Complete Response Letters[1]

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Introduction

Complete Response Letters ("CRLs") were created in 2008 to replace the old "approved," "approvable," and "not approvable" letters the FDA had previously used as a first response to a drug application. CRLs are intended to enable the FDA to provide applicants with a more exhaustive description of deficiencies identified in an application without tipping their hat as to the ultimate approvability of the application. This benefits the applicant, as "not approvable letters" had become a barometer investors and shareholders used to judge the likelihood of a drug applications' ultimate approval. Since this could lead to a lack of funding for a drug that might otherwise be approved, the CRL was created as a neutral response to an application that is not immediately approved.

Applicants, however, should be aware that CRLs are important documents to a drug application's success or failure. Furthermore, in order to maximize the chance for an application's approval, applicants must be aware that: CRLs must be dealt with in a timely fashion; *how* an applicant responds to CRLs is just as important as responding in the first place; how CRLs are disclosed to investors or shareholders carries significant regulatory repercussions; and, how applicants approach and use CRLs can be very different from why the FDA issues CRLs.

I. The Drug Approval Process

<u>The FDA's Mission: Ensuring the delivery of safe food, drugs, and cosmetics to the public.</u>

The FDA protects the public health by ensuring the safety and efficacy of foods, human and animal medicines, medical devices, dietary supplements, and cosmetics.[2] But what does, in the context of drugs, "safe and effective" really mean? No drug is 100% safe or effective, and most have a number of side effects. Some side effects appear only after years of chronic use—and some develop only mild side effects or none at all. Many drugs work better in some patients than in others—and may not work at all in others.

Thus, since no drug is ever perfectly safe or effective, the FDA is tasked with determining when the benefits of a drug outweigh its disadvantages. On an even more challenging level, the FDA is forced to predict whether the *future* benefits of a drug will outweigh its *future* disadvantages. If the FDA is too conservative in approving new drugs, then consumers are denied access to much-needed medicines, however, if the FDA is too liberal in approving new drugs, then consumers will be exposed to risky medicines. It is in striking a balance between these two extremes that the FDA reviews drug applications to approve or deny new drug applications, thereby affecting these drugs' availability in the market.

An Overview of the FDA's Drug Approval Process

The approval of a new and novel drug is a long and costly process that proceeds through a number of testing stages: cell, animal and then human testing. After a likely drug candidate is identified by a pharmaceutical company, that drug usually undergoes testing in limited cell-based assays, which are required to justify testing in animals. Animal testing then screens drug candidates for pharmacological activity and acute toxicity. If the results are promising enough, the FDA will allow limited testing of an investigational new drug (IND) in humans through a

[2] Food and Drug Administration, What Does FDA Regulate, April 10, 2014, *available at* http://www.fda.gov/AboutFDA/Transparency/Basics/ucm194879.htm.

phased series of clinical trials. These clinical trials determine whether a drug is safe to administer to humans, whether it is effective in treating a particular disease or symptom, or if it is safe and effective for its intended use. If so, and all other requirements such as those related to chemistry, labelling and manufacturing are completed, the pharmaceutical company designing the drug will file with the FDA a "New Drug Application" or NDA. The goals of the NDA (or ANDA, or Abbreviated New Drug Application, for generic versions of brand-name drugs) processes require an applicant to satisfy a number of requirements.[3] This ensures that the drug is (1) sufficiently safe and effective for its intended use;[4] (2) that the benefits outweigh the risks; (3) that the drug is appropriately labeled; and (4) that the drug will be manufactured with an adequate degree of quality, stability, and purity. If a drug meets these criteria, then it will be granted approval to enter the U.S. market. Finally, even after a drug is approved for the market, the FDA requires additional post-market monitoring and testing of that drug.[5]

II. The Evolution of the Complete Response Letter

Before August 2008, the FDA responded to a drug application in one of three ways:[6]

- Approval letter: The FDA approved the drug application and the drug could go to market. The contents of approval letters were made available to the public at a later date.
- Approvable letter: The FDA could not approve the application as submitted, but might subsequently grant approval if certain criteria were met.
- Not approvable letter: The FDA could not approve the drug application as submitted.

