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NEW DRUG EVALUATION GUIDANCE DOCUMENT: REFUSAL TO FILE

I. INTRODUCTION

FDA's regulations describe certain circumstances in which the agency may refuse to file (RTF) an application (21 CFR 314.101). Among the provisions included in this regulation is 21 CFR 314.101(d)(3), which states, "The application or abbreviated application is incomplete because it does not on its face contain information required under section 505(b), section 505(j), or section 507 of the act and §314.50 or §314.94." This guidance document clarifies the manner in which FDA is applying this provision [(d)(3)] to make refuse to file decisions. Refuse to file decisions may also be made under the other provisions of 21 CFR 314.101 [i.e., (d)(1),(2),(4),(5),(6),(7),(8),(9) and (e)] but are not specifically addressed in this guidance document.

II. BACKGROUND

As part of its program to improve further its management of the new drug review process, CDER has decided to clarify its practices regarding refusals to file applications that do not, on their face, contain information required under FDA's regulations (21 CFR 314.101(d)(3)). In the past, decisions to refuse to file an application under 21 CFR 314.101(d)(3) generally were based on extreme deficiencies, e.g., the total omission of a needed section or the absence of any study that was even arguably an adequate and well-controlled study. More recently, applications have been refused when less extreme deficiencies existed, but when it was clear that the deficiencies were severe enough to make the application not approvable without major modification. CDER has concluded that explaining its current practice so that it is well-understood could substantially improve the quality of NDA submissions and the efficiency of the new drug evaluation process.

The practice of submitting an incomplete or inadequate application and then "repairing" it in the course of an extended review period is inherently inefficient and wasteful of agency resources. It is probably wasteful of limited industry resources as well. CDER has thus applied 314.101(d)(3) to refuse to file applications that on their face are not reviewable and at least potentially approvable as submitted. Accepting an application that is obviously in need of extensive repair is unfair to those sponsors who have fulfilled their scientific and legal obligations by submitting a complete and fully analyzed application. The incomplete application, submitted prematurely, may delay review of the later, more complete application from another sponsor. Moreover, an incomplete or inadequate application that needs several cycles of FDA response and sponsor

repair consumes excessive FDA (and industry) resources. The incomplete or inadequate application generates more "start-up time" as well as extra reviews, letters, and meetings.

An application that has required major repair during review will also usually prove to be one with a prolonged review time, even if the actual agency review was efficient and swift. Given the strong criticism the agency has received for prolonged approval times, it is important to try to ensure that, as much as possible, review times reflect the period of agency effort, uninflated by the time needed for the sponsor to repair an inadequate application. The agency is committed, in response to user fee legislation (Prescription Drug User Fee Act of 1992), to providing a comprehensive action letter to sponsors within 6-12 months of submission; this could be impossible if the application needed substantial repair before it could be reviewed.

Refusal to file an application must be distinguished from refusal to approve the application after full review (not approvable action). The former is, in general, based on omissions or inadequacies so severe as to render the application incomplete on its face. To be a basis for RTF, the omissions or inadequacies should be obvious, at least once identified, and not a matter of interpretation or judgment about the meaning of data submitted. A not approvable action also could be based on critical omissions of data or analyses, but in addition it can be based on an adverse judgment about what was done (e.g., the adequacy and comprehensiveness of the studies or the quality of the analyses of data), or what has been shown (e.g., lack of evidence of effectiveness or evidence that the benefits of the drug do not outweigh its risks). Such judgments would not, in contrast, be bases for RTF, unless based on facial incompleteness.

III. GUIDANCE

Ideally, good FDA-industry IND interactions and use of pre-NDA conferences will continue to improve submissions and identify applications whose submission would be premature, so that all submitted applications will be complete and reviewable. Although CDER will continue to strive for this ideal, CDER should not, in general, accept for full review applications that can be readily identified as not approvable or non-reviewable because of major flaws or omissions.

Although RTF is not a final determination, and is often an early opportunity for the sponsor to develop a reviewable and potentially approvable application, it is a significant step that delays, at least for a time, full review of the application. It is important, therefore, that it be reserved for applications with defects that make the application plainly inadequate, non-reviewable without major repair, or that make review unreasonably difficult. In general, the deficiencies leading to RTF should be objective and straightforward, not matters of subtle judgment, and should not be quickly reparable. Minor defects or omissions that could be repaired after the review commenced and that would not materially interfere with or delay review of the remainder of the application should not lead to RTF. The potential importance of a therapy could influence the amount of delay considered acceptable. It is reasonable to make inquiries of a sponsor during the first 45 days after the application is submitted to see whether minor defects can be overcome, e.g., by asking for explanations as to how to use the index or where a particular analysis may be found.

The RTF is not an appropriate vehicle for dealing with complex and close judgments on such matters as balancing risks and benefits, magnitude of drug effect, acceptability of a plausible surrogate marker, or nuances of study design (although designs that are obviously inadequate may lead to RTF, see below). Rejection of an application for these kinds of reasons should be effected through a not approvable action after a full review.

The agency may, for particularly critical drugs, not use the RTF procedure, even where it could be invoked, or might review parts of a refused application if it believes that initiating the full review at the earliest possible time will better advance the public health.

