David W. Blois, Ph.D.
Senior Vice President
Global Regulatory Policy

Merck & Co., Inc.
West Point PA 19486
E-Mail: david_blois@merck.com
Tel 484 344 2304
215 652 5000
Fax 484 344 2335

September 11, 2003

MERCK
Research Laboratories

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Docket No. 2003D-0317 - Draft Guidance for Reviewers and Industry on Good Review Management Principles for Prescription Drug User Fee Act Products

Merck & Co., Inc. is a leading worldwide, human health product company. Merck Research Laboratories (MRL), Merck's research division, is one of the leading U.S. biomedical research organizations. Merck supports regulatory oversight of product development that is based on sound scientific principles, good medical judgment, and good management practices. Regulators must be reasonable, unbiased and efficient when they review the quality, effectiveness and safety of our products. Ultimately, the public health is best served when therapeutic advances reach patients without unnecessary or unusual delays.

In the course of bringing our product candidates through the drug review process as it has evolved over the years, we have gained experience over a wide range of review practices. On the basis of that experience we are very interested in and, we believe, well qualified to comment on FDA's "Draft Guidance for Reviewers and Industry on Good Review Management Principles (GRMPs) for Prescription Drug User Fee Act Products."

General Comments

1. We believe the goal of the guidance should be to establish guiding management *principles*. There is a heavy focus in the draft guidance on *current review procedures* but whether these procedures represent GRMPs and, if so, what GRMPs are represented by them, is difficult to discern. A summary list of the GRMPs would provide useful focus to the document.

2. Recommendations to initiate certain processes or make certain assignments "as soon as possible" (lines 351-352, 379-380, 442-443, 477-478), or to complete certain actions "in a timely manner" (lines 1379-1382) are not particularly useful in differentiating "good" review management principles. We recommend that, where the timing of certain processes, assignments, or actions is sufficiently important to warrant inclusion in the

guidance, time frames should be included to define the GRMP. For example, if it is a GRMP to assign the regulatory project manager (RPM) "as soon as possible," assignment within a week, two weeks, or a month appear equally acceptable and wide differences between review divisions are likely to occur. If the GRMP is assignment within three business days, the expectation is clear to Division management throughout the Center. In addition to more clearly defined time frames, we recommend including in the guidance parallel GRMPs to describe the appropriate management response when a GRMP time frame is not met.

3. Where the guidance description includes optional approaches there should be discussion to guide selection of one option over the other. In other words, the question, "when would it be a GRMP to follow path A instead of path B" should be answered unless all options represent equally good review management principles in all situations. What factors should be considered? Who should be involved in the decision? For example, the discussion of use of consultants in the review process gives no guidance to help the reviewer in making a decision to seek an internal consult, much less when to request outside consultation.

4. Defining principles of good review management depends to a great extent on the objectives or goals that the principle is intended to achieve and what constitutes a measure of success. The draft guidance doesn't clearly define these objectives. Thus, it isn't clear whether the intent of GRMPs is to manage resources efficiently, to promote earliest possible public access to new products by prompt and thorough review and approval, to achieve both, or to manage to the Prescription Drug User Fee Act (PDUFA) goal date. On lines 23-24, the draft guidance states that GRMPs "are intended to promote efficient and consistent *management* of application reviews." If efficient and consistent management of review is judged only by "actions within goal dates" without regard to increasing the percentage of first action approvals, the public health value of the GRMPs may be small. On the other hand, GRMPs with a focus on the public health benefit of efficient review may well emphasize the importance of the earliest availability of a new therapy for a serious or life-threatening disease for which there are few satisfactory treatment options.

While the guidance mentions the prerogative claimed by FDA to postpone review of amendments until a subsequent cycle to take action within the PDUFA goal date, it does not address potentially mitigating public health circumstances under which FDA might choose to promote earlier access of an important therapeutic advance for patients with serious diseases and limited options. We recommend that the guidance should recognize that, in the case of a significant new product for a serious or life-threatening disease for which limited therapeutic options exist, a principle of good review management would be to *plan* for first-cycle approval through interactions with the applicant that promote prompt amendments in response to Agency requests and a commitment to review these FDA-solicited amendments.

