Guidance for Industry

Supplements to Approved Applications for Class III Medical Devices: Use of Published Literature, Use of Previously Submitted Materials, and Priority Review

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Food and Drug Administration
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Preface

Public Comment:

Comments and suggestions may be submitted at any time for Agency consideration to:

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Comments may not be acted upon by the Agency until the document is next revised or updated. For questions regarding the use or interpretation of this guidance contact Kathy M. Poneleit (CDRH) at 301-594-2186, or Jerome A. Donlon (CBER) at 301-827-3028.

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Guidance for Industry, Supplements to Approved Applications for Class III Medical Devices: Use of Published Literature, Use of Previously Submitted Materials, and Priority Review

I. Background/Purpose

This guidance[1] is being issued in accordance with section 403(b) of the FDA Modernization Act (FDAMA) of 1997 (Pub. L. 105-115). Section 403(b) provides that:

> Not later than 180 days after the date of enactment, the Secretary (FDA by delegation) shall issue final guidances to clarify the requirements for, and facilitate the submission of data to support, the approval of supplemental applications for the approved articles under the Federal Food, Drug and Cosmetic Act (the act) (21 U.S.C. 301 et seq.) or section 351 of the Public Health Service Act (42 U.S.C. 262). The guidances shall –
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> - clarify circumstances in which published matter may be the basis for approval of a supplemental application;
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> - specify data requirements that will avoid duplication of previously submitted data by recognizing the availability of data previously submitted in support of an original application; and
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> - define supplemental applications that are eligible for priority review.

Section 403(b) of FDAMA is applicable to multiple centers within FDA. Availability of the draft guidance prepared by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) was announced in the Federal Register of March 21, 1997 (62 FR 13650)(CDER/CBER draft guidance). The CDER/CBER draft guidance describes the use of literature and the types of study design that may support supplemental effectiveness claims for approved drug and biological products.

[1] This document is intended to provide guidance. It represents the Agency's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

CDRH issued draft guidance on March 20, 1998, that set forth its perspective on the applicability of the CDER/CBER draft guidance to medical devices. Both the Center for Devices and Radiological Health (CDRH) and the Center for Biologics Evaluation and Research (CBER) have responsibilities for the regulation of medical devices. This document applies to medical devices regulated by either CDRH or CBER and reflects the current thinking of both centers on the subject of this guidance. It does not apply to medical devices licensed by CBER.

The agency received two comments on the draft guidance. Both comments encouraged the agency to issue two separate guidance documents, one for devices and one for drugs and biologics, rather than a single guidance document. Also, both comments requested device-specific examples in the guidance document. One comment requested additional guidance on other provisions of FDAMA.

Although CDRH initially had expected the final guidance issued in accordance with 403(b) to be a single agency document that addressed devices, drugs and biologics, CDRH and CBER have decided, in the interest of clarity and consistent with comments received on the draft guidance, to issue a separate guidance document for medical devices. This final guidance for medical devices builds upon the foundation developed in the CDER/CBER draft guidance regarding the use of published literature, draws upon the existing Premarket Approval application (PMA) regulation, and refers to earlier guidance documents developed by CDRH that describe efforts to avoid duplication of previously submitted data and that define supplemental applications that are eligible for priority review. In this final guidance, device specific examples have replaced the drug examples presented in the CDER/CBER draft guidance. This guidance has been revised to account for all class III products approved as PMAs, including Humanitarian Device Exemption (HDE) products and Product Development Protocols (PDPs)[2]. This guidance also provides examples of how the use of published literature may be used in support of a PMA, PDP, or HDE supplement[3]. The agency intends to issue additional guidance documents on other provisions of FDAMA and will solicit public comment on those guidances in accordance with FDA's Good Guidance Practices.

[2] A Class III device for which a PDP has been declared completed by FDA is considered to have an approved PMA. 21 CFR 814.19. Supplements to PDPs, therefore, will be treated as PMA supplements for purposes of this guidance.

[3] Published literature would most frequently be used to support supplements for new indications for use of an approved device. In accordance with 21 CFR 814.110, an applicant seeking approval for a new indication for use for an approved humanitarian use device must submit an original HDE. Therefore, this guidance would apply to HDE supplements only in unusual circumstances.