Where an application contains more than one indication, it may be complete and potentially approvable for one indication, but inadequate for one or more additional indications. The agency may accept for filing those parts of an NDA that refer to the complete submissions for particular indications but refuse to file those parts that are obviously incomplete for other indications. This is consistent with past practices of approving those parts of an NDA supporting one claim but not approving those parts of the NDA referring to other, inadequately supported, claims.

FDA has generally exercised its RTF authority under 21 CFR 314.101(d)(3) in three circumstances:

1. **Omission of a section of the NDA required under 21 CFR 314.50, or presentation of a section in so haphazard a manner as to render it incomplete on its face. The required sections include:**

   a) a comprehensive table of contents (314.50(b));

   b) a summary of the application (314.50(c)) that includes, among other things, summaries of the technical sections, an annotated package insert, and the marketing history of the drug outside the United States;

   c) the technical sections and integrated summaries required under 21 CFR 314.50(d)(1)-(6); among the inadequacies of content, presentation, or organization that would render a section incomplete on its face are such defects as illegibility; data tabulations (line listings) or graphical displays that are uninterpretable, inadequately labeled, or that do not indicate the origins of the data in them; inadequate notation in summaries of where individual studies can be found or inadequate guidance in study reports to the location of individual data and records; absence of protocols for clinical trials; and omission of critical statistical analyses, such as an "all patients" analysis where one is obviously necessary or the statistical analysis described in the protocol; and

   d) required case report forms and tabulations (21 CFR 314.50(f)).

2. **Clear failure to include evidence of effectiveness compatible with the statute and regulations, for example:**

   a) lack of any adequate and well-controlled studies [21 CFR 314.126], including use of obviously inappropriate or clinically irrelevant study endpoints;

   b) presentation of what appears to be only a single adequate and well controlled trial without adequate explanation of why the trial should be regarded as

fulfilling the legal requirement for adequate and well-controlled investigations;

c) use of a study design clearly inappropriate (as reflected in regulations or well-established agency interpretation) for the particular claim, e.g., active control equivalence trials to support effectiveness of an antidepressant; and

d) for a combination drug product, failure to present studies that assess the contribution of each component [21 CFR 300.50].

3. **Omission of critical data, information or analyses needed to evaluate effectiveness and safety or provide adequate directions for use, for example:**

a) omission, without explanation, of animal carcinogenicity studies for a chronically administered drug;

b) omission, without explanation, of animal reproduction studies for drugs that will be administered to people of reproductive age;

c) total patient exposure (numbers or duration) at relevant doses that is clearly inadequate to evaluate safety;

d) clearly inadequate evaluation for safety and/or effectiveness of the population intended to use the drug, including pertinent subsets, such as gender, age, and racial subsets;

e) absence of a comprehensive analysis of safety data, e.g., as recommended in the Clinical/Statistical Guideline;

f) absence of an analysis of data supporting the proposed dose and dose interval; or

g) absence of bioavailability/bioequivalence data comparing the product(s) proposed for marketing with the product(s) studied in clinical trials (if the to be marketed product is different).

IV. IMPLEMENTATION

1. Level of Authority

The RTF authority has been delegated to the New Drug Review Divisions for all original and supplemental NDAs, including NME's, where a not approvable or approval action would be taken only at the Office level. Appeal of an RTF decision to the Office level is permitted. To the extent possible, CDER intends to promote consistent RTF policies and practices across New Drug Evaluation Offices and Divisions. Copies of the minutes of all filability meetings that result in decisions to refuse to file, and any RTF letters, will be routinely sent to the applicable Offices. A Division should consult with the Office on RTF decisions that pose unusual difficulties or are likely to be particularly controversial. Finally, CDER conducts periodic examinations of refusal to file decisions in a manner similar to the procedure developed recently for CDER review of clinical holds (see Federal Register Notice of May 18, 1993, 58 FR 28983). Such procedures include the Center Director and the Ombudsman. The purpose of this periodic review is not to reconsider individual decisions (the actions would have occurred well before the review). Rather, the review is intended to examine the RTF experience considering, among other things, the various Divisions' consistency in applying the guidance, the need for any additional guidance for sponsors on NDA content or format, and any need for modification of the RTF guidance.

2. Records

A record should be made of any internal meeting that leads to an RTF decision; ordinarily this will be the 45 day meeting. The record should include any checklist prepared in advance and a record of decisions. A brief memo will usually be sufficient if there are no deficiencies found. A brief memo will also usually be sufficient if an RTF decision is reached, as the RTF letter should provide a detailed explanation of critical deficiencies.

Each division may wish to develop its own checklist of points to consider regarding the filability of an NDA in a particular drug class. This would augment the general list above. If any aspects of these checklists did more than

clarify the general list, a means of conveying the additional points to pertinent sponsors should be developed.

3. Communication of RTF Decision to Applicant

When an RTF decision is made, the review division should prepare a letter advising the applicant of the decision and the deficiencies that form the basis for the decision. The letter should distinguish clearly deficiencies that 1) are the basis for RTF from 2) other deficiencies that are simply being communicated to the sponsor to be helpful (so they can be corrected) but that would not themselves have led to an RTF decision.

The letter should state clearly that a full review has not been performed and convey the possibility that later full review could identify additional deficiencies.

If a letter describing all of the deficiencies cannot be completed before the sixtieth day after an application is submitted, a letter may be prepared conveying the decision and indicating that the specific deficiencies will be communicated in a separate letter to be issued within two weeks. Generally, a letter rather than a telephone call should be used to notify an applicant of an RTF decision.