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MERCK
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May 15, 2001

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
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RE: [Docket No. 01D-0086] Draft Guidance for Industry: Disclosing Information Provided to Advisory Committees in Connection with Open Advisory Committee Meetings Related to the Testing or Approval of Biologic Products and Convened by the Center for Biologics Evaluation and Research (CBER)

Merck & Co., Inc, is a leading worldwide, human health product company. Through a combination of the best science and state-of-the-art medicine, Merck's Research & Development (R&D) pipeline has produced many of the most important pharmaceuticals, biological products and vaccines on the market, today.

Merck supports regulatory oversight of product development that is based on sound scientific principles and good medical judgment. Regulators must be reasonable, unbiased and efficient when they certify the quality, effectiveness and safety of medicines. It is the interest of both the sponsor of research and the regulator to see that important therapeutic breakthroughs reach patients without unnecessary or unusual delays.

In the course of bringing our product candidates through developmental testing, clinical trials, and ultimately to the marketplace, Merck frequently participates in open advisory committee meetings which are the subject of this *Draft Guidance For Industry: Disclosing Information Provided to Advisory Committees in Connection with Open Advisory Committee Meetings Related to the Testing or Approval of Biologic Products and Convened by the Center for Biologics Evaluation and Research (CBER)*, dated February 2001, hereafter referred to as the *CBER Draft Guidance.*

Since 1994, Merck has participated in six vaccines and related biological products advisory committee meetings; these have included both open and closed meetings where product and policy issues were discussed. For this reason, we are very interested and well qualified to comment on this *CBER Draft Guidance* regarding the disclosure of information that is provided at open advisory committees regarding the testing or approval of new biological products.

Our comments within this communication are organized into general comments on the draft guidance as a whole, followed by comments on specific sections.

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GENERAL COMMENTS

We note that this *CBER Draft Guidance* closely follows revisions in the disclosure policy guidances issued by CDER[1] and it is presumed that CBER's revised policies will be consistent with those in the *CDER Draft Guidance(s)* already issued, in providing what sponsors may expect regarding disclosure of information before open advisory committee meetings for CBER. Complete harmonization of these processes between CDER and CBER will allow the consistency and predictability that is necessary for sponsors in an otherwise uncertain R & D environment.

In February 2000, Merck commented to FDA on the CDER disclosure policy guidance (hereafter referred to as the *CDER Draft Guidance*) and expressed serious concerns about its impact on a sponsor's ability to provide advisory committees with comprehensive and meaningful scientific information regarding new drug candidates in advisory committee *background packages* (hereafter referred to as *background packages*). A copy of Merck's statement is attached for reference since there are comments that are directly applicable to issues which CBER has retained intact from the *CDER Draft Guidance*.

In our comments of February 2000, Merck stated our position that much of the detailed, comprehensive and issue-oriented information historically provided in sponsors' confidential *background packages* would no longer be provided forthrightly if that *CDER Draft Guidance* were implemented as written. Within this communication, we restate Merck's position, now based upon experience with the revised CDER procedures for dissemination of information. The advisory committee process is impeded when sponsors' obligations to protect competitive information result in guarded release of information important for advisory committee discussions, when information included in *background packages* will be concurrently disclosed to the public.

The Federal Register notice of March 21, 2001 announcing the availability of this *CBER Draft Guidance* reports CBER's intention to use June 1, 2001 as its effective date, which is less than 14 calendar days after the comment deadline of May 21, 2001. If CBER adheres to this schedule, it is highly unlikely that there will be adequate time for review and appropriate consideration of all comments or thoughtful modification of the Draft Guidance. Therefore, to ensure complete review and fair evaluation of all comments, Merck urges that the proposed effective date of this

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[1] *Disclosing Information Provided to Advisory Committees in Connection with Open Advisory Committee Meetings Related to the Testing or Approval of New Drug Products and Convened by the Center for Drug Evaluation and Research Beginning on January 1, 2000. Federal Register (FR)*, November 30, 1999 (64 FR 66920)
and,
Disclosing Information Provided to Advisory Committees in Connection with Open Advisory Committee Meetings Related to the Testing or Approval of New Drug Products and Convened by the Center for Drugs Evaluation and Research, Beginning on January 1, 2000. FR, December 22, 1999 (64 FR 71794) provides procedural information referenced in the disclosure policy guidance (noted above).

CBER Draft Guidance should be extended by 60 days (to July 27, 2001) after the close of the comment period on May 21, 2001.

SPECIFIC COMMENTS ON THE *CBER Draft Guidance*

Merck Comment 1: Section III (Page 3): "Applicability of the Disclosure Procedures Described in this Guidance"

Merck has several comments in this section related to harmonization of terminology of the CBER and CDER guidance documents.