II. Use of Published Literature to Support PMAs, PDPs, HDEs, and PMA Supplements

For devices requiring a PMA or PDP under section 515 of the act, the applicant must establish that there is *reasonable assurance* the device is safe and effective under the conditions of use prescribed, recommended, or suggested in the proposed labeling (21 U.S.C. 360e). Effectiveness of a device should consist principally of well-controlled investigations or other valid scientific evidence as described in 21 CFR 860.7. Section 513(a)(2) of the act states that effectiveness is to be determined:

- with respect to the persons for whose use the device is represented or intended,
- with respect to the conditions of use prescribed, recommended, or suggested in the labeling of the device, and
- weighing any probable benefit to health from the use of the device against probable risk of injury or illness from such use.

The standard of reasonable assurance of safety and effectiveness and the express requirement that the Secretary do a risk-benefit analysis for devices reflect differences between the drug and device provisions of the act. Section 513(a)(3)(A) provides that the effectiveness of a device is to be determined on the basis of well-controlled investigations, including one or more clinical investigations where appropriate, by experts qualified by training and experience to evaluate the effectiveness of the device. The act also provides that the agency may rely on valid scientific evidence (other than evidence derived from well-controlled investigations) in approving device applications.

FDA's regulations implementing the act describe the different types of data that may be considered valid scientific evidence. Under 21 CFR 860.7, valid scientific evidence is considered to be evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness. The evidence required to establish effectiveness may vary according to the characteristics of the device, its conditions of use, the existence and adequacy of warnings and other restrictions, and the extent of experience with its use.

While most applications are supported by original clinical investigations, reports in the medical literature may be the vehicle to establish the existence of valid scientific evidence.[4] In accordance with 21 CFR 860.7, valid scientific evidence may consist of reports of significant human experience with a marketed device. While literature-based evidence typically has been treated as supportive information within the review process, it may be accepted as the sole basis for approval of PMA, PDP, and HDE supplements when the literature is sufficient, detailed, objective, and directly applicable to the subject device.

The type of information in published literature that would be adequate to support supplements for approved pharmaceutical products may not always be comparable to the type of information that would be sufficient to support supplements to PMAs, PDPs, or HDEs. The active ingredient of a drug is ordinarily a known chemical entity, whose performance is predictable when other factors are varied. Devices, on the other hand, frequently are varied and complex in their specifications, construction, and manufacture. The details provided in published literature may not be sufficient to establish that the device that is the subject of the published report is comparable in design, performance, and manufacture to the device that is the subject of the supplement. In those cases, the center may not be able to assess whether the published report can support the agency's review of the subject device.

Assuming the published reports contain sufficient detail to establish that experience with the product that is the subject of the report is applicable to the device that is the subject of a supplement, the detail of the clinical data associated with the published reports will affect the agency's ability to rely on those reports. Clinical data submitted to support a PMA needs to have an appropriate level of detail. Under 21 CFR 814.20(b)(6)(2), a clinical protocol should identify the number of investigators and subjects per investigator, specify the study subject selection and exclusion criteria, study population, study period, safety and effectiveness data, adverse reactions and complications, patient discontinuation, patient complaints, device failures and replacements, tabulations of data from all individual subject report forms and copies of such forms for each subject who died during a clinical investigation or who did not complete the investigation, results of statistical analyses of the clinical investigations, device failures and replacements, contraindications and precautions for use of the device, and any other appropriate information from the clinical investigations. The extent to which published literature provides this level of detail will increase the likelihood that those reports will successfully support a PMA, PDP or HDE supplement.

The extent of documentation necessary to establish that a device is safe and effective for its intended use depends on the particular study, the types of data involved, and the other evidence available to support the claim. However, experience has shown that the published literature do not always contain a complete, or entirely accurate, representation of the device design, performance, manufacture, clinical study plans, conduct, accountability, and outcomes.

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[4] Under 520(h)(3), the publicly available detailed summary of the safety and effectiveness information that was the basis for approving an application for premarket approval *may not* be used to establish the safety or effectiveness of another device by any person other than the person who submitted the information, unless the information is subject to the requirements of 520(h)(4). Accordingly, these summaries of safety and effectiveness cannot be "published literature" used to support approval of a supplement.

