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Division of Dockets Management
HFA-305
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852

VIA ELECTRONIC SUBMISSION

Re: 2006D-0347
Draft Guidance for Industry, Clinical Laboratories, and FDA Staff: In Vitro Diagnostic Multivariate Index Assays

2006D-0336
Draft Guidance for Industry and FDA Staff: Commercially Distributed Analyte Specific Reagents (ASRs): Frequently Asked Questions

Dear Sir or Madam:

Johnson & Johnson (J&J) is pleased to submit the following comments in response to the two draft guidance documents that the Food and Drug Administration (FDA or the Agency) issued on September 7, 2006: Draft Guidance for Industry, Clinical Laboratories, and FDA Staff: In Vitro Diagnostic Multivariate Index Assays (the IVDMA Draft Guidance); and Draft Guidance for Industry and FDA Staff: Commercially Distributed Analyte Specific Reagents (ASRs): Frequently Asked Questions (the ASR Draft Guidance). J&J is the world's most comprehensive and broadly based manufacturer of health care products, as well as a provider of related services for the consumer, pharmaceutical, and medical devices and diagnostics markets. J&J has more than 200 operating companies in 54 countries around the world, employing approximately 110,600 employees, and selling products in more than 175 countries. The fundamental objective of J&J is to provide scientifically sound, high quality products and services to help heal and cure disease, and to improve the quality of life.

J&J recognizes that diagnostic tests provide crucial information that health care professionals use to help diagnose and determine the appropriate treatment of patients. ASRs and the tests FDA seeks to regulate as IVDMIAs both play a tremendous role in achieving these ends. IVDMIAs, a new regulatory category of laboratory developed tests (LDTs), have the potential to aid in crucial treatment decisions. ASRs are key ingredients in many clinically important LDTs.

J&J believes that, taken together, the IVDMIA Draft Guidance and the ASR Draft Guidance represent a shift in FDA's regulatory approach to laboratory tests. J&J is not commenting on FDA's authority to regulate laboratory tests, including IVDMIAs. However, J&J believes that the issues presented in the IVDMIA Draft Guidance and in the ASR Draft Guidance are ones that should be addressed through notice-and-comment rulemaking. As will be described below, J&J agrees with other commenters who have asserted that a draft guidance document is an inappropriate means by which to establish a definition and regulatory status for IVDMIAs. Additionally, J&J believes that a draft guidance document is an inappropriate means by which to introduce new characteristics that change what kinds of products can be considered ASRs under established, existing regulations.

With respect to both IVDMIAs and ASRs, J&J believes that if FDA proceeds with the issues presented in the two draft guidance documents, then there should be transition periods that enable laboratories and ASR manufacturers to adjust to the new policies and standards. Finally, with respect to IVDMIAs, J&J believes that any classification and regulation of this type of LDT should be based on risk. Each of these comments is explained below.

1. A Draft Guidance Document is an Inappropriate Means by Which to Establish a Definition and Regulatory Status for IVDMIAs

The IVDMIA Draft Guidance creates a definition and a new regulatory status for IVDMIAs. In the draft guidance document, FDA imposes pre-market and post-market requirements on IVDMIAs and states that "most IVDMIAs will be either class II or class III devices" subject to pre-market review.¹ Therefore, the IVDMIA Draft Guidance creates a new category of LDTs – IVDMIAs – and announces FDA's intention to begin treating LDTs in this new category as unapproved medical devices.

FDA cannot establish definitions and a new regulatory category through a draft guidance document. Since FDA intends to apply the definition of IVDMIAs to categorize particular LDTs, and to treat IVDMIAs as unapproved medical devices, the definition and new regulatory category created under the IVDMIA Draft Guidance will have the force and effect of law.

¹ FDA, Draft Guidance for Industry, Clinical Laboratories, and FDA Staff: In Vitro Diagnostic Multivariate Index Assays, at 4 (Sept. 7, 2006), available at <http://www.fda.gov/cdrh/oivd/guidance/1610.pdf>.

Pursuant to the Administrative Procedure Act (APA), these constitute “rules”² which can only be established through rulemaking.³ FDA has established other classifications through rulemaking. FDA has not explained why it is following a different approach here. J&J is concerned not only about the creation of the IVDMIA classification this way, but the precedent it would set for other devices.