The title of this document refers to biological products addressed by advisory committees convened by CBER. The document is further limited in scope in the introductory paragraphs of Sections entitled "Purpose and Background" to applications and *background packages* filed with CBER and their disposition. Nevertheless, in Section III, CBER refers to applications handled by **CDER** [emphasis added by Merck] and states:

> "If a BLA, BLA supplement, or a NDA, NDA supplement, or ANDA reviewed by CBER is being discussed at an advisory committee meeting convened by CDER.....will be subject to the disclosure procedures described in this guidance document. However, sponsor submissions and the CBER background packages should be sent to the executive secretary of the advisory committee in the CDER Advisors and Consultants Staff (ACS)."

Section III also states:

> "If a device is being discussed in unison with a BLA (for example, a combination product consisting of both a biologic and a device), that device will be subject to these disclosure procedures to the extent allowed under applicable law."

If the intent of this Section is to clarify that all products reviewed by CBER will be subject to this *CBER Draft Guidance*, including those discussed at advisory committees convened by CDER for biologic/drug combinations and CDRH for biologic/device combinations, then the title of the guidance is misleading.

Recommendations:

(1a): The title of the *CBER Draft Guidance* should be modified as follows: *Guidance For Industry: Disclosing Information Provided to Advisory Committees in Connection with Open Advisory Committee Meetings Related to the Testing or Approval of Biologic Products.*

(1b) All references to applications reviewed by both CBER and CDER or CBER and CDRH should be isolated, clarified with examples or eliminated.

The last sentence of this Section states:

> "The procedures in this guidance also do not apply to: (1) closed advisory committee meetings; and (2) open advisory committee meetings convened solely by components of FDA other than CBER, except as describe in this section."

It is not clear from this sentence whether *background packages* for advisory committee meetings of CDER that review biological products would be subject to the public disclosure requirements of both CDER's and CBER's Draft Guidances.

Recommendation:
(1c) The guidance document should clearly specify that biological products that are reviewed solely by CDER are subject only to the CDER guidance document, but not the CBER guidance document.

Merck Comment 2: Section IV, Paragraph A: "Fully Releasable Sponsor Submissions"

CBER states that fully releasable packages should be marked "AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION" in uppercase, bolded **script.** [emphasis added by Merck]

Why does CBER require "script" rather than "type" or "font" in this sentence, when "script" of any kind is usually understood to be less legible? If script is required, it would defeat the purpose of clarity that is implied by the requirement for "uppercase, bolded."

Recommendation 2: Change "script" to "type" or "font."

Merck Comments 3a, 3b, and 3c: Section IV C (Pages 5-7) "What is typically Disclosable and What is Typically Exempt from Disclosure?"

Merck respectfully differs from CBER in the definition of what should be disclosed in *background packages*. We also object to the potential disclosure of a summary of data or results obtained from an individual.

(3a) The intent of a sponsor's *background package* is to provide an in-depth review of all pertinent information regarding the preclinical and clinical development of a new biological product candidate to advisory committee members, to explain the development program issues in preparation for their full participation in meeting discussions. Merck's *background packages* have routinely included information that this *CBER Draft Guidance* identifies as being "fully disclosable" to the public, as numbered in the Guidance and listed here:

1. Summaries of any safety and effectiveness data that relate to anything other than:
   a) the indication to be discussed in open session of the advisory committee meeting; and, b) anything else the sponsor anticipates will be discussed in the open session;
2. Summaries of clinical or non-clinical safety and effectiveness data

3. Summaries of suspected adverse drug reaction data
5. Clinical and pre-clinical protocols
6. Proposed product labeling sections
7. Names of clinical investigators

As Merck noted in comments filed to CDER in February 2000 which would now apply to this *CBER Draft Guidance* as well, Merck considers these categories of information (1 through 7 above) to fall within Exemption 4 of the Freedom Of Information Act (FOIA), 5 U.S.C. Section 552b c(4) (FOIA). The Federal Advisory Committee Act (FACA), 5 U.S.C. App. ll Section 10(b), which obligates the FDA to make *briefing packets* (also called *background packages*) publicly available at or before the advisory committee meeting, does not apply to these materials. Also, the Federal Trade Secrets Act, 18 U.S.C. Section 1905, prohibits their public disclosure.

Material submitted voluntarily to an agency is confidential and within FOIA Exemption 4 if it is "of a kind that would customarily not be released to the public by the person from whom it was obtained.[2]" *Briefing packets* are voluntarily submitted by biological product sponsors to CBER for use by advisory committees. No statute, regulation, or agency policy requires a sponsor to prepare or submit a *briefing packet* in connection with an advisory committee meeting, nor does any regulation dictate the contents of such packets. Moreover, it is beyond dispute that sponsors do not customarily release to the public their safety and effectiveness data, protocols, adverse events, names of investigators, proposed indications, or draft labeling. Accordingly, under the Critical Mass test, these items are within Exemption 4.

