



Food and Drug Administration
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MAY 02 2007

Ms. Donna Chapman
RA/QA Manager
Bio-Rad Laboratories
9500 Jeronimo Road
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Re: Docket No. 2004P-0055

Dear Ms. Chapman:

The Food and Drug Administration (FDA, the agency) Center for Devices and Radiological Health (CDRH) has reviewed the citizen petition Bio-Rad submitted on February 2, 2004, pursuant to 21 CFR § 10.30. In the petition, Bio-Rad requests that the Commissioner of Food and Drugs issue a written opinion stating that Bio-Rad's practice of "developing unified, truthful labeling for domestic and international sales of its control products is lawful." Specifically, you request that FDA issue an opinion containing the following statement:

Truthful references in labeling to test kits that are not legally available for use in the United States with Bio-Rad's control products do not adulterate or misbrand such control products, so long as a conspicuous disclaimer appears in adequate proximity to the unapproved test kit. Disclaimers that are noted and appear in the same type face as the test kit are adequate to satisfy the agency's concern that Bio-Rad's labeling not promote an unapproved use. Bio-Rad's labeling may refer to test kits that have not been approved or cleared for use domestically if the labeling includes such disclaimers. The agency has reviewed sample unified labeling submitted by Bio-Rad, and believes the form and content of the labeling, and particularly the disclaimers contained in the labeling, are sufficient and lawful.

In support of this request, Bio-Rad argues: (1) that references in Bio-Rad's labeling to unapproved test kits have appeared for many years; (2) that the First Amendment to the United States Constitution forbids the FDA from restricting Bio-Rad's labeling beyond a disclaimer; and (3) that there is a statutory preference for disclaimer.

FDA has reviewed Bio-Rad's petition and the accompanying information. To the extent that Bio-Rad requests that FDA issue an advisory opinion as a legally binding position, FDA declines to respond because the agency may not bind itself to such a position through correspondence. 5 U.S.C. § 553, 21 CFR § 10.115. See also, 57 FR 47314. However, in addition to requesting that FDA adopt a binding position statement, Bio-Rad's petition also requests that FDA allow Bio-Rad to submit in its premarket notification submissions labeling that states control products are intended for use with test kits that are uncleared and unapproved. For the reasons explained below, FDA is denying the request to permit submission of such labeling.

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I. Summary

Bio-Rad's arguments in the citizen petition are largely predicated on its apparent belief that FDA will not permit Bio-Rad to label its control product for intended use with unapproved or uncleared test kits in order "to indirectly encourage product submissions or prevent future, hypothetical off-label use." Bio-Rad thus presumes that there is no issue in relation to whether its product meets the statutory standard for premarket clearance, i.e., whether it is substantially equivalent to a legally marketed device, but that FDA's objection instead solely relates to its concerns about other manufacturers' test kits. This presumption is incorrect.

In order to find a device substantially equivalent, FDA is required by statute to find that the device has the same intended use as the predicate device and has the same technological characteristics as the predicate device, or has different technological characteristics and the information submitted demonstrates that the device is as safe and effective as a legally marketed device and does not raise different questions of safety and effectiveness. 21 U.S.C. § 360c(i)(1)(B). The agency's determination of the intended use of a device is based upon the proposed labeling included in the 510(k) submission. 21 U.S.C. § 360c(i)(1)(E).

Bio-Rad's labeling, as represented in the attachment to the citizen petition, states, "Liquichek ToRCH Plus Control, Positive is intended for use as an assayed quality control serum to monitor the precision of laboratory testing procedures for the analytes listed in this package insert." The analytes in the package insert include many that are not cleared or approved by FDA for use in the United States. These analytes are followed by a footnote that reads, "Test/kit not available in the U.S."

This labeling establishes that Bio-Rad's control product is intended for use with test kits that are not just allegedly "unavailable" but also uncleared or unapproved. A product such as Bio-Rad's that is intended for use with unapproved or uncleared products does not have "the same intended use" as a predicate device that is intended for use only with cleared or approved products. This is because when FDA clears the 510(k) for a device that is intended for use with other devices, it is necessary to be certain that the two devices, when used in combination, are substantially equivalent to a predicate. In order to make this finding of substantial equivalence, a device must be intended for use with a cleared device or the premarket notification submission must include data that supports clearance of both devices. In short, FDA cannot find a product such as Bio-Rad's that has a different intended use than the predicate to be "substantially equivalent" without the review of data which demonstrates equivalence.

Where FDA finds a device substantially equivalent based upon a 510(k) submission that reflects an intended use only with cleared or approved products and the manufacturer later labels the device for use with a product not cleared or approved for use in the United States, the product is adulterated under section 501(f)(1)(B) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. § 351(f)(1)(B), and misbranded under section 502(o) of the Act, 21 U.S.C. § 352(o). The device is adulterated under the Act because the law requires, and the manufacturer does not have, an approved premarket approval application that demonstrates there is a reasonable assurance the device is safe and effective for each of its intended uses. The device is also misbranded because the manufacturer has modified the intended use of the device and did not submit a premarket

notification to cover the modified use(s), as required by section 510(k) of the Act, 21 U.S.C. § 360(k), and 21 CFR § 807.81(a)(3).