"Not Approvable" letters meant that the FDA had refused to allow a drug to go to market and the interaction between the FDA and the applicant on that application was completed, and if

[3] 21 C.F.R. § 314.50.
[4] When the benefits of a drug outweigh its risks.
[5] Food and Drug Administration, Postmarketing Requirements and Commitments: Introduction, Feb. 8, 2012, *available at* http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/.
[6] Complete Response Letter, 73 Fed. Reg. 39588, 39590 (Food & Drug Admin. July 10, 2008).

the applicant decided to continue developing that drug, when ready the process of applying for market entry would begin anew. In the instance of an approvable letter, the applicant was free to continue his efforts for subsequent drug approval by the FDA working on the criteria noted in the letter. This letter most closely resembles the current CRL process. Regardless, the type of letter had a potentially significant real-world impact on the applicant, completely separate from the application's status with the FDA.

The FDA treated drug applications as confidential until a drug is approved or an approval letter was received.[7] Because approvable letters and not approvable letters issued only when approval was withheld, the FDA neither disclosed their contents to the public, nor confirmed their existence.[8] The applicant maintained complete control over what information was made public. However, the type of letter provided an indication—albeit a very informal one—of the application's chances for eventual success. Drug applications that received "approvable" letters were generally considered as more likely to be subsequently approved than drug applications that received "not approvable" letters. This indicator could directly impact the perceived value of the drug product and the sponsoring drug company. In turn, this could affect the applicant's ability to obtain funding for continued development of the drug candidate, or even funding to address the FDA's bases for not approving the application.

Such economic concerns were some of the FDA's reasons for discontinuing its use of "not approvable" letters: "In the past, some drug manufacturers expressed concern that a not approvable letter sent an unintended message that an application would never be approved, which could adversely affect a company's ability to raise capital."[9] In addition, drugs received a not approvable letter were often abandoned and lifesaving treatments were being lost. FDA

[7] *Id.* at 39606.
[8] *Id.* at 39600-01.
[9] *Id.* at 39606.

recognized the issue and the impact on potentially life-saving treatments and in response created the Complete Response Letter.

The Design and Function of the Complete Response Letter

On August 11, 2008, the Centers for Drug Evaluation and Research (CDER) of the Food and Drug Administration (FDA) changed the way it handles drug applications.[10] Now, drug applications are either approved or they receive CRLs,[11] described as, "a more consistent and neutral way to convey that an NDA or ANDA cannot be approved in its current form."[12] A CRL in no way indicates the relative likelihood of future approval, but instead provides the applicant with a list of issues the FDA has identified in the application as filed, and recommended solutions for those deficiencies.

Like the approvable and not approvable letters, the complete response letter indicates that the FDA cannot approve the drug application as submitted.[13] In generating the CRL, the FDA is directed to perform three steps, each reflected in the contents of the CRL:

- Complete review of the drug application- The FDA is supposed to perform a complete review of all drug applications, plus any amendments it has received.[14]
    - An amendment that was entered during the review cycle might not be included in the review: for example, if an amendment is entered late in the review process.[15] The CRL will identify any amendments that were not reviewed by the FDA.[16]

[10] 21 C.F.R. § 314.
[11] 21 C.F.R. § 314.2.
[12] Complete Response Letter, 73 Fed. Reg. 39588, 39606 (Food & Drug Admin. July 10, 2008).
[13] *Id.* at 39590.
[14] 21 C.F.R. § 314.110(a)(2); Complete Response Letter, 73 Fed. Reg. 39588, 39590 (Food & Drug Admin. July 10, 2008).
[15] 21 C.F.R. § 314.110(a)(2).
[16] It is worth noting that failure to review an amendment makes a review less than complete, and actually allows the FDA to use the amendments as the basis for a future CRL.