These items also satisfy the legal requirement for Exemption 4 that applies to information required to be submitted to the government. Such information is within Exemption 4 if its disclosure would cause "substantial competitive harm" to the submitter.[3] Disclosure of safety and effectiveness data beyond what is discussed at the advisory committee meeting, and disclosure of protocols, adverse events, names of investigators, proposed indication, and draft labeling would cause substantial competitive harm to NDA applicants. All of this information could be used by competitors to eliminate the time and effort otherwise required to bring a competing product to market or would allow a competitor to develop programs for competitive products sooner than they otherwise could.

> Recommendation (3a): The list of information considered to be disclosable should be limited to what has traditionally not fit within the legal requirements of Exemption 4 of the FOIA, namely, copies of slides to be presented at the meeting or information previously publicly disclosed.

(3b) CBER has added a paragraph in this Section on page 6 which defines "raw data" and "summaries;" that paragraph is not included in the *CDER Draft Guidance*. The *CBER Draft Guidance* states:

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[2] Critical Mass Energy Project v. Nuclear Regulatory Comm'n, 975 F.2d 871, 879 (DC Cir. 1992)
[3] National Parks & Conservation Ass'n v. Morton, 498 F.2d 770 (DC Cir. 1974); Critical Mass, 975 F.2d at 878-80.

> "Data that summarize individual or multiple subject outcomes/results are considered summaries. Summaries may include examples of specific findings"

This very clearly specifies that summaries are included in material to be made public. Therefore, according to the *CBER Draft Guidance* as written, the results of an individual subject may be made public if "summarized." This raises a serious concern about potential breaches in the confidentiality of patient-specific data within summarized findings.

> Recommendation (3b): Protection of human subjects is the cornerstone of clinical research, in term of both protection of human subjects from physical harm and protection of the privacy of human subjects' data. CBER must avoid any occasion where an individual's medical findings may be released in summary data, deliberately or inadvertently. Otherwise, the *CBER Draft Guidance* will compromise a sponsor's ability to meet obligations to protect the confidentiality of that patient's medical data.

(3c) In the last paragraph of this Section, CBER has adopted the same disclaimer used in the *CDER Draft Guidance*, to accompany briefing materials place on the FDA website:

> *"The statements contained in this document are those of the product's sponsor, not FDA, and FDA does not necessarily agree with the sponsor's statements. FDA has not made final determination about the safety or effectiveness of the product described in this document."*

We restate our objection of February 2000 to this sentence which conveys an imprimatur of review at FDA at a level significantly higher than CBER and significantly higher than may be the case at the time the information is released. It would be logical to assume that review of the application has included examination by the Office of General Counsel (OGC), since the OGC also resides within the umbrella of FDA's executive staff functions. In fact, at the time of an advisory committee meeting, it would be very unlikely that an application would have undergone legal review at that level. Therefore, the disclaimer may be exceedingly broad and may *over*state or overemphasize *disagreement* between the sponsor and CBER about the application, rather than convey that some *agreement* has been achieved through this intensive process.

> Recommendation (3c): The disclaimer should be revised, as follows:
> *"The statements contained in this document are those of the product's sponsor, not of CBER, and CBER does not necessarily agree with all the sponsor's statements. CBER has not made a final determination about the safety or effectiveness of the product described in this document."* [emphasis added]

Merck Comments 4a, 4b, and 4c: Section V (Page 7-10) "Timing of Sponsor's Advisory Committee Submissions and CBER Review"

Merck is providing several comments on this section, including objections to terminology that infers that the CBER Guidance is legally binding, the need to harmonize the timing of specific steps in both the CBER and CDER guidance documents, and a very strong objection to the potential delay of priority product reviews for the express purpose of disseminating a *background package.*

(4a) In paragraph 3, CBER states:

> "If a submission from a sponsor is not received by CBER within the time frames listed below, it will not be forwarded to the committee and will not be considered by the committee."

Draft Guidance documents are not legally binding on sponsors or on FDA; CBER has stated this legal disclaimer at the beginning of this *CBER Draft Guidance.* Nevertheless, this sentence appears to require strict adherence to this CBER timeframe with regulatory consequences for breaches in compliance. This strictly stated cause and effect essentially establishes a regulatory obligation under the guise of guidance.

> Recommendation (4a): This *CBER Draft Guidance* is not legally binding and any terminology which overturns that premise should be eliminated from the document. We urge that the sentence quoted above be deleted from the Draft Guidance.

