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Dockets Management Branch
Food and Drug Administration, HFA-305
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2003D-0317; Draft Guidance for Review Staff and Industry on Good Review Management Principles for Prescription Drug User Fee Act Products (Federal Register, Vol. 68, No. 144, Pages 44345-44346 (July 28, 2003))

Dear Sir or Madam:

Bristol-Myers Squibb (BMS) is a diversified worldwide health and personal care company with principal businesses in pharmaceuticals, consumer medicines, nutritionals and medical devices. We are a leader in the research and development of innovative therapies for cardiovascular, metabolic and infectious diseases, neurological disorders, and oncology. In 2002 alone, Bristol-Myers Squibb dedicated $2.2 billion for pharmaceutical research and development activities. The company has more than 5,000 scientists and doctors committed to discover and develop best in class therapeutic and preventive agents that extend and enhance human life. Our current pipeline comprises of approximately 50 compounds under active development.

For these reasons, we are very interested in and well qualified to comment on the FDA Draft Guidance entitled, "**Good Review Management Principles for Prescription Drug User Fee Act Products**".

We commend the U.S. FDA for this initiative to provide guidance to Industry and the Review staff in CDER and CBER on Good Review Management Principles (GRMPs) for the conduct of the first-cycle review of a new drug application (NDA), a biologics license application (BLA), or an efficacy supplement under PDUFA. BMS anticipates that upon completion of this initiative, Industry and Review Staff will obtain well-defined, consistent and efficient review management principles that will improve overall regulatory decision making and benefit all appropriate stakeholders.

2003D-0317

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BMS appreciates the opportunity to comment on this draft guidance. Upon careful review, BMS has identified several aspects of the draft guidance that appear contrary to FDA's stated objectives and have been cited below.

BMS Comments on the Draft Guidance

General comments

BMS recommends that wherever possible the guidance is comprehensive for all reviews conducted by FDA including pre-NDA submissions, i.e. IND submissions. Timely and efficient review of IND submissions through GRMPs is also critical to rapid and efficient product development, a goal that is central to this guidance. The guidance should also cover adherence to GRMPs for post-approval submissions. Furthermore, there is no discussion related to "rolling" applications (in Section IV.A and Section IV.B) in this draft guidance. This was part of PDUFA considerations and it appears prudent that there should be some discussion of this possible route in this guidance. Specific comments are included below.

I. Introduction

Lines 22-23: Since the document was provided for public comment, it may be noteworthy to add that guidance was developed 'with input from the public, and draws from the experience of the Industry'.

Lines 31-32: It may be worthwhile to note that when an applicant does not follow this guidance, there should be a discussion between the Agency and the applicant as to why the guidance was not adhered to.

II. Background

Line 35: Should be numbered as 'II' and not 'I'.

Lines 62-65: BMS suggests deletion of the comment related to FDA's dependency on resources and applicants for effective implementation of GRMPs. Despite the resource limitations, FDA should strive to achieve effective implementation of this guidance.

III Overall Principles

Line 88: BMS suggests inclusion of 'supplements to NDA/BLA' in this statement to reference utilization of GMRPs for submissions made post initial approval.

Line 91: Add 'and thereafter', after 'final action on the marketing application' to reference utilization of GMRPs for submissions made post initial approval.

Lines 110-111: BMS suggests inclusion of guidance on the discussion between FDA and applicant on patient management for ongoing studies, if an application is determined to have uncorrectable deficiencies.

Lines 113-116: This section notes several important points for successful GRMP. However, the key to success in many situations is good communication between *all* concerned parties. Therefore we suggest to add '(4) interactions between FDA review team and the applicant', which is a common thread throughout this document and is as important as the FDA's internal interactions.

Line 134: Please add 'or at the commencement of review clock' to this statement to allude to the fact that in cases such as a fast track NDA which may be a rolling submission the review clock may not commence with the initial submission.

Lines 134-135: BMS requests the Agency to clarify the meaning of the term "expected" as used in this statement. We suggest the addition of a comment that the applicant should communicate with FDA to understand what FDA expects and confirm the understanding of what is required.

Line 136: Add that the application should be 'readable, well-organized, and compliant in format'.

Lines 150-151: Please specify that the content and use of the amendment needs to be included in the agreement. For example, the initial application may have preliminary results of an ongoing study. If there is prior agreement for the applicant to submit an update to the preliminary report (in the proper timeframe), the agreement needs to specify that the update will be reviewed for both safety and efficacy and is separate from the Safety Update.

