Device Labeling Guidance #G91-1 (blue book memo) (Text Only)

This guidance was written prior to the February 27, 1997 implementation of FDA's Good Guidance Practices, GGP's. It does not create or confer 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. This guidance will be updated in the next revision to include the standard elements of GGP's.

General Program Memorandum #G91-1

Date: March 8, 1991

From: Director, Office of Device Evaluation (HFZ-400)

Subject: Device Labeling Guidance

To: ODE Review Staff

Purpose

The primary purpose of this memorandum is to formalize guidance to ODE reviewers concerning their review of labeling in device marketing submissionsr especially premarket approval applications (PhAs). This guidance is intended to ensure the adequacy of, and consistency in, device labeling information. The guidance is also intended for industry use in preparing device labeling.

Background

General labeling requirements for medical devices have been established in 21 CFR Part 801. Detailed and specific labeling requirements for in vitro diagnostic products were promulgated under 21 CFR 809.10. Neither of these, however, provide specific definitions or explanations of some significant terms such as warnings, precautions, contraindications and adverse reactions. The lack of definitions for such terms leads to misunderstandings and disagreements between PMA applicants and the ODE review staff. Because labeling content is a key factor in the CDRH determination of whether there is reasonable assurance that a device is safe and effective for its intended user such disputes have unnecessarily prolonged PMA review times.

Scope and Application of the Guidance

Portions of the attached "Device Labeling Guidance" that are based upon definitions and requirements in the act and applicable regulations include appropriate references thereto. Guidance on "Indications for Use," "Contraindications," "Warnings," "Precautions" and "Adverse Reactions" paraphrase applicable provisions in the labeling requirements for prescription drugs (21 CFR Part 201). Consistency between drug and device labeling content and the terminology therein will help minimize misunderstandings by medical practitioners and patients.
While this guidance is primarily intended to ensure the adequacy of, and the consistency in, the labeling information for devices subject to premarket approval, it may also contribute to premarket notification reviews. As indicated in the "Blue Book" 510(k) Memorandum #86-3 dated June 30, 1986, a premarket notification must normally only contain proposed labeling sufficient to describe the device's intended use. Accordingly, the S10(k) decision letter finding a device to be substantially equivalent advises that this finding does not connote approval of the proposed labeling. Nevertheless, in the case of in vitro diagnostic devices, devices with special labeling requirements under Subpart H of 21 CFR Part 801, and devices for which the inclusion of

specific directions for use, contraindications, warnings, etc. in the labeling may be critical to a finding of equivalence, the ODE premarket notification labeling review includes an evaluation of the compliance of the proposed labeling, or portions thereof, with applicable requirements under 21 CFR Parts 801 and 809, as appropriate.

This guidance was prepared by Charles H. Kyper, Assistant to the Director, Office of Device Evaluation, with input from the CDRH Office of Compliance and Surveillance, Office of Health Affairs, and Office of Training and Assistance.

It should be understood that the attached guidance is not a regulation and that, as such, variations can occur and should be given appropriate consideration. Based upon the preceding discussion, the need for and usefulness of this guidance should be apparent. ODE reviewers are encouraged to refer to this guidance during labeling reviews and to provide it in correspondence and meetings with representatives of the device industry when appropriate. Reviewers should also keep in mind that this guidance is not intended to limit the consideration of factors that may be specific to the device when reviewing its labeling.

Effective Date: This memorandum is effective immediately.

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Attachment

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DEVICE LABELING GUIDANCE
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I. Definitions

Label: A "label" is a display of written, printed or graphic matter upon the immediate container of any article.[section 201(k).]

Labeling: "Labeling" includes all labels and other written, printed or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article. [section 201(m).]

Intended Uses: The term "intended uses" refers to the objective intent of the persons legally responsible for the labeling of the device. The intent is determined by their expressions or may be shown by the circumstances surrounding the distribution of the device. This objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such representatives. It may be shown by the offering or the using of the device, with the knowledge of such persons or their representatives, for a purpose for which it is neither labeled nor advertised. (21 CFR 801.4)

Directions for Use: The term "Directions for use" provides directions under which the practitioner or layman (e.g., patient or unlicensed health care provider), as appropriate, can use the device safely and for the purposes for which it is intended. Directions for use also include indications for use and appropriate contraindications, warnings, precautions and adverse reaction information. Directions for use requirements applicable to prescription and over-the-counter devices appear throughout 21 CFR Part 801 and, in the case of in vitro diagnostic products, under 21 CFR 809.10.