(4b) Subsections A and B (pages 7-10) outline timelines for: preparation and redaction of *background packages*; discussions between CBER and sponsors; and, release of a sponsors' submissions. In both Sections of the *CBER Draft Guidance*, CBER deviates by 1-3 days for selected activities from the timelines defined by CDER in its *Draft Guidance* for the same activities. In Merck's statement of February 2000, Merck objected to CDER's arbitrary selection of time periods for certain actions which appear to be chosen without suitable justification.

In this *CBER Draft Guidance*, CBER takes that arbitrary decision-making one step further. Not only does CBER select different time periods from CDER, but it offers no explanation for these variations. This differentiation is unfounded and will add confusion for sponsors unnecessarily, particularly when a biologic/drug combination product may be subject to both *Guidances.*

> Recommendation (4b): CBER timelines should be completely harmonized with CDER timelines for the same actions, since CDER has already set the precedent in this public disclosure policy process.

(4c) In Subsection C (page 15), CBER asserts that its obligations under the Federal Advisory Committee Act (FACA) and the FOIA will take precedence over its obligations under the Food and Drug Modernization Act (FDAMA) provisions pertaining to Prescription Drug User Fee Act (PDUFA) obligations and timelines. As outlined on page 15 of the draft guidance, CBER intends to forego its PDUFA obligations to meet its PDUFA performance goals, if an application under *priority* review is also intended for advisory committee review, in order to comply with FACA and FOIA requirements of disseminating *background packages.*

Merck considers this policy statement by CBER to be counterintuitive to CBER's public health objectives. Why does CBER, which is obligated and authorized first and foremost to act to protect public health and welfare, as defined under the Federal Food Drug and Cosmetic Act (FD&C Act) and FDAMA, consider its administrative responsibilities under FACA and FOIA to be preeminent? Although we understand that CBER's obligations under FACA and FOIA are statutory, while PDUFA timelines are not codified into law under FDAMA, there is a clear

understanding that priority reviews of drugs which are breakthrough therapies are perhaps the most important obligation of PDUFA and FDAMA.

Therefore, Merck objects emphatically to CBER's stipulation that review times for *priority* review applications will be ignored if an application is also intended for advisory committee review and there is not adequate time to redact a *background package.* As stated in our comments of February 2000 and revised here for biological products reviews:

> The decision to review an application under *priority* time frames is dependent upon patient need (no alternative therapy) and reapplication of existing resources to the review of the application in question. There should be no "*tacit*" decision to ignore the review clock inferred by any of the following:
>
> • a decision by CBER to require advisory committee review of a *priority* application;
> or,
> • acceptance by an applicant of CBER's decision to require advisory committee review of an application that may otherwise receive *priority* review;
> and/or,
> • the sponsor's decision to submit material requiring redaction.

This *CBER Draft Guidance* does not diminish the public health need for a new biological product candidate nor does it change CBER's resources that may be applied to the review process, other than to require reallocation of those resources (provided under PDUFA II) to different task(s), e.g., more persons to redact in shorter time frame or at an earlier timeframe. Since it is very likely that a *priority* application will require an advisory committee meeting for one or more of the usual reasons (e.g., unique product characteristics, first in its class, etc.), this provision of the *CBER Draft Guidance* is counterproductive to the *priority* review of applications for biological products for which there may not be adequate alternative therapy(-ies) available to patients.

The public health obligation to ensure access to critical therapeutic agents under *priority* reviews must remain the primary CBER priority, before the secondary CBER obligation to provide redacted *background packages* for public review.

> Recommendation (4c): Subsection C of Section V should be deleted in its entirety from the *CBER Draft Guidance* because it is contrary to FDA's public health mandate--for expeditious review of new and critical therapies. It would be unethical for CBER to miss PDUFA-mandated performance goals for a biological product with potential to be a new or significantly improved treatment option, solely in order to disseminate a redacted *background package* submitted in support of an advisory committee consultation (which are discretionary, not mandatory).

SUMMARY

This *CBER Draft Guidance* addresses the difficult and complex issues of public disclosure of *background packages* prepared for advisory committees by sponsors of biological product applications. However, CBER has deviated from precedent already set by CDER and is attempting to rewrite what has been established as the norm in disclosure policy, rather than

follow CDER's lead. In a regulatory environment increasingly characterized by harmonization, CBER should synchronize the timing of steps with those already implemented in the parallel CDER guidance document.

In its *Draft Guidance*, CBER must recognize and not compromise a sponsor's obligation to protect confidentiality of patient data as well as a sponsor's duty to safeguard confidential and trade secret commercial information.

Merck is strongly opposed to CBER's proposal to ignore its review timeline obligations (under PDUFA II) for *priority* applications, in order to accommodate redaction of disclosure-exempt *background packages*. This unique policy proposal is in conflict with the exedient process required for biological products in cases where there may be inadequate alternative therapies available to patients.

