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August 30, 2011

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane
Room 1061, HFA-305
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RE: Comments on Draft Guidance: Commercially Distributed In Vitro Diagnostic Products Labeled for Research Use Only or Investigational Use Only: Frequently Asked Questions; FDA–2011–D–0305

The Biotechnology Industry Organization (BIO) appreciates the opportunity to submit comments regarding the Food and Drug Administration's ("FDA's") draft guidance document entitled *Commercially Distributed In Vitro Diagnostic Products Labeled for Research Use Only or Investigational Use Only: Frequently Asked Questions* ("the Draft Guidance").[1] BIO represents more than 1,100 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnologies, thereby expanding the boundaries of science to benefit society by providing better healthcare, enhanced agriculture, and a cleaner and safer environment. Specifically, related to products labeled for research use only ("RUO") or investigational use only ("IUO"), a number of companies within BIO's membership develop and market *in vitro* diagnostic technologies for a variety of research, investigational, and clinical uses. For this reason, BIO welcomes the opportunity to work with the FDA on the development of policy in this area.

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[1] Draft Guidance for Industry and Food and Drug Administration Staff, Commercially Distributed In Vitro Diagnostic Products Labeled for Research Use Only or Investigational Use Only: Frequently Asked Questions (June 1, 2011).

BIO appreciates FDA's recognition that research reagents and kits may be both the subject of research/investigation, and also be used in the research/investigation of other FDA-regulated products. BIO is committed to working with the Agency to develop policy that ensures that these products are marketed in a manner consistent with applicable law. With regard to the Draft Guidance, BIO is concerned that the definition of "research use" is inappropriately narrow. Further, BIO believes that FDA's interpretation of "intended use" in the Draft Guidance is inconsistent with applicable law, and goes beyond FDA's historical interpretation of "intended use." Finally, BIO urges FDA to take a cautious and measured approach to enforcement under the provisions of the Draft Guidance. Some stakeholders may need to prepare and submit regulatory submissions based on this interpretation, and it is critical that FDA actions do not inadvertently inhibit innovative research activities that could fall under the purview of the Draft Guidance.

I. FDA's Definition of "Research Use" is Inappropriately Narrow in the Context of Other Guidance Documents, and Thus Risks Inhibiting Innovation and Access to Important Research Tools

The Draft Guidance states that FDA intends to "clarify the types of in vitro diagnostic ("IVD") products that are properly labeled [RUO or IUO]."[2] BIO understands that some products on the market are labeled for RUO, yet have been incorporated in laboratory-developed clinical diagnostic tests. Importantly, FDA must proceed in a manner that clearly informs manufacturers of the criteria by which an reagent or kit is properly labeled as RUO. A lack of clarity in the definition and characterization of "research use" may inhibit innovation and the progression of critical research by inadvertently blocking access to important research tools, as well as generating discordance and confusion regarding how different products are regulated. BIO urges FDA to harmonize this Draft Guidance with its other guidance documents and provide a clear set of criteria to define and characterize "research use" between them.

Neither the Federal Food, Drug and Cosmetic Act ("FFDCA") nor FDA's regulations define the term "research use." Rather, FDA has addressed the definition and characterization of "research use" in the context of guidance documents, beginning as early as 1998.[3] Most recently, in a guidance document entitled *Commercially Distributed Analyte Specific Reagents (ASRs): Frequently Asked Questions* ("the 2007 ASR Guidance"), FDA stated that the Agency "considers RUO products to be products that are in the laboratory research phase of development, that is, either basic research or the *initial search for potential clinical utility*, and not represented as an effective in vitro diagnostic product…the focus of the manufacturer- initiated studies is typically to evaluate limited-scale performance and *potential clinical or informational usefulness of the test*."[4] (emphasis added) To distinguish the research phase of development from the investigational phase, FDA noted that in the investigational phase, the safety and effectiveness of

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2 Draft Guidance at 4.

3 Draft Compliance Policy Guide, Commercialization of In Vitro Diagnostic Devices (IVD's) Labeled for Research Use Only or Investigational Use Only (January 5, 1998).