- Description of specific deficiencies- When it implemented the CRLs, the FDA stated that they would describe all known deficiencies in a drug application in almost every circumstance.[17]

    - The FDA may identify additional deficiencies in subsequent resubmissions. It is possible that an amended or resubmitted drug application may create new problems that were not present in an earlier submission. If so, the FDA will list those deficiencies as it becomes aware of them in additional CRLs.

    - An applicant's correction of a deficiency may reveal deficiencies that were present in an earlier submission, but not identified at that time. As unfair as it may seem, if a deficiency was present is an earlier submission, but the FDA becomes aware of it in a subsequent submission, that deficiency may be cited in a new CRL.

    - As described above, if the data is inadequate to support an approval, the FDA may forgo the expected review.[18] In that case, it is likely that the list of deficiencies provided may be incomplete.

    - The FDA may describe deficiencies that are inapplicable to the application submitted. Discussed more below, this is an attempt by the FDA to buy time for a more complete review of the application.[19]

- Recommendations of actions for approval- Whenever possible, the CRL will contain the FDA's recommendations for actions that may put the application in condition for approval.[20] The FDA's official policy is to facilitate the approval of new drugs.[21]

    - In some situations, the FDA may be able to identify a problem, but not be aware of any solutions for it.

    - The FDA's recommendations are no more than suggestions. The applicant is allowed, even encouraged, to pursue alternative solutions for deficiencies. The applicant is not required to perform the actions recommended by the FDA to fix a deficiency—the applicant is required to cure the deficiency, by any means.

[17] Complete Response Letter, 73 Fed. Reg. 39588, 39592 (Food & Drug Admin. July 10, 2008).
[18] 21 C.F.R. § 314.110(a)(1).
[19] Again, this process allows the FDA to be less than definitive, and the application may have no closure. For emerging technology companies and smaller specialty pharma companies, a process without closure is costly and often price too heavy to pay.
[20] 21 C.F.R. § 314.110(a)(4).
[21] Complete Response Letter, 73 Fed. Reg. 39588, 39595 (Food & Drug Admin. July 10, 2008).

However, even where an applicant undertakes actions recommended by the FDA, and these actions are successful, the applicant has no guarantee of approval.

III. Responding to a Complete Response Letter

CRLs under § 314.110 were made to "describe all of the specific deficiencies that the agency has identified," in an NDA or ANDA, and may suggest procedures to cure any such deficiencies. 21 C.F.R. § 314.110(a)(1) and (4). Recipients of a CRL have 12 months to respond in one of three ways under § 314.110(b)(1)-(3):

1. Resubmission- The applicant can resubmit the application in its entirety as a response to a CRL, addressing each of the deficiencies described by the FDA in the CRL, using the suggested methods offered by the FDA in the CRL, or by applying the applicant's own solutions. The significance of the changes to the application will grant the FDA from 2 to 6 months of additional application review time.

2. Withdrawal- The applicant can withdraw the NDA or ANDA in its entirety. Note that such a withdrawal is without prejudice and allows the applicant to refile an application.

3. Request an Opportunity for a Hearing- The applicant can request the opportunity to meet with the FDA to discuss whether there are grounds for denying the application under § 505(d) and (j). However, applicants should be warned that these hearings are open and public hearings, and granting the hearing does not bind the FDA to actually reconsider the application.

Id. These responses allow an applicant to respond to a CRL for the purpose of addressing the issues the FDA raise and which would ostensibly be the basis for a rejection of the application. Given that this is how CRLs are *supposed* to function, the FDA has been using them for additional or alternate purposes.