J&J also notes that the history of FDA’s decisions regarding LDTs requires the Agency to pursue rulemaking to identify and regulate a group of LDTs – IVDMIAs – as unapproved medical devices. In 1997, when FDA promulgated the rule governing ASRs, the Agency considered whether it should independently review in-house developed tests (now referred to as LDTs).⁴ FDA stated then that the Agency “disagree[d] that . . . regulation of all in-house developed tests is appropriate at this time,”⁵ and specifically “decline[d] to accept the suggestion that all in-house developed tests be classified as class II or class III medical devices.”⁶ Thus, in 1997, FDA chose not to exercise authority over LDTs. The IVDMIA Draft Guidance represents a departure from this approach stated in the preamble. This constitutes an advisory opinion,⁷ and can be revoked only by proceeding in the same manner as it was or is generally given.⁸

According to the United States Court of Appeals for the D.C. Circuit, an FDA guidance that modifies or adds to a legal norm based on the Agency’s own authority represents a substantive rule that must undergo notice-and-comment rulemaking. In Syncor International

² 5 U.S.C. § 551(4) (defining “rule” as “the whole or a part of an agency statement of general or particular applicability and future effect designed to implement, interpret, or prescribe law or policy or describing the organization, procedure, or practice requirements of an agency”); see also Exec. Order No. 12,866 (Sept. 30, 1993), as amended by Exec. Order No. 13,258 (Feb. 26, 2002) and Exec. Order No. 13,422 (Jan. 18, 2007) (defining a “regulation” as “an agency statement of general applicability and future effect, which the agency intends to have the force and effect of law, that is designed to implement, interpret, or prescribe law or policy or to describe the procedure or practice requirements of an agency”).

³ 5 U.S.C. § 551(5).

⁴ 62 Fed. Reg. 62,243, 62,249 (Nov. 21, 1997).

⁵ Id. at 62,250.

⁶ Id. at 62,249.

⁷ 21 C.F.R. § 10.85(d)(1).

⁸ Id. § 10.85(g).

Corp. v. Shalala,⁹ FDA had issued a “Notice”¹⁰ that imposed pre-market requirements on nuclear pharmacists, including a review of new drug applications for compounding, which was a substantial departure from an earlier guidance, under which FDA did not require a review of new drug applications. The court found that by seeking to extend its regulatory reach, the Notice had invoked the Agency’s general rulemaking authority and had modified or added to the legal norm.¹¹ Therefore, it was a substantive rule that must be promulgated through notice-and-comment rulemaking.

J&J also notes that at the February 8, 2007 public meeting held by FDA concerning IVDMIAAs, an overwhelming majority of the speakers – representing laboratories, diagnostic companies, patients’ groups, and other stakeholders – stated that FDA could not create “IVDMIAAs” and then deem these products to be subject to Agency regulation through the guidance process. These speakers called for notice-and-comment rulemaking. J&J agrees that notice-and-comment rulemaking is required.

2. A Draft Guidance Document is an Inappropriate Means by Which to Introduce New Characteristics that Change What Kinds of Products are Considered ASRs Under Established, Existing Regulations

Notice-and-comment rulemaking is also required for substantive changes to existing regulations. In the ASR Draft Guidance, FDA introduces characteristics that an ASR must have in order to be considered an ASR. These include that an ASR must consist of a “single moiety,” detect a “single endpoint,” have “no instructions or performance claims,” and “not [be] promoted for use on specific instruments or in specific tests or test systems.”¹² “ASRs” are currently defined under FDA’s regulations¹³ and must conform to regulatory requirements that were established through notice-and-comment rulemaking in 1997.

⁹ 127 F.3d 90 (D.C. Cir. 1997).

¹⁰ A “Notice” is analogous to a guidance document, in that the Notice is referred to in its text as “guidance” and as a “policy statement.” Id. at 92.

¹¹ Id. at 96.

¹² FDA, Draft Guidance for Industry and FDA Staff: Commercially Distributed Analyte Specific Reagents (ASRs): Frequently Asked Questions, at 7 (Sept. 7, 2006), available at <http://www.fda.gov/cdrh/oivd/guidance/1590.pdf>.