4 Guidance for Industry and FDA Staff, Commercially Distributed Analyte Specific Reagents (ASRs): Frequently Asked Questions (September 14, 2007) at 12.

the product are being studied; *i.e.*, the clinical performance characteristics and expected values are being determined in the intended patient populations."[5]

There exist a number of uses of IVD products that fall outside of investigational use and clinical diagnostic applications, but are critical to the advancement of research and innovation. The definitions and characterizations in the Draft Guidance guidance are dissimilar than prior statements in FDA guidance regarding the distinction between research use and investigational use, which contemplate the juxtaposition of research use in the clinical context. In contrast to the 2007 ASR Guidance, the Draft Guidance applies a more narrow view of research use, and characterizes research use as "to evaluate design, limited-scale performance, and issues such as usability of the test."[6] To illustrate the intended scope of this characterization, FDA provided the following examples in the Draft Guidance:

> "Tests that are in development to identify test kit methodology, necessary components, and analytes to be measured;
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> Instrumentation or other electrical/mechanical components under development to determine correct settings, subcomponents, subassemblies, basic operational characteristics, and possible use methods; and
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> Reagents under development to determine production methods, purification levels, packaging needs, shelf and storage life, etc."[7]

Notably, there is no mention of an evaluation of the "potential clinical or informational usefulness of the test," as is found in the 2007 ASR Guidance. Is this exclusion intended to be a shift in the definition of research use vis-à-vis the 2007 ASR Guidance? Does FDA intend to have differing standards for what constitutes "research use" based on the type of product (*i.e.*, ASR vs. IVD)? Is this list of examples intended to be exhaustive or do previous characterizations of "research use" apply as well? For products that are critical to research on important potential clinical or informational usefulness applications, but do not meet this new definition of "research use," how should these products be labeled?

BIO believes that it is critical that FDA clarify what constitutes "research use" consistently across all applicable products. If FDA intends this shift in the characterization of the line between "research use" and "investigational use," the Agency should provide a rationale for this narrowing of the definition of research, and fully consider the impact this shift may have on the advancement of research in this area. More detail should be provided regarding the definition of "research use" that distinguishes it from investigational use, to include detailed examples illustrating where FDA believes this line is crossed. BIO urges FDA to provide a more clear definition that is flexible enough to foster research and innovation, while addressing the Agency's concern regarding improper use of products labeled as RUO or IUO.

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5 *Id.* at 12.

6 Draft Guidance at 7.

7 *Id.* at 7.

II. The Interpretation of Intended Use in the Draft Guidance Is Inconsistent with Applicable Statutory and Regulatory Provisions and Represents a Significant Departure from Prior FDA Interpretations

FDA 's reliance in the Draft Guidance on the downstream concept of "intended use" is misplaced and misguided. "Intended use" in the statutory framework of the FFDCA is the basis for defining a type of product, and whether it properly should be characterized as, for example, a drug or a device.[8] In the regulatory framework, intended use is defined as the "objective intent of the persons legally responsible for the labeling of devices," as expressed in labeling, advertising, or other statements.[9] Thus, "intended use" has been relied upon to establish the intent of the manufacturer, but has never been used to apply to the eventual, independent act of a user of the product.

FDA's reliance on 21 C.F.R. § 801.4 to support enforcement based on this expanded downstream interpretation of "intended use" is not supported in statute or regulation. Indeed, § 801.4 itself does not support enforcement action based on actual use, because the regulation refers to the article being "*offered and used*" for an off-label use. (emphasis added). Although FDA asserts in the Draft Guidance that "intended use" may be shown by "the circumstances surrounding the distribution of the product [citing 21 C.F.R. § 801.4]," FDA has not applied this expanded downstream interpretation of "intended use" to areas outside of the RUO/IUO labeling context. BIO is further concerned that, given FDA's reliance on 21 C.F.R § 801.4 for this interpretation and its parallel to other regulations,[10] this interpretation may be construed broadly by FDA and other enforcement agencies to apply to all FDA-regulated medical products.

Notwithstanding whether FDA's reliance on regulations defining and characterizing "intended use" is proper in the context of products labeled as RUO/IUO, FDA misinterprets "intended use" on the part of the manufacturer to be created by the use of the product after it is beyond the control of the manufacturer (*i.e.*, after ownership in the property is transferred to the customer). This interpretation is contrary to well-established legal precedent, historical FDA practice, and the practicalities inherent in placing a legal requirement onto a manufacturer based on use of a product after it is beyond its control.