Under 21 C.F.R. § 314.100, the FDA has only 180 days in which to respond to the application. Given the complexity of NDAs and ANDAs, and the volume of applications received by the FDA annually, 180 days is entirely insufficient to adequately and accurately respond in any meaningful way to most applications. As a result, CRLs are regularly used by the FDA in order to "buy time" to review the application and for time to address other outstanding applications. This is evident in the CRLs that many companies see, containing bases for deficiency and citing to guidance documents, for example, that are irrelevant to the application in question. Since even minor changes to the application under the resubmission option in § 314.110(b)(1) will award the FDA an additional 2 months, plus the 12 months an applicant is allowed to respond to the CRL, such letters are a valuable tool in acquiring additional time to examine the application.

Knowing that the FDA uses CRLs for such purposes can help applicants in efficiently responding to them. For example, should an applicant receive a CRL containing references to irrelevant guidance documents or other references, it might be a signal that the application reviewer requires additional time. As such, turning around a quick resubmission of the entire application under § 314.110, as opposed to taking a greater portion of the 12 months allotted to an applicant, may not actually help the application's chances of approval. In addition, the additional year granted to the applicant by the CRL process means the applicant has additional time to correct any real deficiencies in its application, as well as take additional steps to polish the application to increase its chance of being approved.

Responding to a CRL is a complicated process that should be taken seriously and must be completed in a timely manner. As a result, it should only be completed with the assistance of experienced regulatory counsel.

IV. What Deficiencies Appear in CRLs and How Do Applicants Overcome Them?

Most successful drug applications receive only one CRL. A few applications received two, three, or four CRLs.[22] It is typical for CRLs to contain multiple deficiencies and these deficiencies often apply to more than one application section. Drug applications earn CRLs for many different reasons, but the most common deficiencies arise from problems with manufacturing sites, safety, efficacy, bioequivalence, faulty statistics, product quality and stability, and proposed labeling.

Deficiencies Related to the Manufacturing Site

The most common deficiency cited in CRLs from applications approved from 2011 to the present was related to the failure to pass an inspection of an applicant's manufacturing sites. The most frequently cited problem involving manufacturing sites was a failure to maintain current good manufacturing practices (CGMPs). CGMPs are a statutorily described set of procedures a drug, food, or medical device manufacturer must follow that involve testing, record keeping, process requirements and monitoring among other detailed, complex and extensive requirements. Other cited problems included the presence of contaminants or impurities in drug products, inadequately sterile equipment or storage, and insufficient documentation of process controls and analytical procedures.

Most applicants respond by fixing the problems cited by the FDA inspectors; for example, by decreasing contaminant/impurity levels in drug products, testing and verifying the

[22] If the FDA withheld approval from a drug application before August 2008, the application received an Approvable Letter or Not Approvable Letter. After that time, the FDA issued Complete Response Letters for unapproved drug applications. For this analysis, Approvable Letters and Not Approvable Letters are treated as identical to CRLs.

sterility of manufacturing equipment, or supplying required documentation. Fresh inspections by the Office of Compliance confirm that the cited manufacturing deficiencies were cured. In this way, many applicants overcame their manufacturing deficiencies before submitting their responses to the CRLs. Other successful applicants declined to fix the deficiencies in their existing manufacturing sites, opting instead to migrate to a different manufacturer or a different manufacturing site that was acceptable to the FDA. In these cases, the applicants offered an acceptable substitution to replace the deficient component of the application.

Deficiencies Related to Drug Safety

Before any drug can be sold in the United States, its sponsor must demonstrate the drug's safety; specifically, that the benefits of the drug outweigh its risks. An applicant need not show that a drug candidate is safe for all people at all times. Sometimes, drug-related health risks are known before the drug application is submitted or was revealed by independent studies. Most frequently, however, safety risks are revealed by studies submitted alongside the drug application (*i.e.*, efficacy or bioequivalence studies). Of note, our review of FDA-released data on applications that have been made public shows several safety deficiencies were uncovered by supplemental studies submitted in applicants' *responses* to the CRL.