II. Safety and Effectiveness Considerations (21 CFR 860.7)

In determining the safety and effectiveness of a device for its intended use, the following factors are to be considered and addressed in the device's labeling by the inclusion of appropriate information:

- The persons for whose use the device is represented or intended
- The conditions of use for the device, including conditions of use prescribed, recommended or suggested in the labeling or advertising of the device, and other intended conditions of use;
- The probable benefit to health from the use of the device weighed against any probable injury or illness from such use;
- The reliability of the device; and,
- Other relevant factors.

III. Indications for Use

General Statement of Indications for Use

The general statement of the "Indications for Use" identifies the target population in a significant portion of which sufficient valid scientific evidence has demonstrated that the device as labeled will provide clinically significant results and at the same time does not present an unreasonable risk of illness or injury associated with the use of the device. As appropriate, the labeling should state that the device (trade name) is "indicated" or "intended for use"

(1) in the treatment, mitigation, prevention or diagnosis of a recognized disease or condition or an important manifestation of a disease or condition; and/or,

(2) in the relief or mitigation of symptoms associated with a disease or condition; and/or,

(3) as an aid or adjunct to a mode of therapy or diagnosis.

Additional Information

When indicated or intended for use in selected subgroups of a population with a disease, symptom, or syndrome, the labeling should

(1) describe the available evidence and state the limitations of usefulness of the device;

(2) identify specific tests needed for the selection or monitoring of the patients;

(3) if available, provide information on the approximate kind, degree and duration of improvement to be anticipated; and

(4) if relevant, include information regarding the recommended intervals between device use, the usual duration of treatment, or any modifications of such.

When safety considerations are such that the device should be reserved or restricted for use in certain situations (e.g., cases not responsive to other devices, surgical procedures or drugs), this information shall be stated.

When there are specific conditions that should be met before the device is used on a long-term basis (e.g., demonstration of responsiveness to the device in a short term trial), the labeling should identify the conditions or, if the indications for long-term use are different from those for short-term use, the labeling shall identify the specific indications for each use.

When there is a common belief that the device may be effective for a certain use or there is a common use of the device for a condition but the preponderance of evidence related to the use or condition demonstrates that the device is ineffective, FDA may require that the labeling state that there is a lack of evidence that the device is effective for that use or condition.

IV. Contraindications

This section describes situations in which the device should not be used because the risk of use clearly outweights any possible benefit. Examples that may, but not always, contraindicate the use of a device include:

Hypersensitivity to an ingredient of a permanently implanted device;
Substantial risk of being harmed because of age, sex, concomitant therapy, disease state or other condition; or,
Continued use in the face of an unacceptably hazardous adverse reaction.

Known hazards and not theoretical possibilities are to be listed, e.g., if hypersensitivity to an ingredient in the device has not been demonstrated, it should not be listed as a contraindication. The "Contraindications" section shall immediately follow the "Indications for Use" section of the labeling. If no contraindications are known, this section of the labeling should state "None known."

V. Warnings

Describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur.

Include an appropriate warning if there is reasonable evidence of an association of a serious hazard with the use of the device. A causal relationship need not have been proved.

A warning is appropriate when the device is commonly used for a disease or condition for which there is a lack of valid scientific evidence of effectiveness for that disease or condition and such usage is associated with a serious risk or hazard.

VI. Precautions

Include information regarding any special care to be exercised by the practitioner and/or patient for the safe and effective use of the device, for example:

- Indicate or emphasize any need for protective wear during use.

- Identify any laboratory tests or other evaluations that may be helpful in following the patient's response or in identifying adverse reactions and, if appropriate, specify the frequency of such tests or evaluations before, during and after use of the device.

The "Precautions" section of the labeling includes precautionary statements not appropriate for inclusion under other sections of the labeling. Additional guidance regarding precautions will be found in the "Special Patient Populations" section below.

VII. Special Patient Populations

Limitations on the usage of a device may be necessary for various reasons including lack of long-term safety and effectiveness data, lack of safety and effectiveness data for specific patient populations (e.g., pregnant women), growth processes still occurring in the body, and anatomical or physiological limitations on the effectiveness of the device.

If the safety and effectiveness of the device for use in specific patient populations have not been established on the basis of valid scientific evidence, the "Indications for Use" section shall specifically identify the persons for whose use the device is indicated and the "Precautions" section shall include the following statement:

"Safety and effectiveness in (e.g., pregnant women, children under the age of ..., etc.) have not been established."

If use of the device in a certain patient population is associated with a specific hazard, the hazard shall be described in the "Precautions" section or, if appropriate, the hazard shall be stated in the "Warnings" or "Contraindications" section and the "Precautions" section of the labeling shall refer to it, e.g., "See 'Warnings' section for information on....."