Even if, *arguendo*, FDA's reliance on this regulation were proper, the Agency's interpretation of intended use in the Draft Guidance is contrary to established legal precedent. Courts have supported a claims-based theory of "intended use," in which the manufacturer's intended use is determined by the claims made for the product in connection with sale, and not based on the customer's actual use of the product.[11] In fact, one court likened this approach to "mean that every merchant who sells carrots to the public with knowledge that some of his consumers

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8 See 21 U.S.C. § 321(g).

9 See 21 C.F.R. § 801.4

10 See e.g., 21 C.F.R. § 201.128

11 See e.g., Ass'n of Am. Physicians & Surgeons, 226 F. Supp. 2d 204, 217-18 (D.D.C. 2002)) (""even the FDA has repeatedly stated that it may only regulate claimed uses . . . , not all foreseeable or actual uses.")

believe that the ingestion of carrots prevents eye diseases hold the carrots out for use as a drug, as that term is defined in the Act."[12]

As the Fourth Circuit has noted, "no court has ever found that product is 'intended for use' or 'intended to affect' within the meaning of the [Act] absent manufacturer claims as to that product's use."[13] Finding an intended use based on mere knowledge that a medical product would be used off-label would exceed FDA's statutory authority.[14] The Government may not open to FDA's regulation "all off-label uses, based solely on the manufacturer's knowledge that those uses are common-place.[15] This "would surely conflict with Congress's will and would eviscerate the long-established foundation of federal food and drug law, which allows, not the FDA, but the 'manufacturer of the article, through his representations in connection with its sale, [to] determine the use to which the article is to be put." *Id.* (quoting S. Reg. No. 73-493, at 3 (1934)).

The expanded downstream concept of "intended use" set forth in the Draft Guidance runs afoul of these and other similar court rulings, which limit the objective intent of the manufacturer to labeling and advertising of the product within the manufacturer's control. To expand the definition of "intended use" to include downstream use of the product ignores this legal precedent, and establishes a significant shift in paradigm for the regulation of product promotion. FDA's interpretation is not supported in statute or regulation, and cannot be implemented. .

III. FDA's "Halt Sales" Provision in the Draft Guidance is Inappropriate and Lacks Sufficient Clarity for Implementation

The Draft Guidance states that, if a manufacturer knows, or should have known, that a customer intends to use a product labeled as RUO for a clinical diagnostic use, it must halt sales to that customer. This provision is inappropriate, because it shifts the function of monitoring and enforcement from FDA to regulated industry. Under the Draft Guidance, manufacturers would have to establish procedures to police their customers regarding how they use the products for sale. The FFDCA instills in FDA the authority and responsibility for enforcing compliance under its statute. The FFDCA does not contemplate a system where manufacturers of a product regulated under the statute must police the downstream use of their products after the point of sale. Under the statute, this duty is placed on FDA, which has developed the necessary resources and expertise to adequately carry out the monitoring and enforcement function. It is entirely inappropriate and contrary to applicable law to shift this burden to regulated industry.

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12 Millet, Pit and Seed Co., Inc. v. United States, 436 F. Supp. 84 (E.D. Tenn. 1977) (mem. op.), vacated and remanded for merits hearing, 627 F.2d 1093 (6th Cir. 1980).

13 Brown & Willimason Tobacco Corp. v. FDA, 153 F.3d 155, 163 (4th Cir. 1998) (citing Coyne Beahm v. FDA, 966 F. Supp. 1374, 1390 (M.D.N.C. 1997), aff'd on other grounds, 529 U.S. 120 (2000). See also Buckman v. Plaintiffs' Legal Comm., 531 U.S. 341 (2001).

14 See, e.g., Assn. of Am. Physicians & Surgeons, Inc. v. FDA, 226 F. Supp. 2d 204 (D.D.C. 2002) (striking down FDA's "pediatric rule" – which was grounded in the argument that an intended use in pediatric patients could be inferred because drugs intended for adult use routinely are used in pediatric patients.)

15 Id. at 218.

Even if, *arguendo*, this scheme were appropriate, FDA's description of the expanded concept of intended use lacks sufficient clarity for implementation. For example, the Draft Guidance refers to the provision of "technical support" by the manufacturer as a basis for determining the intended use of a product labeled for RUO/IUO. It is not clear under the Draft Guidance what constitutes "technical support."

A logical extension of this provision to other regulatory rubrics (*e.g.*, drug and biologic promotion) threatens to quash the long-standing safe harbor for the ability of a manufacturer to provide balanced scientific information to a practitioner in response to an unsolicited request. Because the "intended use" concept on which the draft relies operates in both the general device context and in the drug arena, the draft guidance threatens the well-established practice of manufacturers providing scientific and technical information in response to unsolicited requests.