5. The draft guidance includes workload priorities and workload staffing among FDA's criteria for deciding whether to extend the clock on an amendment and whether to review an amendment.[1] We do not consider it a good review management principle for FDA to discriminate between applications on the basis of workload priorities (suggesting that one applicant's application takes precedence over that of another) or staffing (an internal management issue over which the applicant has no control). Significant application deficiencies that are not addressed by the amendment, or amendments that are so complex that they cannot be adequately reviewed in the time available are criteria that may be appropriate for postponing review of an amendment to a subsequent review cycle. In other words, the decision criteria should focus on the best outcome for the particular application, not on external factors.

Under PDUFA, applicants agreed to provide resources to support the review process in exchange for review goals equally applied to all applications. Applicants expect applications to be reviewed under PDUFA on the basis of the merits of the content of their applications and any amendments that are submitted in compliance with regulations and goals. In the spirit of the PDUFA goals, except in rare and unusual circumstances, we believe that the GRMPs governing review of amendments should be that, (1) a major amendment submitted before the final three months of the review period will be reviewed within the review cycle submitted because there is ample review time remaining to review the amended application; (2) a major amendment *submitted within 3 months of the original goal date* that extends the review clock will be reviewed in the cycle submitted, and (3) FDA may opt not to review amendments submitted within 3 months of the PDUFA goal when (a) an extension of the review clock cannot be taken; (b) the remaining review time is insufficient to conduct the review; or (c) the content of the amendment would not lead to approval within the first cycle.

6. Because much of good review management depends on timelines for the initiation of various activities and their completion, it would be helpful to include in the draft guidance a sample timeline for a typical standard review and a typical priority review. While it is clear that every review presents its own unique challenges, this would illustrate a "gold standard" against which a review team could compare its plan for review.

7. The draft guidance does not mention third party review. PDUFA I included language in its definition of the "costs of resources allocated for the process for the review of

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[1] Lines 154-158: "The FDA may decide to defer review of amendments to a subsequent review cycle for several reasons, including, but not limited to, significant application deficiencies that otherwise preclude approval of the application that are not addressed by the amendment, *competing workload priorities, and limitations in resource availability."* (Emphasis added), and lines 912 - 919: "Under PDUFA, major amendments submitted during the last three months of the first-review might lead to a three-month extension of the review clock. The review division retains the authority to determine whether to extend the review clock in response to such amendments. In making this decision, the review division should consider the contents of the amendment, the status of each discipline's review for the application, *the division's workload and staffing*, and the likelihood that review of the major amendment could lead to approval of the application during the first review cycle." [Emphasis added]

human drug applications" that essentially excluded use of PDUFA fees for outside consultants.[2] Negotiations that led to reauthorization of user fees (PDUFA II) included discussion of the use of outside reviewers under certain circumstances, and the language defining the "costs of resources" was revised to allow use of user fees for consultant review of human drug applications. The revised language was preserved in PDUFA III. We recommend inclusion in the final GRMP guidance of discussion that recognizes that outside reviewers may be engaged by the FDA as well as description of conditions under which it would be a GRMP to make use of the option.

Specific Comments

1. Lines 134-135: *"A complete application should contain all required and expected information to support approval of the requested claims, labeling and dosage forms."*

Recommendation: The meaning of the phrase "expected information" requires clarification. For example, if "expected information" is information agreed upon in prior communications with the agency, including the pre-NDA/BLA meeting, in addition to information required by regulation, the guidance should so specify.

2. Lines 160-161: *"In some cases, submitting a complete application may require a decision by the applicant to delay initial submission beyond a corporate target date."*

Recommendation: The reference to corporate target dates appears to represent a supposition by FDA that corporate directives determine the date for filing an application regardless of factors that may affect progress of the development program or the content of the application. This is unfounded and, therefore, it is inappropriate to include in regulatory guidance. The comment should be deleted in preparing the final guidance.