II. Analysis

A. Bio-Rad's History of Device Labeling

Bio-Rad states in its citizen petition that FDA has historically permitted Bio-Rad to refer to unapproved test kits in Bio-Rad's device labeling. Bio-Rad refers specifically to products such as the Lyphochek Immunoassay Plus Control and the Lyphochek Tumor Marker Control that received FDA clearance with labeling that refers to an intended use with test kits that have not been cleared or approved. Bio-Rad notes that mention of such uncleared and unapproved test kits on the labeling for these, and other similar products, is followed by a footnote that reads either "Test kit/instrument not available in the USA" or "Test/kit instrument has not been approved or cleared by the FDA for this analyte. Please refer to 21 CFR § 809.30 for additional information regarding the regulation of analyte specific reagents."

In those instances where FDA cleared a device whose 510(k) submission included labeling that reflected an intended use with uncleared and unapproved test kits, the finding of substantial equivalence is applicable to use of the device only with the cleared or approved test kits. Where a predicate device may have had labeling that reflected an intended use with uncleared and unapproved test kits, FDA's finding of substantial equivalence for that product also was applicable only to use of the device with cleared or approved test kits. Since 1996 FDA has referenced, and enclosed, in any substantial equivalence order, the 510(k) submitter's intended use, including any specific additional test kits intended for use.

FDA should have clarified for Bio-Rad at the time that it reviewed the controls with the labeling, including the intended use requested for review, that FDA could not find a device substantially equivalent if it's labeling included use with uncleared and unapproved test kits. We regret that we did not explain this earlier.

Bio-Rad's historic use of labeling with references to uncleared/unapproved test kits is not due to an FDA finding that such devices are or can be substantially equivalent to products intended for use with cleared and approved products

B. First Amendment

Bio-Rad also contends that the First Amendment requires FDA to permit "disclaimers" such as the footnotes on Bio-Rad device labels stating that a test kit intended for use with the device is not available in the United States or is not cleared or approved for use in the United States. Bio-Rad characterizes FDA's interest in objecting to such disclaimers as encouraging premarket submissions for uncleared and unapproved products. FDA's interest is more accurately stated as protecting the device approval and clearance process by ensuring that the products FDA clears meet the statutory substantial equivalence standard.¹

¹ This interest includes, but is not limited to, encouraging submissions, an interest Bio-Rad concedes is "substantial." Because FDA's primary interest in this instance is ensuring that a product under review meets the statutory

As explained previously, FDA cannot find a device intended for use with uncleared and unapproved products substantially equivalent to a product that is intended for use only with cleared and approved products because the Act requires that a device be found substantially equivalent only where it has the "same intended use" as the predicate device. 21 U.S.C. § 360c(i)(1)(A). An intended use with approved and cleared products is not the same, within the meaning of the Act, as an intended use with unapproved and uncleared products. A device that does not require PMA approval and that is intended for use with an uncleared or unapproved product could be cleared only if both products are eligible for 510(k) clearance and the premarket notification submission included data to support finding both products substantially equivalent so that both products would receive 510(k) clearance, either individually or for use in combination.

FDA's objection to Bio-Rad's labeling thus relates to the intended use that the labeling establishes and its failure to meet the "substantial equivalence" standard and is not a prohibition on speech. "[I]t is constitutionally permissible for the FDA to use speech, in the form of labeling, to infer intent . . ." Whitaker v. Thompson, 353 F.3d 947, 953 (D.C. Cir. 2004). In this case, FDA is relying upon Bio-Rad's labeling to determine whether the product, for the labeled intended use, can be cleared and legally marketed in the U.S. Using labeling as evidence of a product's intended use is an appropriate and narrowly tailored means by which FDA can determine the regulatory status of a product and whether it will meet the statutory and regulatory requirements for clearance.

C. Preference in the Act for Disclaimers

Bio-Rad also argues that the Act expresses a preference for the use of disclaimers on device labels. Bio-Rad cites § 513(i)(1)(E) of the Act, 21 U.S.C. § 360c(i)(1)(E), which identifies the labeling as the statutory point for determining intended use, and states that the agency "may require a statement in labeling that provides appropriate information regarding a use of the device not identified in the proposed labeling if, after providing an opportunity for consultation with the person who submitted such report, the Director determines and states in writing -- (I) that there is a reasonable likelihood that the device will be used for an intended use not identified in the proposed labeling for the device; and (II) that such use could cause harm." Bio-Rad states that this language "articulates the policy that the appropriate remedy for potential off-label use is information proscribing or limiting the use."

The statutory language Bio-Rad cites is inapposite since the statements on Bio-Rad's labeling concern an "on label" use, not an "off label" use. By including on its official device label an intended use with unapproved and uncleared test kits, Bio-Rad has established this use as the intended, "on label," use rather than an off label use. Section 513(i)(1)(E) of the Act specifically directs FDA to determine intended use based upon the labeling submitted with a 510(k) submission. Where Bio-Rad submits device labeling that reflects an intended use with products that are not legally marketed in the U.S., this is the "on label," intended use.

substantial equivalence standard, however, FDA is not addressing in this response the constitutionality of actions taken to encourage submission of applications for premarket review of unapproved and uncleared products.

III. Conclusion

In summary, it is constitutionally permissible for FDA to require that the labeling Bio-Rad submits with 510(k) submissions for its control products reflect an intended use that meets the statutory substantially equivalent standard. As a result, FDA is denying Bio-Rad's petition and will continue to require that 510(k) submissions for control products reflect an intended use only with products that are legally marketed in this country or, if they are not legally marketed in this country, are to be reviewed and cleared as part of the same 510(k) submission.

If you have any questions with regard to this response, please contact Heather Rosecrans, Chief, Premarket Notification Staff, at (240) 276-4021.

Sincerely yours,



Linda S. Kahan
Deputy Director
Center for Devices and
Radiological Health