get agreement from the FDA that the electronic datasets and the associated navigation and documentation are acceptable before the submission through test datasets. Be innovative with the science; be innovative with the technology used to assemble the dossier, but not with its content. The FDA is looking for a seamless navigation of a comprehensive robust file which adheres to all the regulations and statutes.

A summary of the steps to be taken is provided in Appendix 1. Refer to this regularly throughout the development process.

The Ancillary Benefits to a Proactive Approach

By taking all the proactive steps in the previous section, the likelihood of an RTF letter is very small. In addition, these steps have other benefits.

A collaborative spirit will have been built up with the FDA reviewers, which should ensure not only a prompt acceptance of the file, but also ensure that the momentum can be carried forward into the full review as the reviewers will know exactly what they are receiving and can focus on doing their job rather than dealing with deficiencies.

By planning and building a submission on an ongoing basis, there is the ability to perform internal and external integrated reviews of the data, along with the format and content of the file. Nothing should ever be submitted to the FDA in a format that the company is not familiar with. This also means that questions from the FDA can be answered efficiently during the review as the company and its partner have an intimate knowledge of the data, its format, and the analysis programs.

The implementation of the dossier on an ongoing basis will also be attractive to potential partners or in-licensors. If it is decided that partnering with another biopharma company or out-licensing the product is at least a consideration, the existence of a robust developing submission, in particular the electronic components including the datasets, will be a major differentiator. It will enable the streamlined review of the data and increase the overall credibility of the company.

Conclusion

Refuse-To-File letters are generated for many different reasons - a few readily solvable, some insoluble, some extremely objective, some subjective - but the impact of such a letter is always negative, embarrassing at best, catastrophic at worst, and always a delay in the review process.

However, in all cases, they can be avoided by collaboration with the FDA, adherence to the guidelines, high quality execution, constant vigilance and realistic decision making.

Appendix 1: How to Avoid an RTF Letter

1. Plan

- a. Follow the Regulations
- b. Follow the MAPP
- c. Build in Check Points
- d. Identify a 3rd Party Consulting Organization
- e. Have an Independent Review Performed

2. Communicate with the FDA

- a. Establish Contacts Across Functions
- b. Conduct an End of Phase II Meeting
- c. Conduct a Pre-NDA/BLA Meeting
- d. Document All Agreements

3. Focus on Core Competencies

- a. Ensure In-House Functional Expertise
- b. Outsource Non-Core Competencies
- c. Do Not Build Technical Infrastructure

4. Partner

- a. Establish Contacts Across Functions
- b. Conduct an End of Phase II Meeting
- c. Conduct a Pre-NDA/BLA Meeting
- d. Document All Agreements

5. Constant Vigilance

- a. Perform Regular Senior Management In-Depth Reviews
- b. Have QA & QC Performed by Consulting Organization
- c. Make Mid-Course Corrections
- d. Do Not File if an RTF Letter is Inevitable

6. Quality

- a. Test Everything
- b. Hold Staff and Partners Accountable
- c. Use Industry and FDA Standards
- d. Agree Dataset Format, Navigation and Documentation with FDA Beforehand

About the Author



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Hugh Donovan has over 40 years of drug development experience. He has managed Biostatistics, Data Management and Programming groups in medium-sized pharma, large-sized pharma, small biotech, large biotech companies and large CROs, in both Europe and the US. Most recently, he oversaw a Global Data Operations group of over 2,000 people in ten different countries. He has been responsible for data in over 25 FDA submissions, and 0 RTF Letters.

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