3. Lines 278-282: "*The pre-NDA/BLA meeting package should contain a comprehensive summary of all relevant data generated during the development program, identify pivotal trials and primary endpoints, and discuss all critical and potentially critical issues (i.e., any issues that may affect FDA's ability to review the application and/or approve the product).*"

21 CFR 314.47(b)(2) - *"'Pre-NDA' and 'pre-BLA' meetings"* states in part, *"The primary purpose of this kind of exchange is to uncover any major unresolved problems, to identify those studies that the sponsor is relying on as adequate and well-controlled to establish the drug's effectiveness, to identify the status of ongoing or needed studies adequate to assess pediatric safety and effectiveness, to acquaint FDA reviewers with the general*

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[2] Sec. 735(7) -- "The term 'costs of resources allocated for the process for the review of human drug applications' means the expenses incurred in connection with the process for the review of human drug applications for--

(A) officers and employees of the Food and Drug Administration, employees under contract with the Food and Drug Administration who work in facilities owned or leased for the Food and Drug Administration, advisory committees, and costs related to such officers, employees, and committees...."

information to be submitted in the marketing application (including technical information), to discuss appropriate methods for statistical analysis of the data, and to discuss the best approach to the presentation and formatting of data in the marketing application.... ...(T)he sponsor should submit to FDA's reviewing division at least 1 month in advance of the meeting the following information: (i) A brief summary of the clinical studies to be submitted in the application; (ii) a proposed format for organizing the submission, including methods for presenting the data; (iii) information on the status of needed or ongoing pediatric studies; (iv) any other information for discussion at the meeting."

As stated on lines 224-226 of the draft guidance,[3] and underscored in the language of the regulation, the focus of a pre-NDA/BLA meeting is on the content (identification of studies the sponsor is relying on, status of ongoing studies, and general information to be submitted), and the format for presentation of the data in the marketing application. The pre-NDA/BLA meeting is not intended to be a detailed discussion of study results. The expectation of a "comprehensive summary" of "all relevant data generated during the development program" in the background package for a pre-NDA/BLA meeting is at odds with the primary purpose of the meeting. Indeed, a comprehensive summary may not be available when preparing the pre-NDA/BLA meeting background document.

Recommendation: Sponsors generally develop and submit mock data tables in background documents for pre-NDA/BLA meetings in lieu of tables displaying the actual data in order to show their proposed data layout in the absence of the actual data generated by the program. This has proven to be an effective strategy. We recommend inclusion of such a strategy in the final guidance document.

4. Line 284 - 285: *"The applicant is strongly encouraged to describe both the strengths and weaknesses of a proposed application."*

This section implies a scientific discussion of data results. As noted above, the draft guidance and current regulations describe the pre-NDA/BLA meeting as focusing on the process and the formatting of the application. This paragraph seems to be inconsistent with the earlier statement of goals for the meeting. Further, it would seem inappropriate to expect reviewers to engage in a detailed discussion about the scientific issues and data at this time point, although certain issues could be identified in the context of the discussion of data presentation and formatting.

Recommendation: The draft guidance appears to confuse the purpose of a pre-marketing application meeting by recommending the inclusion of a comprehensive summary of data in the background package and implying that the meeting should include discussion of the merits of the application which, presumably, would be data driven. Where unexpected outcomes occur during the development of a product, it would seem to be a GRMP to

[3] "The meeting should focus on the format of a proposed application and creating a shared understanding between the FDA and the applicant of an acceptable content to support initial planning for efficient review management."

encourage early sponsor-FDA interaction to address their implications rather than wait until the pre-NDA/BLA meeting to do so. Further, given the time available for the pre-NDA/BLA meeting (1 - 1 1/2 hours), engaging in any scientific discussion may take a significant amount of time thereby pre-empting achievement of the primary goal of the meeting.

5. Lines 306 - 311: *"Between the pre-NDA/BLA meeting and the time of submission, the applicant is encouraged to inform the review division if plans for the content or format of the application change significantly. In addition, the applicant should provide the review division with updates regarding the timing of the planned submission. Such information is useful to the review division in assigning projects and effectively managing limited resources."*

Recommendation: It would be useful, both to FDA staff and to applicants, if the guidance described the GRMP by which FDA staff are expected to utilize the information described in lines 306-311 in assigning projects and managing resources.

6. Lines 329 - 331: *"The FDA's recommendations are best followed in their entirety; partial adherence to FDA's recommendations may significantly undermine the potential benefit of presubmission communications."*

Recommendation: This language should be modified in that it implies only one way to prepare the application - the way that FDA has told the applicant to do it. The sentiment should be that there should be a full understanding of FDA's issues or concerns and there should be an agreement in terms of how to resolve them, rather than an expectation that an applicant should blindly follow the FDA's recommendations, particularly if the applicant believes that there are mitigating factors that would support an alternative approach.