Lines 153-158: Please add that the FDA may decide to defer review of amendments if the application is 'approvable as is'. Add that if FDA decides to accept an amendment it may result in extension of the review clock if it is determined to be a 'major amendment'. The retention of the right to refuse review of an amendment is understandable, but FDA should resource sufficiently to accommodate any solicited and sometimes even unexpected amendments during first review cycles. This can potentially save time in the end. BMS suggests rewording the statement regarding the review of amendments to read as: "Experience shows FDA may request an amendment in response to an issue raised during review. When such an amendment provides information required by FDA to complete a review during the first cycle, and there are no other issues that would cause the application to require a second review cycle, FDA should accept and review that amendment in order to avoid the time and resource commitment required for a second review."

IV. Process Principles

A. Presubmission

Line 209: Milestone meetings

BMS supports the Agency's emphasis on the value of effective and timely communication with the applicant during the presubmission phase of drug development. In particular, we acknowledge the Agency's view of end-of-phase 2 (EOP2) and pre-NDA/BLA meetings as invaluable opportunities for both the Review Division and the applicant to interface on the development plans and the organization/focus of the planned NDA/BLA. However, we believe that there are additional opportunities during development that should be emphasized and taken advantage of in order to enhance communication and transparency during this phase. In particular, end-of-phase 1 interactions can be very helpful in alerting the appropriate Division of evolving toxicity information. Likewise, sponsors can benefit from the Agency's broader experience and insights on particular issues associated with a drug class or sensitivities of vulnerable populations under consideration for Phase 2 evaluation. Particularly, for new chemical entities or truly novel indications, there may be some added value to establishing a mechanism whereby appropriate members of the Division Review Team and the sponsor have an opportunity on an annual basis to discuss via teleconference the evolution of the development program. This would maximize the potential for communication and exchange of ideas between sponsors and the Division to ensure the submission of high quality, complete applications.

Line 261: Milestone meetings

Adequate preparation of both parties is essential to ensure productive interactions and feedback during EOP2 and pre-NDA/BLA meetings. As noted in the proposed guidance, an essential element in this preparation process is a clear, concise background package. Another important element in this preparatory process is pre-meeting feedback from the Division regarding issues/concerns that surface during the Division's review of the background package. This has been very helpful in allowing the sponsor to come to the meeting prepared to discuss issues most relevant to the Division and thereby maximizing the time available for the meeting. We believe that Division feedback on background packages before meetings should be emphasized in the GRMP guidance.

Line 294: Risk Management Plan

It is not clear how communication between the ODS and Review Divisions and the sponsor should be coordinated or arranged. There is an opportunity in this guidance to identify the RPM to fill this role. The opportunity to propose a risk management plan (RMP) as part of the pre-NDA/BLA background package is acknowledged. The concept of a RMP plan will certainly be evolving, as it becomes a more routine component of pre and post approval development programs. Regardless, the elements of a RMP should be under consideration as early as an end-of phase 1 interaction. As a result, BMS believes

that applicants and Review Divisions should share ideas and expectations regarding RMP as early as possible in the drug development program.

Lines 329-331: BMS suggests deleting this last sentence, as it is obvious.

B. Applicant Receipt Process (Prefiling)

Line 377: Review team

We suggest the guidance include text such that when membership of the Division's core Review Team has been established, that the review team members be conveyed to the applicant. Based upon prior experience with individual members of the team, the applicant may anticipate the type of information and displays that may be requested during review of the application. This type of insight may help to reduce the time needed for responses to questions during the application review.

Lines 379/400: In addition to the above, the RPM should be reminded that the applicant should be notified when the FDA review team members/consultants are initially nominated, added or changed.

Lines 411-419: Applicants should be informed of consults to other Review Divisions as soon as they are requested, along with any details of why the consult was requested.

Line 490: Scheduling filing meetings

During the period leading up to the filing meeting, any concerns regarding a RTF action should be conveyed to the applicant as soon as possible. This would allow for the opportunity of immediate correction, if possible.

Lines 525-528: BMS requests that the intent of this statement be clarified.

Line 531: BMS requests addition of a statement that the RPM is also informed if Reviewers independently contact the sponsor for information on applications.

C. Filing

Line 569: Please change "and" to "an".