¹³ See 21 C.F.R. § 864.4020(a) (defining “Analyte Specific Reagents” as “antibodies, both polyclonal and monoclonal, specific receptor proteins, ligands, nucleic acid sequences, and similar reagents which, through specific binding or chemical reaction with substances in a specimen, are intended for use in a diagnostic application for identification and quantification of an individual chemical substance or ligand in biological specimens.”).

The characteristics introduced in the ASR Draft Guidance are not included in the existing definition of ASRs or in any of the regulations governing ASRs. J&J notes that many reagents that are currently sold as ASRs in accordance with the ASR regulations are no longer considered to be ASRs under the ASR Draft Guidance. Consequently, the ASR Draft Guidance changes what kinds of products constitute ASRs, thus substantively changing the established, existing ASR regulations, which will have the force of law. Notice-and-comment rulemaking is therefore required.

3. There Should be a Transition Period to Allow Laboratories to Adjust to Any Regulation of LDTs by FDA and to Permit Continued Availability of ASRs

LDTs that constitute IVDMIAs are considered to be unapproved medical devices. As such, FDA will require that these LDTs be cleared or approved by the Agency, and to meet other requirements. To date, laboratories have developed LDTs outside the scope of FDA regulation and have not been regulated by FDA. Instead, clinical laboratories are regulated by the Centers for Medicare & Medicaid Services (CMS) under the Clinical Laboratory Improvement Amendments (CLIA).

Under the IVDMIA Draft Guidance, unless laboratories comply with FDA's regulatory requirements – including for clearance or approval – the LDTs that FDA considers to be IVDMIAs will be unlawful. This will preclude laboratories from being able to develop and offer IVDMIAs. Without availability of IVDMIAs, patients and physicians will not have access to tests that have the potential to aid in crucial treatment decisions. Similarly, many laboratories have come to rely upon “building blocks” that FDA now considers not to be ASRs. If these products suddenly become unavailable, laboratories will not be able to offer some of the tests they now provide.

Therefore, J&J believes that there should be a transition period to enable laboratories to develop systems through which to comply with FDA regulations and to maintain a supply of ASRs. We agree with comments made at the February 8, 2007 public meeting on IVDMIAs that called for a two to four year period for laboratories to submit pre-market notifications or PMA applications to FDA. This would allow for IVDMIAs to continue to be available while laboratories become accustomed to FDA regulation. A similar transition period should be provided to ASR suppliers. J&J notes that FDA followed this same approach when it began regulating companies that reused devices.

4. Any Classification and Regulation of LDTs Should be Risk-Based

Under the IVDMIA Draft Guidance, FDA has based the regulation of IVDMIA on technology – the fact that an IVDMIA employs the use of an algorithm.¹⁴ FDA's existing

¹⁴ See FDA, IVDMIA Draft Guidance, *supra* note 1, at 3.

regulations governing medical devices, however, prescribe that the Agency classify and regulate products based on risk. A different regulatory scheme should not be created for and imposed on IVDMIAs.

The philosophy behind device regulation under the Federal Food, Drug, and Cosmetic Act is that regulation is risk-based. The IVDMIA Draft Guidance does not follow that approach in defining whether a test is an IVDMIA. Thus, the classification scheme is not risk-based.

5. Conclusion

J&J believes that the changes to FDA's current regulatory system introduced in these two draft guidance documents have significant implications for public health and health care. J&J therefore urges FDA to reconsider the announcement of these significant changes through the issuance of draft guidance documents. The concerns we have regarding this approach transcend the two specific draft guidance documents. As one of the largest device companies in the world, we consider regulatory predictability to be critical to making decisions. Making these kinds of fundamental changes through draft guidance documents is incompatible with this predictability. If FDA pursues the changes introduced in the draft guidance documents, J&J requests that FDA issue proposed rules under the APA.

J&J thanks FDA for the opportunity to make these comments to the draft guidance documents regarding IVDMIAs and ASRs, and looks forward to working with the Agency on these important issues.

Sincerely yours,



Dorothy J. Clarke
Senior Counsel
Office of the General Counsel
Johnson & Johnson

cc: 2006P-0402
Citizen Petition Regarding FDA Regulation of Laboratory Developed Tests