7. Lines 343 - 345: *"Upon receipt in the Central Document Room in CDER or the application review division in CBER, an NDA or BLA is assigned an application number. In some cases, a number can be assigned prior to submission if requested by the applicant."*

Recommendation: Clearly, this describes two different mechanisms - pre-assigned numbers and numbers assigned upon receipt. The guidance should indicate whether these mechanisms are both considered equally "good" review management principles or, describe circumstances or criteria that favor one method over the other.

8. Lines 365 - 371: *"To ascertain the completeness of the application on its face, the RPM should conduct an administrative review, including.... Deficiencies identified during this review should be communicated to the applicant promptly to enable immediate correction if possible. Administrative issues can be sufficiently substantive to warrant a refuse-to-file action.... This review is the NDA Regulatory Review in CDER and is finalized after the filing meeting with the attachment of filing meeting minutes."*

Recommendation: To be useful for sponsors in improving submissions as well as to RPMs expected to conduct the administrative review, and to establish consistency across divisions, the components of administrative review under GRMPs should be outlined.

In addition, the draft guidance states that deficiencies identified in the administrative review should be communicated to the applicant promptly. It then notes that the review is finalized *after* the filing meeting. It is not clear whether communication of deficiencies to the applicant is expected to take place before or after the review is finalized[4]. If the deficiencies are communicated to the applicant before the review is finalized, is concurrence by the Chief of the Project Management Staff or other division official required prior to communication with the applicant? These details should be incorporated into the final guidance.

9. Lines 380 - 383: *"Review team assignments are usually based on the reviewers assigned to the IND for the product. However, in certain cases new or additional reviewers may be assigned as dictated by workload, competing priorities, application complexity, or review discipline staffing."*

Recommendation: The focus of the guidance is on *good principles* for managing the review process, not expedients made necessary by unanticipated events. The GRMP intended to be expressed in the above statement is not clear because it includes two different concepts: the "usual," current practice of assigning the review team based on the reviewers who reviewed the IND (presumably a GRMP), as well as assigning new reviewers or additional reviewers. Because review work includes other obligations in addition to market application and supplement review, it may be helpful to describe principles for the hierarchy of review priority to guide reassignment of work when events dictate divergence from the ideal. For example, if uninterrupted marketing application review (including supplements) constitutes, in principle, the ideal in review management for market applications, reassigning such work as IND review would be preferred over reassigning NDA, BLA, or supplemental application review. This would provide guidance for Review Division management to follow when faced with resource limitations and conflicts.

With respect to additional reviewers, the draft guidance provides little information. Examples of situations that are likely to benefit from the assignment of additional reviewers would help to convey the GRMP concepts. For example, in the case of a complex application containing multiple indications, the assignment and coordination of additional clinical and statistical reviewers may be advantageous.

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[4] The following statement from lines 533-535 suggests that the deficiencies are conveyed before finalization of the review: "During the application receipt process, the FDA will routinely convey readily correctable issues to the applicant in a timely manner as they are identified with the expectation that they should be addressed quickly."

10. Lines 400 - 402: *"Additionally, based on the content of each application, consults may be issued for additional review of any of the above disciplines."* (Statement refers to clinical, pharmacology/toxicology, CMC, biometrics, clinical pharmacology, clinical microbiology, and bioresearch monitoring)

Recommendation: Without further detail or, perhaps, inclusion of some hypothetical examples, it cannot be determined from this statement when it would be a GRMP to seek consultation on the review of a typical technical section of an application. A clearer presentation of the principle involved may emerge by describing such things as who decides when a consultation should be requested; what criteria are considered in seeking a consult; and whether a consult request should normally include specific questions for the consulting reviewer to address. In addition, the timing of a decision to request a consult on an issue as well as whether the primary and consult reviews should be conducted concurrently or consecutively are important review management issues that are not addressed in this section [lines 423 - 424 state only that "reviewers should identify the need for consultant input as early as possible in the review process..." - see Page 1, "General Comments," Item 2]. A principle to address the timeliness of completing the consult review should also be considered, especially when consultation is sought from a different Review Division since PDUFA goals tend to direct assignments and review priorities within each Division. Further, the guidance only indirectly addresses whether "consultants" includes the option to use outside consultants (see lines 425 - 426) as well as internal consultants. Discussion to guide reviewers on when good review management calls for consideration of the use of an outside consultant would be helpful (See Page 2, "General Comments", number 3; Page 3, "General Comments," number 7)