IV. Conclusion and Recommendations

In summary, BIO is concerned that the Draft Guidance lacks adequate clarity for implementation, and believes that certain provisions are inappropriate and inconsistent with applicable law and historical FDA practice. FDA's implementation of a "reason to know" theory of objective intent through issuance of a Draft Guidance is inconsistent with CDRH's prior analysis and statements to the Institute of Medicine that CDRH believes it would be necessary for FDA to pursue a statutory amendment to provide the agency with the express authority to consider an off-label use when determining the "intended use" of a device.[16]

Rather than permissibly clarifying its views relating to the labeling and marketing of IVD products, FDA's interpretation creates a substantive rule that modifies or adds to a legal norm through restrictions on sales to clinical laboratories and additional evidence of intended use supporting a claim of adulteration or misbranding, which courts have held that the Agency must do formally through notice and comment rulemaking, not informally through guidance.[17]

FDA must follow its own regulations on advisory opinions which state that "[a]n advisory opinion represents the formal position of FDA on a matter…and obligates the agency to follow it until it is amended or revoked."[18] The FDA issued an advisory opinion regarding its interpretation of 21 C.F.R § 801.4 (and a related regulation at 21 C.F.R § 201.128) and the

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16 The 510(k) Working Group recommends that CDRH explore the possibility of pursuing a statutory amendment to section 513(i)(1)(E) of the Federal Food, Drug, and Cosmetic Act (21 USC §360c(i)(1)(E)) that would provide the agency with express authority to consider an off-label use, in certain limited circumstances, when determining the "intended use" of a device under review through the 510(k) process. Such circumstances would include the availability of compelling evidence that the primary use of the marketed device will be off-label. If the Center were to pursue such an approach, it should also clearly define what type and level of evidence would be sufficient to determine that the off-label use is the primary intended use.

http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDRH/CDRHReports/UCM220784.pdf *See also:* http://www.iom.edu/~/media/Files/Report%20Files/2011/Medical-Devices-and-the-Publics-Health-The-FDA-510k-Clearance-Process-at-35-Years/510k%20Clearance%20Process%202011%20Letter%20to%20FDA.pdf

17 Syncor Int. Corp. v. Shalala, 127 F.3d 90, 95 (D.C. Cir. 1997).

18 21 C.F.R. § 10.85.

evidence that it will use to determine objective intent in a Federal Register notice dated November 18, 1994.[19] FDA did not publish an amendment or revoke this advisory opinion prior to seeking to change its position in the Draft Guidance. Under FDA's regulations, the advisory opinion represents the formal position of FDA and obligates the agency to follow it until it is amended or revoked in the same manner as the notice of the advisory opinion was originally given.[20] Thus, FDA's change in position requires public notice of proposed rulemaking to give interested persons "an opportunity to participate in the rulemaking through submission of written data, view or arguments."[21]

If FDA elects nonetheless to move forward with some or all of the provisions discussed above, the Agency should do so through notice and comment rulemaking because it is advancing new interpretations of existing statutory and regulatory interpretations. In any case, FDA should proceed in a phased-in manner to allow time for companies to submit the required regulatory submissions to ensure that access to many important research tools and continued patient access to important clinical diagnostic information is not blocked.

Please let me know if you have any questions regarding the above.

Respectfully submitted,

Paul Sheives, JD
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19 See Citizen Petition Regarding the Food and Drug Administration's Policy on Promotion of Unapproved Uses of Approved Drugs and Devices; Request for Comments, 59 Fed. Reg. 59820, 59824. (Nov. 18, 1994) ("Under current FDA policy, companies may also disseminate information on unapproved uses in response to unsolicited requests for scientific information from health care professionals. Scientific departments within regulated companies generally maintain a large body of information on their products. When health care professionals request such information, companies can provide responsive, nonpromotional, balanced, scientific information, which may include information on unapproved uses, without subjecting their products to regulation based on the information. This policy permits companies to inform health care professionals about the general body of information available from the company..... FDA reiterates that it does not wish to regulate either oral presentations or enduring materials that are independent and nonpromotional in nature.").

20 21 C.F.R. § 10.85(d)(1).

21 5 U.S.C. § 553(c).