Typical safety deficiencies follow a common scenario: drug candidates are administered in a safety, efficacy, or bioequivalence study. Analyses of these studies reveal that a small percentage of subjects exhibited some common health problem, such as an increased incidence of cancer or cardiovascular events. The FDA then requires the applicant to show whether the potential health problem is linked to the drug candidate. Many successful applicants overcame such safety deficiencies by performing additional clinical tests or studies to show that the

potential health risks are not linked to their drug candidate or some other aspect of the testing. Alternatively, some applicants repeat their clinical studies in a larger group of patients or animals to disprove a link between a drug candidate and a potential health risk. Other applicants merely rely on data from other studies by other investigators to overcome safety deficiencies. Each of these approaches has been successfully used by applicants to overcome identified deficiencies in an application. However, drug applications may receive approval despite confirming an affirmative link between a drug and a potential health risk. The FDA does not require a drug to be perfectly safe—it requires a drug's benefits to outweigh its risks. Perceived health risks can be minimized by several strategies according to the data. Framing risk factors and said effects relative to benefits is a powerful tool for applicants to increase chances of approval.

Applicants may demonstrate health risks are smaller than originally believed or change product labeling to warn of potential health risks. Other applicants receive approval after they agree to obtain additional data about the adverse risks of their drugs at a future date, *after* the drug was sold on the market. Another successful strategy is showing that the drug provides benefits not offered by any other drugs. For instance, some applicants demonstrate the absence of typical side effects, enabling the drug to be used by certain patients that may not be able to use other varieties of a drug or its competitors. Other applicants show that their drug candidate works at lower doses, which may also minimize the occurrence of side effects, or emphasize their drugs exhibit efficacy in patient populations that fail to respond to other commercially available drugs.

Deficiencies Related to Drug Efficacy

The data shows most efficacy-based deficiencies arose when the FDA identified a population that failed to respond adequately to the drug candidate. Some applicants overcome the deficiency by submitting results from additional efficacy studies that show increased or sufficient efficacy in the challenged populations. Failure to overcome sufficient FDA-identified deficiencies occur when an applicant fails to demonstrate efficacy in these populations or produced additional data that confirmed the lack of efficacy in the challenged subpopulations. In these cases, the FDA usually withholds approval of drug use in those subpopulations, but grants approval for drug use in populations where efficacy is sufficiently demonstrated. It is important to note that the instances of approval on Phase II Clinical data appear to be on the rise. However, an approval on only Phase II data for efficacy as a response in a CRL must be compelling, and it is likely that the safety profile of the product will have to be equally as compelling to receive FDA approval.

Deficiencies Related to Generic Drug Bioequivalence

NDAs must show the safety and efficacy of a drug candidate. An abbreviated new drug application (ANDA), on the other hand, seeks the approval of a generic version of an existing and approved drug. Generic drugs are not required to show safety and efficacy of its active ingredient, since those showings of safety and efficacy would have been made in the application of their innovator drug analogs. Instead, generic drugs must show that they perform in the same manner as the innovator drug, despite differing excipients, through bioequivalence studies in order to receive approval by the FDA.

Bioequivalence deficiencies are cured in one of three ways. First, applicants may demonstrate bioequivalence by reanalyzing clinical samples obtained from subjects, if they are

available. Second, applicants may substitute another bioequivalence study for an originally proffered study. While most applicants simply perform new bioequivalence studies, it is possible to submit results from bioequivalence studies already published by other investigators. Finally, applicants may perform safety and efficacy studies in lieu of showing of bioequivalence in an effort to show similarity to the original drug, but increased safety and efficacy.

Deficiencies Related to Product Quality/Stability

Several deficiencies arise from concerns about the quality or stability of a proposed drug product that may be cited by the FDA in a CRL. Some applicants attempt to cure quality deficiencies by decreasing the levels of contaminants, impurities, or degradation products in their drugs. Others perform additional validation studies to show that their drug products possessed adequate purity and stability in spite of the FDA-cited issues. In one case, where the applicant later confirmed the stability of three out of four doses of a particular drug, the FDA granted approval of those three dosages.