11. Lines 413 - 417: *"Postmarketing drug safety staff from CDER...and CBER...are expected to work in collaboration with the review division staff in reviewing RMPs* [Risk Management Plans] *and providing expert advice to applicants and the review divisions."*

Recommendation: This language suggests that Postmarketing Drug Safety staff are available to provide advice on Risk Management Plans directly to applicants as well as to review divisions. We recommend that all advice on RMPs should flow through the review division to assure that agreements are understood by all parties.

12. Lines 457 - 461: *"In some instances, a preliminary designation of review priority may be made prior to submission. However, an official decision about review priority can be made only after the application is received for review. In some cases, a presubmission assessment of application review priority may be changed once the application is actually submitted for review."*

Recommendation: Whether it is considered a GRMP for applicants to request and the agency to make preliminary designation of review priority is unclear from this discussion. The admonition with respect to the preliminary nature of such a designation and the possibility for it to be changed suggests little benefit to either the applicant or the agency from preliminary designation. Guidance on GRMPs should distinguish between

review practices that are possible but not necessarily "good" in the sense that they should be encouraged because of their beneficial effect on the review process. Practices that reflect good principles should be the focus of the guidance. Practices that are merely possible but, in principle, are generally not advantageous are, perhaps, best not discussed lest their appearance in the guidance suggests that they are recommended.

13. Lines 502 - 504: *"The filing meeting for a standard application should be scheduled in time to finalize and communicate the filing decision by the 60-day filing date, often placing the filing meeting approximately 45 days after receipt of the application."*

Recommendation: By implication, specifying that this timing applies to "standard" applications suggests that a different time frame may apply to "priority" applications. The guidance should describe GRMPs for filing meetings on priority applications as well.

14. Lines 512 - 515: *"To help ensure that the application receipt process proceeds smoothly, the applicant should prepare and submit an application in accordance with presubmission recommendations from the FDA, providing a complete application as previously discussed."*

Recommendation: In view of the stressed importance of presubmission meetings between the applicant and the agency to discuss and agree on elements of content and format of an application, we recommend changing "presubmission recommendations from FDA" to "presubmission agreements between the FDA and the applicant."

15. Lines 579 - 581: *"In many instances, it may be useful for each discipline to document the filing process decisions in a brief filing review."*

Recommendation: The language, "In many instances, it may be useful..." suggests that FDA does not consider it a GRMP to routinely document filing process decisions in this way. Therefore, some detail on when GRMPs would call for brief filing reviews should be provided. The guidance should also clarify whether such documentation is application specific (that is, whether all disciplines should write brief filing reviews on certain applications) or discipline specific (written reviews are only recommended for disciplines whose conclusions may result in a refusal to file decision.)

16. Lines 586 - 589: *"The filing meeting is often held approximately 45 days after receipt of a standard review application, but in some cases, the review team should consider compressing the receipt/filing process."*

Recommendation: The general nature of this statement makes it impossible to discern what FDA considers "good review management" to be with respect to the filing meeting. Would it be preferable if *all* filing meetings were scheduled earlier than 45 days from receipt? If not, what makes some applications candidates for an earlier meeting? Should filing meetings for all priority applications be scheduled early and, if so, what time-frame, based on experience, could be recommended? The value of the document would

be improved by providing specific recommendations to establish the presumed "gold standard" for the various activities discussed thereby providing review teams with a yardstick against which to measure their progress.

17. Lines 648 - 652: *"Specific information requests from the FDA should be addressed expediently to facilitate the review. The applicant should be aware that amendments containing responses to filing review issues identified by the FDA and communicated according to the PDUFA goals may or may not be reviewed by the FDA during the first review cycle."*

Recommendation: While there is emphasis on early identification and communication of application deficiencies in the discussion of the receipt and filing review processes, the notion that it may be a GRMP for FDA not to review the amendments expediently submitted by the applicant in response to such early communications requires some explanation. On its face, this appears to represent a poor principle for review management in that it clearly requires expenditure of resources by both FDA and the applicant but denies any chance of first cycle approval.