Finally, the proposed effective date of June 1, 2001 does not allow adequate consideration of comments and should be extended by 30 days after the end of the May 21, 2001 comment period, to July 27, 2001.

We welcome the opportunity to comment on this *CBER Draft Guidance* and, if appropriate, to meet with you to discuss these issues.

Sincerely,

Helen O Colen for Henrietta Ukwu

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ATTACHMENT

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February 15, 2000

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RE: [Docket No. 99D-4959]

Draft Guidance for Industry on Disclosing Information Provided to Advisory Committees in Connection with Open Advisory Committee Meetings Related to the Testing or Approval of New Drugs and Convened by the Center for Drug Evaluation and Research, Beginning on January 1, 2000

Merck & Co., Inc., is a leading worldwide, human health product company. Merck's corporate strategy -- to discover new medicines through breakthrough research -- encourages us to spend more than $2 Billion, annually, on worldwide Research and Development (R & D). Through a combination of the best science and state-of-the-art medicine, Merck's R & D pipeline has produced many of the important pharmaceutical products on the market, today.

Merck supports regulatory oversight of product development that is based on sound scientific principles and good medical judgment. Regulators must be reasonable, unbiased and efficient when they review the quality, effectiveness and safety of our products. It is in both of our interests to see that important therapeutic advances reach patients without unnecessary or unusual delays.

In the course of bringing our product candidates through developmental testing, clinical trials, and ultimately to the marketplace, Merck frequently participates in open Advisory Committee meetings which are the subject of this draft guidance. Indeed, over the past 6 years, Merck has participated in approximately 9 open Advisory Committee meetings during which our pending applications were reviewed. For this reason, we are very interested and well qualified to comment on this draft guidance regarding the disclosure of information that is provided to open CDER Advisory Committees regarding the testing or approval of new drugs.

General Comments

We commend the U.S. FDA for examining this difficult issue. However, Merck has serious concerns about this draft guidance as written and, if implemented as written, its impact on the sponsor's ability to provide Advisory Committees with comprehensive and meaningful scientific information regarding new drug candidates as part of Advisory

Committee packages. It is Merck's position that much of the detailed, comprehensive, and issue-oriented information historically provided in sponsors confidential *Advisory Committee background packages* (hereafter referred to as Packages) would no longer be provided in these Packages if this draft guidance is implemented as written. This position is discussed further below.

Specific Comments

I. Preamble—*Federal Register (FR)* Notice

Merck commends CDER on the thoroughness of the data that were used to estimate the annual information collection burdens with regard to this guidance document and does not disagree with the estimates provided.

II. Guidance Document

1) Pages 3-5, Sections A-C

The intent of a sponsor's Package is to provide an in-depth review of all pertinent information regarding the preclinical and clinical development of a new drug candidate to the Advisory Committee members, who are scientifically sophisticated experts, in advance of the meeting. Members of Advisory Committees are best served by receiving in-depth, issue-oriented packages to acquaint themselves with the development program issues prior to the meeting and thereby are prepared to participate fully in the meeting discussions. In order to provide this detailed information to the Advisory Committee, Merck's Packages have routinely included information that this draft guidance identifies as being fully disclosable to the public, but which we believe would cause substantial competitive harm if disclosed, such as:

- summaries of non-pivotal safety and effectiveness data
- summaries of any safety and effectiveness data that relate to anything other than a) the indication to be discussed in open session of the advisory committee meeting, and b) anything else the sponsor anticipates will be discussed in the open session
- summaries of adverse reaction data
- clinical and pre-clinical protocols
- identification of clinical investigators

Additionally, in order to provide the Advisory Committee with full information about the new drug candidate, our packages have routinely included proposed draft labeling which we also consider to be exempt from public disclosure.

In the draft guidance, CDER strongly encourages sponsors to submit Packages that do not contain any information that the sponsor asserts is exempt from disclosure under the Freedom of Information Act (FOIA) and thus would be publicly disclosable in their entirety. CDER's preference to receive fully disclosable sponsor Packages is evident from the required submission timelines outlined in the draft guidance for fully releasable sponsor Packages (i.e., 21 business days prior to the meeting vs. sponsor Packages containing disclosure-exempt material (48 business days prior to the meeting). Thus, with the implementation of this draft guidance as written, much of the detailed and issue-oriented information previously provided in confidential Packages would no longer be provided, given both the timeline and disclosure constraints cited above. Consequently, the resulting Package will be less useful and less informative to the Advisory Committee in preparation for the meeting.

2) Pages 4-5. Section C, paragraph 2, second line:

"Although full reports of safety and effectiveness data might be used by a competitor to support approval of a competing product, a summary could not be so used and, therefore, generally does not constitute confidential commercial information."