VIII. Adverse Reactions

An adverse reaction is an undesirable effect, reasonably associated with the use of the device, that may occur as part of the effect of the device or may be unpredictable in its occurrence.

This section includes all adverse reactions reasonably associated with the use of the device, including those mentioned in the "Contraindications", "Warnings" and "Precautions" sections of the labeling. The listing of the adverse reactions should be followed, if appropriate, by statements directing the reader to other sections of the labeling for additional information regarding these adverse reactions and any steps that should be taken.

Adverse reactions should be listed in descending order according to their clinical significance as determined by their severity and frequency. Provide frequency data from adequately reported clinical studies when the data is not well known to the device user (practitioner and/or patient) and/or when needed in deciding between the use of the device and an alternative procedure or approach.

IX. Prescription Devices

A prescription device is, by definition under 21 CFR 801.109, a device which, because of any potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, is not safe except under the supervision of a practitioner licensed by law to direct the use of the device, and hence for which "adequate directions for use" (21 CFR 801.5) cannot be prepared.

A prescription device, other than surgical instruments, is misbranded if its label does not bear:

(1) the statement, "Caution: Federal law restricts this device to sale by or on the order of a ", the blank to be filled with the word "physician", "dentist", or with the descriptive designation of any other practitioners licensed by the law of the State in which that person practices to use or order the use of the device; and

(2) the method of application or use of the device.

A prescription device is misbranded if its labeling does not bear:

(1) information for use including indications, effects, routes, methods, frequency and duration of administration, and any relevant hazards, contraindications, side effects, and precautions under which practitioners licensed by law to administer the device can use the device safely and for the purpose for which it is intended, including all purposes for which it is advertised or represented, with the exceptions that

(a) such information may be omitted from the dispensing package if, but only if, the directions, hazards, warnings, and other information are commonly known to practitioners licensed by law to use the device and the FDA Commissioner is requested to offer an opinion on a written proposal stating reasonable grounds to omit such information from the dispensing package;

(b) such information will not be required on so called reminder-piece labeling which calls attention to the name of the device but does not include indications or other use information; and

(2) the date of the issuance or the latest revision of the labeling, except for labels and cartons, that bears directions for the use of the device.

X. Restricted Device

Under the authority of section 515(d)(1)(B)(ii) of the Federal Food, Drug, and Cosmetic Act (the act), the approval order for a premarket approval application (PMA) may require, as a condition of approval, that the sale, distribution and use of the device be restricted but only to the extent permitted under section 520(e) of the act. Under section 520(e) of the act, FDA may require that a device be restricted to sale, distribution and use only upon the written or oral authorization of a practitioner licensed by law to administer or use such devices (i.e., prescription device) or upon such other conditions that FDA may prescribe. Such a requirement must be based upon a determination by FDA that, because of the device's potentiality for harmful effect or the collateral measures necessary to its use, there cannot otherwise be reasonable assurance of its safety and effectiveness. If the device is restricted to use by persons with specific training or experience in its use or by persons for use in certain facilities, FDA must determine that such a restriction is required for the safe and effective use of the device. A person cannot be excluded from using a device, however, solely because that person does not have the training and experience to make him/her eligible for certification by a

certifying board recognized by the American Board of Medical Specialties or has not been certified by such a Board.

When the sale, distribution and use of a device are restricted in a PMA approval order or by regulation under section 520(e) of the act, the label must include appropriate statements of the restrictions imposed by FDA (e.g., restrictions on the sale, distribution and use of the device or restrictions on the use of the device to persons with specific training or experience in its use or to persons for use in certain facilities). The label shall bear the statement, "Caution: Federal law restricts this device to sale, distribution and use by or on the order of a ", the blank to be filled with the word "physician", "dentist", or with the descriptive designation of any other practitioners licensed by the law of the State in which that person practices to use or order the use of the device and, if applicable, followed by a descriptive phrase of the training or experience required (e.g.,"trained and/or experienced in ",the blank to be filled with, as appropriate, "the use of this device" or specified therapeutic or diagnostic procedures) and/or the facilities to which use is restricted.

In accordance with the provisions of section 502(r) of the act, advertisements and other descriptive printed material issued by the manufacturer, packer or distributor with respect to a restricted device must include the following among other things:

(1) a true statement of the device's established name (common or usual name unless there is an official name designated by FDA or recognized in an official compendium), printed prominently and in type at least half as large as that for any trade or brand name for the device; and

(2) a brief statement of the intended uses of the device and relevant warnings, precautions, side effects, and contraindications.

Except in extraordinary circumstances, FDA cannot require prior approval of the content of any advertisement except in the case of any printed matter which FDA determines to be labeling as defined in section 201(m) of the act.