Incompleteness, lack of clarity, failure to identify deviations from prospectively planned statistical analyses, use in a different setting from the intended use, and inadequate descriptions of how critical outcome measurements or assessments were made are common problems. These inadequacies associated with published reports are due to a variety of factors. For some peer reviewed articles, peer reviewers may have access only to a limited data set and analyses. Such reviewers ordinarily do not see the original protocol and amendments, and thus may lack sufficient information to detect critical omissions and problems in the reported data. The peer review process also may be affected by variability in the relevant experience and expertise of the peer reviewer. In a relatively small number of cases, omissions in published reports may be due to careless reporting or intentional fraud.

Situations When Published Reports May Support Supplements

Despite the limitations discussed above, there are a variety of situations where the use of published literature may be appropriate to support supplements for approved medical devices. The examples described below are intended to identify such situations and to provide guidance about the utility of such reports.

Example 1 - Reports of Prior United States Marketing Experience. Reports of prior United States marketing experience may be available for: a) Class III devices that were on the market prior to May 28, 1976 (commonly called a "preamendment device") and for which the applicant subsequently has been required to submit safety and effectiveness information under 515(b) of the act; and b) marketed devices, whether pre- or post- amendment, that have been studied by individuals other than the applicant for different/new uses. Often, applicants submitting supplements for these types of devices have access to a body of published literature that reports experience with the applicant's specific device, or experience with a device of similar technology and performance, which may be applicable to the safety and effectiveness review of the supplement.

Example 2 - Reports of Foreign Marketing Experience. In this situation, clinical trials using a device have been conducted outside the United States and there is published literature reporting the results of these trials. If these trials have not been sponsored by the applicant, the applicant may or may not be able to acquire access to the underlying data and details of the study conduct and results. The agency will consider the extent to which the reports are convincing in and of themselves, but applicants should be aware that access to this information may be necessary to support supplement approval.

Example 3 - Reports of Foreign Marketing Experience Combined with Applicant Sponsored Studies. In these situations, the applicant has sponsored studies of the subject device, but those studies alone are insufficient to demonstrate that the device is safe and effective for the supplemental use. Published literature describing foreign device trials using the applicant's product may exist. The applicant may or may not be able provide the details of the underlying data and the study conduct. These studies, when combined with the trials

sponsored by the applicant, may be sufficient to support the demonstration of safety and effectiveness of new uses of the device.

Data Underlying Published Reports

In all of these examples, access to underlying data and other detailed information not provided in the published literature increases the likelihood that the published reports can support approval of a supplement. These additional data and information may include:

a. The protocol used for the study, as well as any important protocol amendments that were implemented during the clinical study and their relationship to study subject accrual or randomization of the study subjects. The information may be needed to evaluate the effect of the modification on the designed randomization scheme or patient accrual as well as poolabililty of the results before and after the modification.

b. The prospective statistical analysis plan and any changes from the original statistical plan that occurred during or after the clinical study, with particular note of which analyses were performed pre- and post-unmasking (sometimes referred to as unblinding) if such a study design was employed.

c. Randomization codes, if such a study design was employed, and documented study entry dates for the study subjects.

d. Full accounting of all study subjects, including identification of any subjects with clinical data who have been excluded from either the safety or the effectiveness analyses for any reason, and analyses of results using all subjects with clinical data (either as a "worst case analysis" or "intention-to-treat").

e. Electronic or paper record for each study subject for critical outcome measures and relevant baseline characteristics. Where individual subject responses are a critical outcome measure (e.g., objective responses in cancer patients, pain reduction, or detection of a bacterial agent), detailed bases for the assessment, such as the case report, hospital records, laboratory report, and narratives.

f. Complete information for all patients who died during the study and for those who discontinued the study ordinarily is necessary to detect important safety problems as well as to ensure that the study evaluation is as unbiased as possible. Adverse event reporting in the published literature submitted to support supplements should be considered in association with those adverse events reported in the original PMA, PDP, or HDE or subsequently approved supplements. The applicability of the adverse event information in the published literature depends on the existing safety information, whether the new indication is different from that of the original application (e.g., injectable collagen used for facial wrinkles versus urethral

injection for urinary incontinence), and whether the new population or use presents a new and serious safety issue.

