BECKMAN COULTER

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13 September 1999

Dockets Management Branch
Division of Management Systems and Policy
Office of Human Resources and Management Services
United States Food & Drug Administration
Room 1061 (HFA-305)
5630 Fishers Lane
Rockville, MD 20852

Re: Guidance on Labeling for Laboratory Tests
Draft Guidance – Not for Implementation
Draft released for comment on June 24, 1999
Posted June 30, 1999 at
http://www.fda.gov/cdrh/ode/1352.html

Ladies & Gentlemen,

Beckman Coulter appreciates the opportunity to comment on FDA's "Draft Guidance on Labeling for Laboratory Tests" as issued for comments on June 24, 1999. This letter provides general comments regarding the proposal. Comments on specific aspects of the draft guidance are provided in the attached table.

Beckman Coulter is a major international manufacturer and worldwide distributor of medical and scientific test systems, including *in vitro* diagnostic test systems. The company was formed in October 1997 by the combination of what was then Beckman Instruments, Inc., based in Fullerton, California and Coulter Corporation, based in Miami, Florida. Beckman Coulter headquarters are located in Fullerton, California. The company's 1998 sales totaled $1.7 billion.

Beckman Coulter has a number of general comments regarding the draft guidance. In particular, it is not clear from the text of the document why FDA believes the guidance is needed or what particular problems with device labeling it is intended to address. The draft guidance appears to be establishing new requirements for the labeling for *in vitro* diagnostic reagents. Regulations specifying the information to be

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provided in the labeling of these reagents are published at 21 CFR, Section 809.10. The implication of this proposal is that the information required by these regulations is inadequate. However, Beckman Coulter is not aware of any expressions by the user community, during the over twenty years since the regulations were adopted, that the information required by the regulations is inadequate.

However, even assuming it is appropriate to include information of the type proposed by FDA in the draft guidance in the labeling for *in vitro* diagnostic devices, Beckman Coulter believes that the use of a guidance document is not appropriate. Since the requirements for *in vitro* diagnostic test labeling are established by regulations, any changes to these requirements should be made by amending the existing regulations. The use of guidance documents may be appropriate to explain or clarify existing requirements; they are not appropriate to create new requirements.

Beckman Coulter also does not understand why FDA has expressed the requirements stated in the draft guidance in terms of labeling content. The draft guidance appears to be distinguishing between "substantial equivalence", the current standard applicable to Section 510(k) Notices, and what the guidance calls "operational truth". Both methods are described as ways to demonstrate that a product is effective for its intended use. If this is the case, then the draft guidance is more appropriate as a communication addressed to individuals preparing submissions for the Office of Device Evaluation and should be stated as addressing the contents of those submissions.

On a more specific level, the draft guidance appears to be using terminology in a way that is not consistent with other published information. For example, the guidance's use of the terms "sensitivity" and "specificity" is not consistent with the way those terms are used in the labeling regulations, cited above, or documents such as in NCCLS GP10A or in Workshop Manual FDA92-4165. If FDA decides to issue this guidance, it needs to ensure that the terminology used is consistent with established and recognized uses of those terms.

Beckman Coulter also questions FDA's apparent assumption that the package insert needs to include this type of information in order for the physician to understand the test. Where specific physician information of this type is determined to be necessary, as in some tests approved through the PMA process, a separate physician's brochure usually is prepared.

Finally, Beckman Coulter believes that adoption of this guidance conflicts with the obligations established in Section 205 of the FDA Modernization Act of 1997. That Section requires FDA to use the least burdensome methods of establishing substantial equivalence for medical devices. By specifying additional detailed information on the

method of demonstrating efficacy that FDA wants manufacturers to include in their labeling, the guidance indirectly requires manufactures to generate this information. Thus, while the guidance discusses only the content of labeling, indirectly it also is imposing new, burdensome requirements for establishing substantial equivalence.

Again, Beckman Coulter appreciates the opportunity to comment on this proposed guidance. Any questions regarding the comments provided in this letter or the attached table can be addressed to my attention at the letterhead address.