Biologic products differ from small-molecule drugs in many ways, but are treated similarly by the FDA in regards to the use of CRLs. In the past, for example, the FDA has expressed concerns about three different drugs derived from biological sources. These drugs posed unique problems with the potential to affect the drugs' quality: differentially glycosylated drug molecules; potential contamination by porcine viruses; or unknown immunogenicity. However, the applicants applied a similar strategy to overcome the FDA's concerns as applicants have used to address deficiencies in small-molecule drugs. They all developed new assays to ensure the quality and stability of their drug products, and agreed to improve or expand those assays after the drugs entered the market. As a result, all three were approved by the FDA.

Deficiencies Related to Statistical Errors in the Application

A number of deficiencies were caused solely by faulty statistical analyses. These deficiencies may be corrected using several different strategies. Some applicants cure their deficiencies by simply performing the statistical analyses correctly, i.e. correcting their math. Some applicants may completely replace a flawed statistical analysis with a second study that was sufficient to show safety and efficacy on its own, but this presets obvious cost and time complications. Other applicants supplement their analyses with data from additional clinical studies performed by them or published by other investigators. In most cases, bad statistical analyses are cured without additional clinical studies.

Deficiencies Related to Proposed Product Labeling

Almost every CRL required the applicant to make changes to proposed labeling, often to implement specific changes imposed by the FDA. In some applications, revisions are required to prevent confusion by doctors, pharmacists, or patients. In few cases, required labeling changes reflect restrictions in the approved drug's use as a result of findings from research studies submitted to the FDA. Applicants overcome these deficiencies by simply making appropriate changes to their labelling and incorporating those revisions proposed by the FDA. While the single most common deficiency, labeling issues are also the easiest to fix.

V. How Do I Overcome the Deficiencies in my CRL?

There is no guaranteed method to overcome the deficiencies in a CRL. However, there are a number of strategies that an applicant can adopt to maximize the chances for a successful response to a CRL.

- A resubmission must address all of the deficiencies identified in the CRL.[23] If not, it will result in another CRL (and a new 12-month or greater review cycle). However, the FDA recognizes that not every problem can be fixed. Sometimes, it is sufficient to merely minimize the problems associated with the drug's use by persuading the FDA that the benefits of the drug outweigh its risks.
- Often, a CRL will cite to guidance documents that, upon review of the drug applicant, are not applicable to the drug product. These guidances should not be ignored, but instead the applicant should explain in the response why those guidances are not relevant to the drug at issue in the application. Again, ignoring a deficiency will simply result in another CRL.

- The FDA categorizes deficiencies by type, but the underlying causes may lie elsewhere. For example, many CRLs cited safety, efficacy, and bioequivalence deficiencies where the studies were adequate, but it was actually the statistical analyses that were faulty. While an applicant could cure these deficiencies by performing new clinical studies, addressing the underlying statistical errors is probably a more efficient alternative solution.

- While there is no guarantee that the FDA's proffered solution to a given deficiency will suit, it is an informed suggestion by a sophisticated party with extensive experience in the drug approval process.

- The FDA does not require applicants to follow the FDA's suggested solutions to fix deficiencies. The FDA has recognized that more than one acceptable solution might exist for any given problem.[24] The FDA has also recognized that the applicant may have information that the FDA doesn't; information that could affect the actions the agency recommends. Instead, the FDA simply requires applicants to fix the problem and has accepted outside-the-box strategies as acceptable solutions for many different deficiencies. However, successful applicants carefully explain how their creative strategies fully address the concerns identified by the FDA.