18. Line 678 - Subsection IV. D. - *Review Planning*

Recommendation: The description of the review planning process is vague and lacking in detail. This section would be enhanced by providing further detail around the following:
i. Timing - while the draft guidance indicates that *"In most cases, the initial review planning activity should be combined with the filing meeting..."* the timing for completing the review plan is not discussed further.
ii. Responsibility - who is responsible for the planning (Division Director? Deputy Director? RPM? Supervisory RPM?)
iii. Workload and staffing in the review division and consultant divisions - how does the person responsible for review planning assess these factors? Are workload and staffing statistics routinely available to review teams?
iv. Is it expected, as a GRMP, that a written review management plan (for example, in the form of a project management timeline) will be prepared? If so, who is responsible for preparing it and updating it as the review progresses? Is it shared with Division management so that progress against the plan can be evaluated?

19. Line 710 - 714: *"An applicant can best support the planning process by providing accurate projected timelines for response to information requests and submission of expected amendments (e.g., safety updates). Failure to meet projected timelines has a systemic impact on the FDA review process, reaching beyond the intended submission's discipline-specific material."*

Recommendation: It would be beneficial to expand on the statement that failure by the applicant to meet projected timelines has a systemic impact on the review process reaching beyond the intended submission's discipline-specific material. We recommend

that, instead of applicants unilaterally projecting timelines for responses, the timing should be discussed with the RPM. The RPM should be prepared to advise the applicant on the reviewer's expectations and contingencies for completion of the review involved. Given such information, an applicant may be able to revise the timing of a submission to accommodate the reviewer's particular needs. Interactions of this kind would allow informed agreement on timelines for responses that are reasonable and appropriate for both the applicant and the FDA.

20. Line 718 - 719: *"In planning for the review process, the FDA is committed to managing efficiently the communication of concerns to the applicant and the timing of the applicant responses."*

Recommendation: The connotation of FDA managing the "communication of concerns to the applicant and the timing of the applicant responses" is cause for concern. It should be considered a GRMP to communicate deficiencies to the applicant as early as possible after they are identified and without consideration of the possible timing of the applicant's response. After all, the agency has claimed its prerogative not to review, in the first review cycle, amendments submitted by the applicant - even those in response to deficiencies identified in the filing review - a prerogative that must be invoked judiciously. The only goal of the review team should be to assure that reviewers have access to the necessary information to objectively evaluate the risks and benefits of the product under review at the earliest possible time. GRMPs are, first and foremost, those that encourage and promote first cycle approvals because, aside from earlier patient access to new therapies, it is simply more efficient not to go through an "action/resubmission" cycle. We don't believe that "communication" needs or benefits from management in the manner suggested by this sentence. Furthermore, this sentence easily could be taken as justification for manipulating the timing of the flow of information to and from the applicant to favor one application over another by deferring some to second cycle reviews while clearing the way for others to proceed to first cycle approval. This concept should be removed from the final guidance and replaced with language confirming that in no case will the review division delay or defer communication of concerns to sponsors in order to control the timing of applicant responses.

21. Lines 876 - 885: *"A decision regarding whether to send the DR letter in such cases* [when the review is completed only shortly before (1 or 2 weeks) the PDUFA goal date or shortly before planned comprehensive action prior to the PDUFA goal date] *should be discussed with the review division director. The review division director's decision should be based on an analysis of the overall status of the application review and the most efficient way to complete the review within the PDUFA goals. Consideration should be given to the seriousness of the identified deficiencies and the expected time required for the applicant to respond satisfactorily, knowledge of any other serious deficiencies that might prevent approval of the application on the first cycle, competing division workload priorities, and division resource allocation."*

The language describing the basis for the review division director's decision focuses only on completion within PDUFA goals. The language describing factors to be considered fails to mention the seriousness of the disease for which the product is intended or its potential to meet an unmet need. For such products, prompt communication of the review findings, even if late in the review cycle, can be important to accelerate public availability of the product.

Recommendation: As review divisions implement and adhere to GRMPs as described in the draft guidance, the situation where a review is not completed until almost 2 weeks prior to a planned action date should be rare. Given the definition of a discipline review (DR) letter, its content is virtually final at the time the review is finished since the content of the letter is not reviewed or agreed upon by the Division Director and its content is not to be considered final by the applicant. Therefore, any inefficiency in issuing the letter should be minor in nature. We encourage the agency to issue DR letters in all but the most unusual of circumstances.