Page 5, Section C, paragraph 4, 1st line:

"Ordinarily the following materials in advisory committee packages will be considered disclosable, unless they contain information that the sponsor demonstrates will cause substantial competitive harm if disclosed."

These sentences are not clear and may not be accurate; they may mislead companies inexperienced with presenting data before Advisory Committees into declaring a summary as *non-confidential* incorrectly. In the context of a sponsor's Package that includes information intended to be released on slides at an Advisory Committee meeting, these statements may be considered generally true. However, there are many instances when summary data *per se* could be used to a competitive advantage.

The vast majority of the information CDER proposes to release falls within Exemption 4 of the FOIA, 5 U.S.C. Section 552b c(4) (FOIA). The Federal Advisory Committee Act (FACA), 5 U.S.C. App. II Section 10(b), which obligates the FDA to make briefing packets publicly available at or before the Advisory Committee Meeting, does not apply to these materials. Also, the Federal Trade Secrets Act, 18 U.S.C. Section 1905, prohibits their public disclosure.

Material submitted voluntarily to an agency is confidential and within Exemption 4 of FOIA if it is "of a kind that would customarily not be released to the public by the person from whom it was obtained.[1]" Briefing packets are voluntarily submitted by pharmaceutical companies to CDER for use by Advisory Committees. No statute, regulation, or agency policy requires a sponsor to prepare or submit a briefing packet in connection with an Advisory Committee meeting, nor does any regulation dictate the contents of such packets. Moreover, it is beyond dispute that sponsors do not customarily release to the public their safety and effectiveness data, protocols, adverse events, names of investigators, proposed indications, or draft labeling. Accordingly, under the Critical Mass test, these items are within Exemption 4.

These items also satisfy the legal requirement for Exemption 4 that applies to information required to be submitted to the government. Such information is within Exemption 4 if its disclosure would cause "substantial competitive harm" to the submitter[2]. Disclosure of safety and effectiveness data beyond what is discussed at the Advisory Committee meeting, and disclosure of protocols, adverse events, names of investigators, proposed indication, and draft labeling would cause substantial competitive harm to NDA applicants. All of this information could be used by competitors to eliminate the time and effort otherwise required to bring a competing product to market or would allow a competitor to develop programs for competitive products sooner than they otherwise could.

Merck Recommendation: These sentences should be revised as follows:

> *"Although full reports of safety and effectiveness data might be used by a competitor to support approval of a competing product, a summary of data, as presented on a slide, might not be so used and, therefore, generally does not constitute confidential commercial information."*
>
> *"Ordinarily the following materials in advisory committee packages will be considered disclosable when provided in the format of a slide for presentation at the meeting. There may be instances when they contain information that the sponsor demonstrates will cause substantial competitive harm if disclosed."* [Emphasis Added]

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[1] Critical Mass Energy Project v. Nuclear Regulatory Comm'n, 975 F.2d 871, 879 (D.C. Cir. 1992)
[2] National Parks & Conservation Ass'n v. Morton, 498 F.2d 770 (D.C. Cir. 1974); Critical Mass, 975 F.2d at 878-80.

Although it is understood that Advisory Committees report to the Office of the Commissioner (so as not to be biased by allegiance to the Review Divisions) and that they are organizationally situated within the umbrella of FDA's executive staff, the following disclaimer may seriously mislead those to whom the information is released:

> *"The statements contained in this document are those of the product's sponsor, not FDA, and FDA does not necessarily agree with the sponsor's statements. FDA has not made final determination about the safety or effectiveness of the product described in this document."*

This sentence conveys an imprimatur of review at FDA at a level significantly higher than CDER and significantly higher than may be the case at the time the information is released. For example, one might assume that review of the application has included examination by the Office of General Counsel (OGC), since the OGC also resides outside of CDER but within the umbrella of FDA's executive staff functions. In fact, at the time of an Advisory Committee meeting, it would be very unlikely that an application would have undergone legal review and CDER's review may only have been conducted at the first technical level. Therefore, the disclaimer may be exceedingly broad and misleading and should be changed to limit its impact to the areas that have properly been involved in review of the application at the time the information is disclosed. Further, this disclaimer may *over*state or overemphasize *disagreement* between the sponsor and CDER about the application, rather than convey that some *agreement* has been achieved through this intensive process.