Lines 613-623: The Reviewers cannot know what might be correctable or not until they talk to the applicant. We suggest that the guidance include direction to the RPM and review team to interact with the applicant at this point.

Line 656: Communication between FDA and Applicant.

This section focuses on activities if an application is deemed unacceptable. It might be helpful for this section to also include information to the RPM on filing meeting follow-

up for acceptance of an application, i.e. notification of the sponsor that the application has been filed, preferably through documentation to the applicant. Right now an applicant only receives a phone call, with the only documentation to the applicant being the 'Acknowledgement of Receipt' letter that the application was received. The filing of the application is as an important milestone, if not more so.

D. Review Planning

Lines 682-692: Special consideration should be given to complex products, such as combination formulations. It is recommended that these products be assigned to experienced RPMs with skills in cross-center coordination.

Lines 694-700: Please include requests for inspections, labeling interactions, and post approval commitments as bulleted activities.

Lines 718-722: BMS believes that "managing the review of applicant responses" is a clearer statement than "managing the timing of applicant responses". The applicant should be informed of the Review Team timelines, in order to plan their own resource allocation appropriately. Labeling negotiation is another activity where applicant input is clearly needed.

E. Review

Lines 747-748: It is suggested that the type of ongoing communication should be specified.

Lines 824-825: It is suggested that the type of interaction among review disciplines should be clarified.

Line 839: BMS suggests moving this to "Communications with Applicants during the Review".

Lines 863-865: An earlier comment on lines 153-158 is pertinent here also.

Lines 887-891: The text should include language, which emphasizes that there is intent to review amendments within the first cycle, if at all possible, as cited as an important point in the Overall Principles section of this draft guidance.

Lines 904-907: The text should clarify how the review division determines which material should have been part of the original application; otherwise, the determination appears arbitrary.

Lines 958-959: In the spirit of effective communication between the FDA and the applicant, it is important that both parties have a common understanding of the expected review timelines.

F. Advisory Committee Meetings

Line 968: BMS recommends that the potential need for an Advisory Committee (AC) meeting be evaluated even before the application is submitted (such as at the pre-NDA meeting). This should be possible to achieve if there has been reasonable communication during development program.

Line 981: The FDA review team and the applicant should complete identification of invited guests to the AC in a manner such that investigation of potential conflicts of interest may be completed (time should be specified). The applicant should receive notification of the specialty of the invited guests no later than one month before the meeting and the individual names must be sent no later than one week before the meeting.

Lines 1019-1021: The defined time point prior to the meeting that the Reviewing Division's questions to the AC would be made available to the applicant AC should be specified. The specified time should be sufficient to allow the applicant to develop a well-researched response. In the past, the Reviewing Division's questions often have not become available until very late allowing little time for the applicant to prepare a response.

Lines 1025-1040: The paragraph concerning the review division's presentation to the AC presumes that a presentation from the review division will always occur. Many times a presentation from the review division is not necessary. The GRMP should acknowledge that the review division may not need to make a presentation, and discuss how not making a presentation is to be interpreted by the AC and the applicant. The 'working together and sharing information' between FDA and the applicant should include 'discussion'. BMS strongly supports the pre-AC meeting sharing of FDA/applicant presentations. We realize that this is not consistent with current AC guidance and interpretation in some Divisions. In addition, some guidance to focus the respective presentations may be warranted. For example, it may be best if the applicant focuses on presenting data, to address specifics that help answer the questions. Then FDA would focus on presenting why they have a particular issue with what the sponsor has presented.

Lines 1060-1070: BMS acknowledges the need for FDA to communicate with the AC the rationale for its regulatory action when FDA's final regulatory decision is at odds with the AC recommendation. Hence, we request the Agency to describe in the guidance specific measures that it proposes to ensure that any such written communication between FDA and AC will be confidential. For example, the sentence in the draft guidance on line 1066 to 1067 could be revised to say "The memorandum should be marked confidential and should contain text that reminds AC members of the confidential nature of such communication".

Lines 1087-1089: The guidance should stipulate that the review division and the applicant has a pre-specified period of time in advance of the AC meeting to exchange presentations, e.g., 5 days, even if a caveat is needed that revisions to slides may follow.

As currently written this paragraph could potentially set up the Review Division with a reason for being late with provision of their presentation to the applicant to avoid redundancy. From the applicant's point of view, redundancy in the presentation is a small price to pay in exchange for having sufficient time to prepare for the issues that the review division will bring to the AC.