We recommend the GRMP guidance should include public health considerations in addition to action goal dates as factors that need to be considered in making decisions that affect the potential for first-cycle approval or the time to public access to new products.

We recommend that "expected time" for the applicant to respond satisfactorily, competing division workload priorities, and division resource allocation should not be factors considered by the review division in determining whether or not to send a DR letter. "Workload priorities" and "division resource allocation" should be specifically cited as factors not to be considered. In *principle,* communication of review findings to the applicant in a DR letter favors shorter time to approval. Competing internal priorities or resource allocation issues don't alter this principle. In addition, these factors encourage favoring one application over another on the basis of issues unrelated to the content of the application, thereby compromising the "level playing field" that the PDUFA goals established.

22. Lines 887 - 890: *"The review division will decide whether it is appropriate to review amendments submitted during the first-cycle review or defer review to a subsequent review cycle based on the division's workload and priorities and the review timeline with respect to the nature of the deficiencies."* And...

Lines 899 - 902: *"The division's workload and priorities, and the review timeline and nature of the deficiencies addressed in the amendment also are critical to deciding whether to review them during the first cycle."*

Recommendation: These statements appear to confuse *principles* with exigencies. Division workload, priorities, and resources are contingencies that have an impact on a Division's review performance. *Principles*, however, are fundamental. Principles are constants that don't change with changing conditions. GRMPs are management goals that

have been identified as favoring efficient review. Division workload, priorities, and resources should not alter the underlying principles of good review management. On the contrary, where resource issues adversely affect efficient review, GRMPs should prompt the necessary management intervention to correct the resource deficit.

23. Lines 953 - 958: *"Requests for meetings primarily focused on status updates generally are not an efficient use of the review division's limited time and resources and may actually slow the review process because of the need for preparation. Such meeting requests ordinarily will be denied. More efficient means of providing the applicant with an update on the application review status should be used (e.g., a telephone call between the RPM and the applicant.)"*

Recommendation: We agree that "status update" meetings are generally not efficient for the agency or for the applicant. However, we recommend the Centers consider implementing a process to assure that the RPM has access to up-to-date information about the status of applications and clear authority to convey information to the applicant so that telephone calls between the RPM and applicant are routinely effective in communicating the information to the applicant (see related comment # 33).

24. Lines 958 - 959: *"Routine conveyance by the FDA of the interim review process timelines and speculative action dates is discouraged."*

Recommendation: We recommend reconsideration of this position. Conveying the projected timeline to the applicant and encouraging the RPM to share updates to the timeline with the applicant as they occur would provide useful information to the applicant and is likely to reduce the volume of status inquiries. As noted on lines 24-26, a key aspect of GRMPs is "their emphasis on effective communication between the Agency and applicants throughout the drug and biologic product development and review process." Efforts to censor or control such communication should be discouraged.

25. Lines 991 - 993: (Planning for an Advisory Committee) - *"The applicant should be notified when it is determined that an AC meeting will be needed and should be consulted during the scheduling process."*

Recommendation: Under planning for an Advisory Committee, there should be a specific timeline under which the RPM would advise the applicant of the likelihood of an Advisory Committee. Generally, the applicant would need at least three months to prepare for an Advisory Committee. Therefore, this should be discussed within the Agency during the 45 day meeting and a decision should be reached at that point and communicated to the applicant. The decision could be based on the likelihood of having an Advisory Committee meeting or that one will not be required.

26. Lines 1158 - 1160: *"Applicants are discouraged from printing labels for commercial distribution prior to receipt of an approval letter, because the label is not considered approved by the FDA until then."*

Recommendation: FDA should consider whether it means "labeling" instead of "label" in the above sentence based on the definitions in the FD&C Act.[5] The same consideration should be given to the use of the word "label" on line 1169.

27. Lines 1185 - 1188: *"Agency actions at the end of the application review can be to approve the application for marketing...or to provide the applicant with a comprehensive list of deficiencies...."*

Recommendation: We recommend that the phrase "comprehensive list of deficiencies" in the above sentence be replaced with the phrase "complete list of deficiencies."

28. Line 1228: *". weeks before the PDUFA goal data....*

Recommendation: The word "data" should be changed to "date."