Sincerely,

Vlad Ghiulamila
Manager
Global Regulatory Compliance

Attachment: Table of Comments

Specific Comments on the Guidance on Labeling for Laboratory Tests

Draft Guidance – Not for Implementation

Posted June 30, 1999 at http://www.fda.gov/cdrh/ode/1352.html

SECTION	TEXT	COMMENT
Introduction (page 2 of 4)	"The evaluation of laboratory test performance should compare a new product's test results to some appropriate and relevant diagnostic benchmark that can be used to correlate results from the new test with the clinical status or condition of individuals/patients for whom the test is intended to be used."	There is already a benchmark process to evaluate new laboratory tests. New Class I and Class II IVD tests must show substantial equivalence to a predicate test. The PMA process already requires a new Class III IVD test to be compared to a clinical status or condition in order to demonstrate clinical utility. Therefore, the benchmark for 510(k) is a previously cleared or pre-amendment device. The benchmark for a PMA is a clinical status or condition. Therefore, it is not clear why the FDA issued this guidance or what issues were intended to be resolved. The new Draft Guidance would have the labeling include information that directly correlates laboratory results to the clinical state of the patient. This type of detail is not appropriate for most IVD tests. The majority of IVD tests provide numeric measurements of specific analytes at a given point in time. What these results mean with respect to the specific condition of the patient is determined by the physician who also takes into account all relevant clinical information. While IVD test results may be closely correlated with the clinical status or condition and particular disease states of individuals/patients for whom the test is intended to be used, they are seldom used alone.
Introduction (page 2 of 4)	"Determination of the clinical status of patients whose specimens are used in an evaluation may be based on laboratory and/or clinical endpoints."	The author does not define "laboratory and/or clinical end-points". If the author by this statement intended to refer to "reference intervals" and "cut off values", there is not a one to one correlation between reference intervals and cut off values versus disease states. Clinical and laboratory results are not the sole determinant of diagnoses. If the author means "clinical endpoints" to equal "outcomes", laboratory results alone cannot be relied upon as the sole basis for evaluating the efficacy of IVD tests. A physician considers a wide variety of clinical data, including x-rays, physical exams, laboratory data, and personal experience in determining a final diagnosis. A diagnosis is not based solely on laboratory data.

SECTION	TEXT	COMMENT
Introduction (page 2 of 4)	"Characterization of test performance is important to allow labeling that will clarify the performance of the device for both laboratories and health care givers."	The meaning of this sentence is unclear. Labeling that is compliant with 21 CFR 809.10 (a) & (b) has articulated the performance of IVD tests to the general satisfaction of the user community for over 20 years.
Operational Truth (page 2 of 4)	"The case definitions being used as the reference point in determining performance should be clearly referenced and explained either in performance tables and/or supporting text. "	This section proposes to have labeling include information established from autopsy, outcome studies, diagnostic algorithms or other methods, and compare to established case definitions. While the PMAs for some Class III IVD products require studies as described in this section of the Draft Guidance, including this amount of detail in a product insert is of limited value. Case definitions are appropriate to include in a submission to the FDA to verify claims of safety and efficacy. These requirements are more appropriate to a PMA Guidance Document, not a Labeling Guidance Document. Users need information that is succinct and in summary form. Compliance with existing 21 CFR 809.10 (a) & (b) provides the appropriate amount of detail. Supplemental information is often provided by the manufacturer in a Physician's Brochure and/or a Technical Bulletin.
Operational Truth (page 2 of 4)	"Sponsors are encouraged to consult with FDA to ensure case definition being chosen for study will meet agency requirements."	Sponsors already meet with the agency, routinely.
Laboratory Equivalence (page 2 of 4)	"Performance of a new test is characterized in terms of comparison to a predicate."	The boldface **"Laboratory Equivalence"** title of this paragraph should be changed to **"Substantial Equivalence"**. This is the current method for bringing the majority of new products to market. Approximately 90% of IVD tests requiring pre-market clearance are reviewed using the substantial equivalence standard of section 510(k). Only in the absence of substantial equivalence, must the sponsor demonstrate Operational Truth to establish clinical utility. The current system is designed to use the FDA's limited resources as efficiently as possible.
Proposed Labeling (page 3 of 4)	"All package inserts for laboratory tests should clearly explain how performance has been deduced or determined."	As noted above, labeling that is compliant with 21 CFR 809.10 (a) & (b) has articulated the performance of IVD tests to the general satisfaction of the user community for over 20 years.

SECTION	TEXT	COMMENT
Proposed Labeling (page 3 of 4)	Estimates of sensitivity, specificity, and ROC (Receiver Operating Characteristic) Curves along with confidence intervals are appropriate measures of performance and may be presented in labeling."	ROC analysis is not a tool frequently used by most clinical laboratorians to evaluate an IVD test. ROC and confidence limits are tools to determine clinical sensitivity and clinical specificity and may be appropriate for certain esoteric Class III IVD tests. The physician considers a wide variety of clinical data, including x-rays, physical exams, lab data, and personal experience in determining a final diagnosis. Using an ROC analysis can have no meaning in the majority of clinical situations. This sentence should be edited to: "Estimates of clinical sensitivity, clinical specificity..." to avoid ambiguity.
Proposed Labeling (page 4 of 4)	"A test that has been characterized to a predicate but has not been compared to 'true' diagnostic states should be labeled without sensitivity or specificity claims."	The intent of this section is unclear and/or incomplete. In order to remain consistent with 21 CFR 809.10 (b) (12) and to avoid ambiguity this sentence should be edited to read: "A test that has been characterized to a predicate but has not been compared to 'true' diagnostic states should be labeled without clinical sensitivity or clinical specificity claims".

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