Lines 1096-1100: BMS suggests adding "FDA will work with the applicant to complete review of the amendment within the same review cycle, when the need for such an amendment arises".

Line 1098: Specifics of the amendment contents should be discussed between FDA and the applicant. An applicant, in trying to be helpful, may add a lot of unnecessary information that could potentially lead to a 'major amendment' designation and may not able to be reviewed in the time left on the clock.

Line 1111: Explicit timing of FDA and applicant discussion should be specified and should include logistics management.

G. Wrap-up and Labeling

BMS agrees that the key to successful completion of the first-cycle review is to prepare for final negotiations on the label well in advance of the final action goal date. As suggested by the guidance, we hope that most of the concerns for the final labeling text would have been conveyed to the applicant throughout the review cycle and in advance of the formal labeling negotiations. This concept has been reflected through this section of the guidance and we agree that there should also be *"early communication of potential labeling issues following secondary review and Division or Office level input"*. We understand that this feedback may be preliminary, but it would give the applicant an early opportunity to review and comment on the FDA labeling proposal.

As a follow up to the Agency's attempt to *" have review teams schedule internal labeling meetings well in advance of the PDUFA goal date to facilitate the discussion of labeling content and identify major labeling issues"*, BMS suggests that a formal labeling meeting be scheduled into the FDA and applicant's calendar at least 4 weeks (minimum of 2 to 3 weeks) before the final action date. There have been a number of instances where the industry has been on a teleconference with the Agency days, if not the night before, the action date to resolve some very key issues. This type of activity could potentially impede timely completion of the first-cycle review.

Line 1158: *"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. Labels printed in advance of the actual receipt of an approval letter can contain differences from the final approved label and may have to be destroyed"*. Labels, in the content of this section, seems to be used to refer to the package insert. However, in the strict regulatory sense the label is the *"written, printed or graphic matter upon the immediate container"*. The label and the package insert collectively are called "labeling".

This paragraph should be modified and could possibly read as follows: "*Applicants are discouraged from printing labeling for commercial distribution prior to receipt of an approval letter, because the labeling is not considered approved by the FDA until then. Labeling printed in advance of the actual receipt of an approval letter can contain differences from the final approved labeling and may have to be destroyed*". It should be noted that the term "labeling" is used throughout the guidance and this is the first instance of the use of the term "label". Clarification from the Agency for this deviation in terminology from the rest of the document would be appreciated.

H. Action

Lines 1197-1198: It is suggested the statement regarding issuance of a non-approvable letter because "... the application is unlikely to be approved" be clarified with an example or be deleted.

Lines 1240-1241: BMS recommends adding the following underlined language for clarity: "...discussions and agreements on the labeling by the review team and the division with the applicant in advance of the action package being submitted to the signatory authority."

Lines 1309 -1310: "The RPM should call the applicant prior to sending the facsimile and subsequently confirm and document their receipt of the action letter....."

Lines 1329-1331: It appears that this paragraph needs context around it. The issue of formal dispute resolution is a key one, but as currently stated it is not in contextual agreement with the rest of the section (i.e. there is no other narrative discussing formal dispute resolution).

Lines 1342-1344: This sentence states that: "The official written regulatory action contains important information regarding the basis of the Agency's approval decision in cases where the application is approved...." While BMS agrees that approvable, non-approvable and refusal to file letters contain significant detail for the sponsor, in BMS' experience approval letters do not typically provide any "important information" as to how approval was obtained (e.g. a summary of pivotal trials conducted). Please clarify the use of "important information" as used in the statement referenced above.

Lines 1369-1377: The majority of this paragraph is redundant in light of Section IV.H.1.e. (Process of Conveyance of Action) with the exception that in this paragraph reference is made to the sensitive nature of this information and how it can affect financial markets in the case of publicly traded companies. BMS agrees that this is a critical point to be made, but the rest of the paragraph seems to repeat the information provided earlier.

I. Cycles of Review

No comments on this section.

V. Implementation and Evaluation

BMS suggests that more details related to the implementation and performance evaluation be included in the revised guidance. For example, timeline for completion of reviewer training, extent of public participation in the development of an evaluation plan and timeline for starting and completion of the performance evaluation.

BMS appreciates the opportunity to provide comment and respectfully requests that FDA give consideration to our recommendations. We would be pleased to provide additional pertinent information as may be requested.

Sincerely,

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Pharmaceutical Research Institute
Bristol-Myers Squibb Company