29. Lines 1273 - 1275: *"If approval is anticipated, the draft action letter should specify all the conditions of approval, including labeling text, any postmarketing study commitments, and any restrictions on distribution of the product when warranted."*

Recommendations: Because it is often noted that there is no such thing as "conditional approval" (other than approval under 21 CFR 314, Subpart H), it may be better to state that the letter should specify "all agreements and commitments by the applicant."

Restrictions on distribution would be, presumably, a feature of a risk management plan. Unless it is FDA's intent only to include information on restrictions on distribution, the guidance might recommend, instead, including a summary of any risk management plan agreed upon by the applicant.

30. Lines 1283 - 1286: *"If the application is not expected to be approved on the first cycle, the draft action letter should list all the deficiencies identified by the reviewers that must be remedied prior to approval and should also specify how the applicant is expected to respond to each deficiency."*

Recommendation: Clarification should be provided on the point in the above sentence that the action letter should specify <u>how</u> the applicant is expected to respond to each deficiency.

31. Lines 1288 - 1296: *"The draft letter should be circulated to all members of the review team and their team leaders and supervisors for review and concurrence before being*

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[5] See FD&C Act, Section 201(k), "The term 'label' means a display of written, printed, or graphic matter upon the immediate container of any article..."; and Section 201(m), "The term 'labeling' means all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article."

forwarded along with the action package to the signatory authority. Depending on the review and decisions made...."

Recommendation: It may be helpful to provide some timing parameters to improve the efficiency of circulation of the final review. Is there some range of time that is considered a GRMP within which a reviewer or team leader is expected to review the draft letter and move it forward. This would also help the RMP to plan finalization of the letter for signature.

32. Subsection beginning at line 1305: *"e. Process for Conveyance of Action"*

Recommendation: This subsection notes that the signed letter is archived in division files and a copy is sent to the applicant via facsimile. The RPM calls the applicant to document that it was received and documents the fact in the action package. It is not clear whether or not the original letter is actually mailed to the applicant.

33. Lines 1323 - 1327: *"It is generally not an efficient use of Agency resources during this final critical period to be responding to frequent and redundant inquiries from the applicant. There should be only one point of contact, the RPM, between the applicant and the review division to ensure consistency of communication and to avoid misunderstandings."*

Recommendation: We agree that frequent and redundant inquiries are not an efficient use of the resources of the agency or the applicant. We further agree that the RPM should be the one point of contact. Frequency and redundancy of inquiries, however, may be spawned, in part, by the unsatisfactory nature of the communication. While we recognize that there are limits to the information that can be made available, we recommend the Centers consider implementing a process to assure that the RPM has up-to-date information during the critical end-of-review process, is clear on what information can be shared with the applicant, and understands the role of the RPM as the single point of contact for information about the application. We also recognize that the end-of-review period is a busy time for the RPM and, therefore, we suggest that it may be helpful for the applicant and the RPM to discuss and agree on a plan for communication at this late stage of the review process. This would help to assure that communications between the RPM and applicant are effective for the applicant and minimally obtrusive to the RPM. It could largely eliminate inquiries that are considered redundant by the agency (See also comment number 23 above).

34. Lines 1379 - 1382: *"Following receipt of an action letter, the applicant may wish to hold a brief telephone conference with the principal signatory in the office and/or review division to ensure full understanding of the decision."*

Recommendation: The guidance should stipulate that a request for this teleconference is not subject to the standard meeting management procedures with respect to the timing of

the meeting request, the need for submission of background material, and the timeframe for scheduling and completing the telephone conference.

Conclusion

In conclusion, we appreciate the effort by the Agency to identify, document, and promote GRMPs through guidance. The availability of such principles should greatly improve the overall consistency and effectiveness of the review process. We respectfully request the Agency to consider the recommendations we have proposed as it finalizes its guidance on GRMPs. We believe that a statement of clear objectives for GRMPs; a summary listing of the actual principles, perhaps as an appendix; inclusion of a typical GRMP based timeline for standard and priority reviews; and adding recommended ranges to better define what is meant by "in a timely way" and "as soon as possible" improve understanding of the guidance.

We welcome the opportunity to comment on this draft guidance and, if appropriate, to meet with you to discuss these issues.

Sincerely,

for David W. Blois, Ph.D.
Senior Vice President
Global Regulatory Policy