Sufficiency of Published Reports

Published literature alone may be sufficient to support approval of supplements. There have been approvals based primarily or exclusively on published reports. Examples include the approval of several retinal gasses for the treatment of uncomplicated retinal detachments, a stent for coronary placement, and sodium hyaluronate for pain in osteoarthritis of the knee. The following factors increase the likelihood that such published reports will, by themselves, be adequate:

a. The reports reflect multiple studies conducted by different investigators, each of the studies has an adequate design, all published studies are reported, and the findings across studies are consistent.

b. The reports reflect high level of detail, including clear and adequate descriptions of statistical plans, analytic methods (prospectively determined), study endpoints, and a full accounting of all enrolled patients.

c. The reports identify relevant endpoints that can be objectively assessed and that are not dependent on investigator judgment (e.g., radiographically documented endpoints, restoration of function, or overall mortality). Such endpoints are more reliable than more subjective endpoints, such as relief of pain or symptoms reported by the study subject.

d. The reports identify results of *a priori* statistical analysis plans that provide consistent conclusions of safety and effectiveness rather than unplanned statistical analyses (sometimes referred to as “data dredging”).

e. The reports describe studies conducted by investigators of recognized competence who have a demonstrated history of compliance with the laws and regulations governing the study of human subjects.

III. Data Requirements that Will Avoid Duplication of Previously Submitted Data by Recognition of the Availability of Data Previously Submitted in Support of PMAs, PDPs, HDEs or PMA Supplements

Since 1986, FDA has had a regulation that addresses the data necessary to support evaluation of a PMA supplemental application. The abbreviated regulatory requirements for PMA supplemental applications are established under 21 CFR 814.39(c), which states that "all procedures and actions that apply to an application under Sec. 814.20 also apply to PMA supplements *except that the information required in a supplement is limited to that needed to support the change*" (emphasis added). This regulation avoids unnecessary resubmission of previously submitted materials under the original application. FDA has and will continue to incorporate the information in the original PMA, PDP, or HDE that applies to the changes requested in the supplement, without requiring the applicant to submit the same or duplicative data. FDA also will incorporate information from other submissions at the request of the applicant if the information is relevant and the applicant has the right of reference.

FDAMA added a provision to section 515(d)(6)(B) of the act that addresses data submission standards to support supplemental applications. With respect to PMA supplements for an incremental change to the design of a device that affects safety or effectiveness, new section 515(d)(6)(B) requires FDA to approve such supplement if, among other things, clinical data from the approved application and any supplement to the approved application provide a reasonable assurance of safety and effectiveness for the changed device. Nonclinical data may be sufficient to demonstrate that the design/product modification creates the intended additional capacity, function, or performance of the device. The new provision clarifies, however, that FDA may require, when necessary, additional clinical data to evaluate the modification of the device to provide a reasonable assurance of safety and effectiveness. This addition to the statute is consistent with FDA's past practices and FDA will continue to request in PMA, PDP and HDE supplements only that additional data necessary to support the change. It remains the applicant's responsibility to justify why previously submitted data provide reasonable assurance that the device is safe and effective[5] for its intended use.

[5] except for HDE supplements, which would not require effectiveness data

IV. PMA Supplemental Applications that are Eligible for Priority Review

FDA has a longstanding history with respect to review of products whose approval is expected to provide significant public health benefits. FDA first articulated a priority review policy for PMAs in 1989 in a CDRH General Program Memoranda (#G89-2, "IDE/PMA Expedited Review Process"). A 1994 General Program Memorandum (#G94-2, "PMA/510(k) Expedited Review") clarified that FDA would grant expedited review when the agency determined that such review would provide a specific public health benefit. Section 202 of FDAMA codified in new section 515(d) of the act the requirement that such priority review be available. FDA has and will continue to grant priority review when such review will provide significant public health benefits. For further details regarding priority review for PMAs, PDPs, and HDEs, as well as supplements for those submissions, please refer to the updated CDRH policy General Program Memorandum (#G98-1, "PMA/510(k) Expedited Review") which can be found at the CDRH website at http://www.fda.gov/cdrh/modact/expedite.pdf. This policy also applies to CBER's PMA supplemental applications that are eligible for priority review.