XI. Patient Information Labeling

Patient information labeling includes labeling directed to the patient as well as family members and others who administer home use devices to patients, e.g., care providers who oversee the use of infant apnea monitors and nebulizers. In determining whether patient information labeling is appropriate for a prescription device, the following factors, among others, should be considered:

- Should the patient be aware of alternative(s) to the use of the device if a choice is available?

  Are substantial risks or discomforts associated with the use of the device?

  Is the need for strict patient adherence to a specific treatment regimen required?

  Does substantial public or professional controversy exist about the device and its related procedures?

Patient information labeling shall include the indications for use and relevant contraindications, warnings, precautions and adverse reactions using terminology well known and understood by the average layman. Technical terms should be kept to a minimum

and should be defined when necessary. If applicable, directions to ensure safe and effective use of the device by the patient shall be included. Patient information labeling, if possible, should not exceed the seventh grade reading comprehension level.

The following sources may provide useful information regarding the information to be included as well as the terminology to be used in patient information labeling:

1. U.S.P. Dispensing Information, Volume II, Advice for the PatientR, Drug information in Lay Language
2. American Medical Association Drug Evaluations

XII. Disclaimer of Liability

Inclusion in the labeling of a disclaimer regarding the safety and effectiveness of the device for its indicated or intended use is to be avoided. Instead, labeling and promotional material may include an objective and accurate representation of the clinical experience with the device whereby the practitioner and patient are made aware not to expect a completely safe and effective outcome with the use of the device in all cases.

Inclusion of disclaimers of liability for any medical expenses or any direct or consequential damages resulting from or caused by any defect, failure or malfunction of the device will not inhibit FDA in imposing the notification and otherremedies (repair, replacement or refund) provisions of section 518 of the act. The provisions of section 518 may be imposed whenever FDA determines that:

(1) The device presents an unreasonable risk of substantial harm to the public health;

(2) There are reasonable grounds to believe that the device was not properly designed and manufactured within the state of the art; or

(3) There are reasonable grounds to believe that the unreasonable risk was not caused by failure of a person other than the manufacturer, importer, distributor or retailer of the device to exercise due care in the ... use of the device.

XIII. Misbranding

Pertinent provisions in the law and implementing regulations related to medical device labeling and enforced by FDA appear below. It is important that these provisions be kept in mind both in the development of labeling by the device industry and in the labeling review by CDRH.

Section 502 of the Federal Food,Drug, and Cosmetic Act (the act) provides that a device shall be deemed misbranded if:

(1) Its labeling is false or misleading in any particular.

(2) The label does not bear the name and place of business of the manufacturer, packer or distributor and an accurate statement of the quantity of contents in terms of weight, measure or numerical count.

(3) Any required word, statement or other information to appear on the label or labeling is not prominently placed thereon with such conspicuousness and in such terms as to render it likely to be read and understood by the ordinary individual under customary conditions of purchase and use.

(4) Labeling does not bear adequate directions for use and

such adequate warnings against use in those pathological conditions or by children where its use may be dangerous to health, or against unsafe dosage or methods or duration of administration or application in such manner and form as are necessary for the protection of users.

(5) In the case of a restricted device, its advertising is false or misleading in any particular.

(6) In the case of a restricted device, advertisements and other descriptive printed matter (other than labeling) issued by the manufacturer, packer or distributor do not include a brief statement of the intended uses of the device and relevant warnings, precautions, side effects and contraindications.

In determining whether a device is misbranded because the labeling or advertising is misleading, section 201(n) of the act permits the following to be taken into account among other things:

(1) representations made or suggested by statement, word, design, device, or any combination thereof; or

(2) the extent to which the labeling or advertising fails to reveal facts material in the light of such representations or material with respect to the consequences which may result from the use of the device to which the labeling or advertising relates under the conditions of use prescribed in the labeling or advertising or under such conditions of use as are customary or usual.

Regulations applicable to medical devices provide that the inclusion of any of the following representations in device labeling constitutes misbranding of the device:

21 CFR 801.6 - False or misleading representation with respect to another device or a drug

21 CFR 807.39 -Any representation that creates an impression of official approval because of registration or (e.g.,i clusion of FDA establishment registration number)

21 CFR 807.97 - Any representation that creates an impression of official approval because of complying with the premarket notification regulations (e.g., inclusion of premarket notification reference number)

XIV. Prohibited Acts

Section 301(1) of the act prohibits the use in any labeling or advertising for the device of any representation or suggestion that approval of an application with respect to the device is in effect under section 515 of the act (premarket approval) or that the device complies with the provisions of section 515.

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