Merck Recommendation: Merck recommends a revised statement in the guidance as follows:

> *"The statements contained in this document are those of the product's sponsor, not of CDER, and CDER does not necessarily agree with all the sponsor's statements. CDER has not made a final determination about the safety or effectiveness of the product described in this document."* [Emphasis Added]

4) Page 7, Section V., A---Fully Releasable Sponsor Submissions

It is not clear why there is a difference of four days between the time that the sponsor's fully releasable package (22 days prior to the meeting) and the division's unredacted package (18 days prior to the meeting) are sent to Advisory Committee members. (Since the division's package is unredacted, the additional time is not used for redaction.) In addition, it is also not clear why the sponsor does not

receive the unredacted review division's Package for review and comment at the time it is sent to Advisory Committee members. Experience indicates that early review division's Packages, often created in haste to accommodate time schedules like these, often contain conclusions from preliminary data or cursory reviews which, when discussed and evaluated more closely, are often found to be inaccurate or speculative.

In the interest of full disclosure of the issues before the Advisory Committee meeting, it would be reasonable to assume that all issues should be known to sponsors so that an appropriate Package may be created and sent to Advisory Committee members. In this regard, there should be no reason why the unredacted review division's Package should *not* be disclosed to the sponsor, since it will likely contain information (pertaining to content and tone) that will be material to the sponsor's preparations for the meeting.

Merck Recommendation:

The guidance should be revised to state that the review division's Package will be released to the sponsor in the unredacted form at the same time it is sent to Advisory Committee members. Alternatively, since sponsors are being encouraged to submit packages not requiring redaction, perhaps the review division should be encouraged to do the same. This should require supervisory review of the primary reviewer's technical report earlier in the review process.

5) Page 7, Section V., A, #10

This guidance is not binding on sponsors and it is not in the interest of sponsors (nor is it the obligation of sponsors) to release copies of their Advisory Committee Packages to the public.

Merck Recommendation: The following statement should be deleted from the draft guidance:

"sponsors are encouraged to bring to the meeting, for public distribution, a reasonable number of hard copies of the slides they will be presenting."

6) Pages 8-9, Section V., B. Re: sponsor Packages Requiring Redaction

The draft guidance cites different submission timelines for fully releasable sponsor packages (21 business days prior to the meeting) vs. sponsors packages containing disclosure-exempt material (48 business days prior to the meeting). In our experience, the 48 business day timeframe required for submission of sponsor materials considered to be exempt from disclosure is not practical within the time

constraints of the typical NDA review process. A comprehensive and reader-friendly Package requires a minimum of 6 to 10 weeks to draft and to navigate internal (within company) review, revisions, approval and final assembly before release for CDER review. Under this time constraint, the sponsor would be expected to begin drafting this document as much as five months before a projected Advisory Committee meeting date, assuming that the date or even the need for an Advisory Committee hearing has been established that far in advance. If one assumes a 10 month or *standard* review period, very few of the issues relating to the application would have been identified by the CDER review team as potential topics for Advisory Committee deliberation at this juncture in the review process.

While it is reasonable to expect that many of the issues encountered can be readily predicted during pre-submission meetings with sponsors, often significant unanticipated issues arise later in the process after reviewers have had the opportunity to review the application in depth. For this reason, it is not realistic to expect that sponsors would be able to provide a completed package that addresses all potential issues 48 business days prior to the Advisory Committee meeting date. The requirement to submit a disclosure-exempt package 48 business days prior to the meeting may eliminate the sponsor's ability to address pertinent issues in the Package, thereby denying Advisory Committee members the opportunity to review the sponsor's data or views on these issues in advance of the meeting.

For applications which may receive *priority* review, i.e., where the time frame for review would be targeted for 6 months, the decision to present the application to an Advisory Committee will need to be made at the time the application is submitted and a disclosure-exempt Package would need to be submitted soon after the application is filed, -- two conditions which may be virtually impossible to achieve. [See additional comments about the impact of this draft guidance on priority reviews in Comment 7, below.]

Merck Recommendation:

In order for sponsors to continue to provide Advisory Committees with issue-oriented Packages, the draft guidance should stipulate identical timelines for fully disclosable and disclosure-exempt sponsor Packages, with all necessary redaction review and discussion activities occurring subsequent to the submission to the sponsor's Package, 21 business days prior to the meeting. If this recommendation cannot be implemented, the following alternative may provide an acceptable alternative.

Experience indicates that most potentially redactable elements of a Package are discrete sections or topics rather than individual words or phrases. Thus, it

should be possible for the sponsor and CDER to agree on those elements without having a completed Package. In this alternative scenario, the sponsor would have the option to identify and justify in general terms the elements of the Package that should be redacted, for CDER's consideration in the timeframe stipulated by the draft guidance, i.e., 48 days in advance of the meeting date. Once general redactions are agreed upon, the sponsor could submit the completed Package that addresses all these issues on a time frame that resembles that for a fully releasable package. Acceptance of these terms would require a sponsor's commitment not to subsequently claim or identify additional redactable material without also jeopardizing the timing of the Advisory Committee meeting and possibly extending the review clock as a consequence. At the same time, this compromise would require that no new information be requested to be included in the Package by CDER staff.