- The FDA is empowered to waive "any criteria of an adequate and well-controlled study" if an adequate substitute is offered or if compliance with the requirement is unnecessary or impossible.[25] Some applicants cure deficiencies by presenting colorable arguments that the FDA's requirements were impractical or unnecessary. The FDA may grant a waiver if it finds the applicant's compliance with the requirement is not necessary or not

[23] 21 C.F.R. § 314.110(b)(1).
[24] Complete Response Letter, 73 Fed. Reg. 39588, 39595 (Food & Drug Admin. July 10, 2008).
[25] 21 C.F.R. § 314.90.

achievable, the applicant has satisfied the requirement through an acceptable alternative, or "[t]he applicant's submission otherwise justifies a waiver." While the FDA does not dispense waivers lightly, they remain a potential strategy to overcome certain deficiencies.

- Many successful strategies evolve after discussions with the FDA. The FDA assigns individuals to each IND/NDA/ANDA who is to provide helpful feedback to applicants, including feedback when an applicant is trying to develop a solution to a CRL. As with any agency, the feedback is only as good as the person providing it. This does not mean that applicants should not engage in a discussion, but it does mean that the applicant may need to be prepared to design their own strategy with the assistance of regulatory counsel.

VI. Considerations for Request for Opportunity for Hearing:

An applicant may ask the FDA for a hearing on the question of whether there are grounds for a CRL.[26] Within 60 days of the request, or other time period agreed upon by the FDA and the applicant, the FDA will either approve the drug application or else deny approval for one of the reasons listed in 21 C.F.R. § 314.125, such as inadequate manufacturing procedures, false or misleading labeling, issues of drug safety, or failure to correct a deficiency.[27]

If the application is denied, the FDA will provide an opportunity for hearing and the FDA will publish a notice in the Federal Register of an opportunity for hearing about the drug candidate. The applicant and any manufacturer of a similar or related drug product may file a written request to participate in the hearing within 30 days. Failure to timely respond to the notice constitutes a waiver of the opportunity for hearing. Within 60 days of the publication of the notice, the interested parties must submit the studies that justify the hearing, plus factual analyses of those studies. Any interested parties may submit comments regarding the drug application. The Commissioner of the FDA will then review the submitted information and

[26] 21 C.F.R. § 314.110(b)(3).
[27] *Id.*; *see* 21 C.F.R. § 314.125(b).

decide whether to grant a hearing, at which the question of whether there are grounds for denying approval of the drug application will be reviewed.

If there is a hearing, it will be presided over by the Commissioner, a member of the Commissioner's office, or an administrative law judge.[28] These hearings are not public hearings, and appearance and participation in these hearings are governed by 21 C.F.R. §§ 12.40-12.45. There are several potential consequences to opting for a hearing on the approvability of the application:

- The drug application forfeits its confidential status.
- If the drug is not approved upon immediate reconsideration, the identity of the drug and information about its review by the FDA will be published in the Federal Register.
- This option merely provides an opportunity for hearing—it does not actually guarantee that an applicant will receive a hearing. This process has several procedural requirements and if an applicant fails to meet them, the hearing will be denied.
- This option allows competitors to submit comments to the FDA about the approvability of the applicant's drug.
- The opportunity for hearing is open to any applicant with an application for a similar or related drug. It may provide an opportunity for competitors to further the approval of their own similar or related drugs.

A demand for a hearing and the hearing itself are time-consuming and therefore costly. The regulations surrounding these hearings are detail oriented and not always simple. In the end, it is likely cheaper and easier to respond to a CRL.

VII. Considerations for Withdrawing the Application

An applicant may withdraw a drug application at any time and resubmit at a later date without prejudice to the application. If the FDA has identified any deficiencies at that time, it

[28] *Id.* at 39595.

will give that information to the applicant as part of a CRL.[29] If the applicant chooses to resubmit the drug application at a later date, it will be treated as a new submission, which will trigger a fresh 180-day first-review cycle, unlike shortened review cycles available to some resubmissions.[30] Unlike a resubmission, a new submission will also require the payment of fresh drug application fee. It should also be noted that such a withdrawal and subsequent resubmission may have a negative impact on a Company's small business waiver if the Company qualified for such waiver in its first application. While the Act, the Federal Register and the FDA's own Guidances are silent on this issue, it must be considered particularly by those companies for whom the application fee is a nontrivial amount.

Mishandling CRLs and the Risks Posed

The FDA created the CRL to give applicants complete power over application information for the express purpose of removing disincentives against investment in pharmaceutical development.[31] While an applicant has no regulatory duty to disclose the contents of a CRL or even to admit that one was issued,[32] however, if an applicant chooses to use this information in a dishonest way—or even just a careless way—he may run afoul of the law.

Such laws include, with particularly severe and varied repercussions, the laws governing the behavior of corporations and their employees. Securities laws, for example exist to provide legal protections against the disclosure of materially fraudulent information to investors.[33] Publicly-owned companies are required to make certain public disclosures, either annually or at

[29] 21 C.F.R. § 314.65.
[30] 21 C.F.R. § 314.110(b)(1).
[31] Complete Response Letter, 73 Fed. Reg. 39588, 39600-01 (Food & Drug Admin. July 10, 2008), *available at* http://www.gpo.gov/fdsys/pkg/FR-2008-07-10/pdf/E8-15608.pdf.
[32] We do not comment on an applicant's obligations to his shareholders.
[33] *Id.* at 1213-1218.

more regular intervals,[34] and companies may be liable for the disclosure of material misstatements or omissions made in those public documents.[35]

For example, in 2002, Biopure submitted a biologics license application for its product, Hemopure.[36] During the review process, the FDA halted clinical trials of the biologic due to safety concerns and issued a Complete Response Letter. Contemporaneously, Biopure filed several registration statements with the SEC that failed to mention the clinical hold and/or mischaracterized the CRL as a letter "requesting additional information." Biopure raised money from investors though the sales of additional stocks, issuing further fraudulent statements in press releases. When Biopure eventually disclosed the clinical holds and the CRL, the company and its officers faced securities fraud charges by the SEC and additional actions instituted by disgruntled shareholders.

Other pharmaceutical companies have chosen to mischaracterize their communications with the FDA concerning their drug applications.[37] Those companies and their corporate officers have faced charges of securities fraud, insider trading, civil fraud, plus lawsuits from outraged shareholders. The FDA protects the confidentiality of unapproved drug applications so as not to disincentivize investment in developing pharmaceuticals. However, the SEC wields powerful weapons against drug applicants who abuse that confidentiality, which in the case of a CRL, is often too easy to do. An applicant is in a much better position if it chooses to disclose the receipt of a CRL, and if it chooses characterize its meaning or contents, should do so with the careful review of those statements by regulatory and securities counsel.

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[34] 15 U.S.C. §§ 781-nn (2000 & Supp. IV 2004). The Securities Exchange Act of 1994 imposes mandatory disclosure requirements on companies that are publicly trades in the United States.
[35] *See* 17 U.S.C. § 78(b) (2000); 17 C.F.R. 240.10b-5 (2007).
[36] Liora Sukhatme, Deterring Fraud: Mandatory Disclosure and the FDA Drug Approval Process, 82 N.Y.L.R. 1210, 1226-31 (2007).
[37] Liora Sukhatme, Deterring Fraud: Mandatory Disclosure and the FDA Drug Approval Process, 82 N.Y.L.R. 1210 (2007).

IX. Conclusion

The NDA, and ANDA processes are long, complex and expensive, and the CRL is but one step in bringing a drug to market. However, Complete Response Letters, particularly after replacing the old approved/approvable/not approvable letters are important not only to the approval of the drug application itself, but as a source of possible costs and regulatory risks to the company that owns the drug. The issues raised above, if addressed appropriately, can increase the likelihood that the application is approved, while reducing costs and lowering the risks of the application process, but only if the applying company is aware of the nuances of the Complete Response Letter, and the proper way to respond to it.