This alternative represents a reasonable compromise between the need to have sufficient time for CDER assessment of proposed redactions and the realities of including new issues during that stage of the NDA review process.

Additionally, the timelines for submission of CDER's Package to Advisory Committee members fail to give the sponsor adequate opportunity to challenge the inclusion of exempt material in the CDER Package before the unredacted version is provided to the Advisory Committee, 18 business days prior to the meeting. According to the draft guidance timelines, the sponsor does not receive a redacted version of the CDER Package until 14 business days prior to the meeting, thereby precluding any discussion between the sponsor and CDER regarding possibly exempt material within the CDER package prior to its dissemination to the Advisory Committee. The draft guidance also states that all discussions between CDER and the sponsor regarding redactions in the CDER package must be completed within 6 business days (between 14 days and 8 days prior to the Advisory Committee meeting) and that the sponsor be notified of CDER's decision regarding redactions on the same day that the redacted Package is sent to the Advisory Committee (i.e., 7 days prior to the meeting).

Merck Recommendation:

Merck's experience indicates that it would be prudent for the guidance to be revised to state that the CDER package will not be distributed to the Advisory Committee, either in unredacted or redacted form, until there is agreement between CDER and the sponsor on inclusion of exempt material to avoid unnecessary inaccuracies and potential contradictions on statements made in public at the meeting.

7) Page 10, Section V., C., Effect on Review Clock for Priority Reviews

Merck strongly objects to the inclusion in the draft guidance of CDER's stipulation that review time for *priority* review applications will be extended *by 2 months* if a disclosure-exempt sponsor's Package is submitted. The decision to review an application under *priority* time frames is dependent upon patient need (no alternative therapy) and reapplication of existing CDER resources to the review of the application in question. There should be no "*tacit*" decision to extend the review clock inferred by any of the following:

- a decision by CDER to require Advisory Committee review of a *priority* application;

or,

- acceptance by an applicant of CDER's decision to require Advisory Committee review of an application that may otherwise receive *priority* review;

and/or,

- the sponsor's decision to submit material requiring redaction.

This provision conveys authority in a non-binding draft guidance that contradicts agreements set up under the Prescription Drug User Fee Act or PDUFA II[3], which is binding because it is law. This guidance does not diminish patient need nor does it change CDER resources, other than to require reallocation of those resources (provided for under PDUFA II) to different task(s), e.g., more persons to redact in shorter time frame or at an earlier timeframe. Since it is very likely that a *priority* application will require an Advisory Committee meeting for one or more of the usual reasons (e.g., unique product characteristics, *first in its class*, etc.), this provision of the draft guidance is counterproductive to the *priority* review of applications for drugs for which there may not be adequate alternative therapy(ies) available to patients.

In effect, by this provision, CDER is stating in this draft guidance that a sponsor should not bother to request *priority* review of an application for a product with an important medical need, but which may be complicated and require both an Advisory Committee meeting and the dissemination of a disclosure-exempt Package for the meeting, since the time expected to be saved will be lost via this extension. Further, since this extended timeline will encourage sponsors to submit briefing packages that are fully disclosable, those packages will not provide to the Advisory Committee the appropriate issue-oriented, in-depth information on the new drug candidate which may be required to address concerns raised by CDER about this application.

[3] Subtitle A of Food and Drug Administration Modernization Act of 1997 or FDAMA

Since the sponsor has very little say, if any, in the matter of CDER's decision to take an application to an Advisory Committee meeting, this guidance should not automatically be punitive to the sponsor for agreeing to participate in such a meeting or for agreeing to submit information that is disclosure-exempt. Nor would it be in the interest of patients to delay priority applications for therapies without adequate market alternatives from reaching the market.

Merck Recommendation:

This 2-month extension provision should be deleted from the guidance because this provision has no basis in law and would violate FDA's commitments under PDUFA II. Merck suggests that CDER consider reallocation of resources to address *priority* reviews in the agreed upon time frames stipulated by PDUFA II.

Summary

This draft guidance addresses the difficult and complex issue of public disclosure of Packages prepared by sponsors and CDER. With the implementation of this draft guidance as written, much of the detailed, comprehensive and issue-oriented information, previously provided by sponsors in confidential Packages, would no longer be provided, due to the timeline and disclosure constraints cited above. The resulting packages will ultimately be less useful and less informative to the Advisory Committee and would not be in the Committee's best interests. Merck opposes the extension of the review timeline for priority applications by 2 months, to accommodate redaction of disclosure-exempt sponsor Packages. We believe this extension is not founded in law and is unethical when one considers that it would delay marketing approval of *priority* applications, those for which no adequate alternative therapies may be available for patients.

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

Sincerely,

Bonnie J. Goldmann, M.D

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