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BY HAND

June 12, 2002

Dockets Management Branch
U.S. Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061, HFA-305
Rockville, MD 20852

Re: Docket No. 01A-0375

Dear Sir or Madam:

We are writing on behalf of Matria Healthcare to express the company's opposition to the request made by the Pennsylvania Department of Health ("PaDOH") in its above-referenced docket for an advisory opinion from FDA ("PaDOH Request for Advisory Opinion"). PaDOH's request argues that a Pennsylvania ("PA") regulation, 28 Pa. Code § 5.41, permitting laboratories only to accept specimens for testing upon the request of a member of the healing arts or other such persons designated by state statute, is not preempted by requirements under the Federal Food, Drug, and Cosmetic Act (the "Act") applicable to the Appraise A1c Sample Collection Kit ("Appraise") and similar over the counter ("OTC") in vitro diagnostic devices ("IVDs") like Appraise. We request that FDA reject Pennsylvania's position and find the PA regulation preempted.

I. Introduction

There are a number of reasons for FDA to reject Pennsylvania's position. First, PaDOH's argument ignores the legal presumption under the Act that all devices are OTC, except those which are exempted by regulation from the statutory requirement of adequate directions for use under section 502(f)(1) of the Act. Second, it ignores the specific counterpart requirements under 21 CFR §§ 801.119 and 809.10 which satisfy the requirements for adequate directions for use for IVDs. Third, PaDOH incorrectly asserts, contrary to a previous agency advisory opinion, that the PA regulation is not a requirement applicable to a device. Finally, PaDOH incredibly finds no conflict between the PA regulation and FDA's OTC requirements for the device, despite the fact the PA regulation renders an OTC in vitro device unusable in Pennsylvania by requiring the

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opinion itself, expressly considered specific FDA requirements for OTC in vitro blood diagnostic kits that exist and are imposed separately from the finding of substantial equivalence. Moreover, the opinion only analyzed preemption under the express preemption provision in section 521 of the Act and did not consider whether the State laws were impliedly preempted under Federal common law. Because these arguments were not considered, we believe the advisory opinion regarding the B-D test is incorrect, and does not provide precedence for considering this opposition.

C. The Law of Preemption

Section 521(a) of the Act expressly preempts State and local requirements that relate to the safety or effectiveness of a device, or to any other matter included in a requirement that is “different from or in addition to any requirement” applicable to a device under the Act. FDA’s regulation on preemption provides that “[s]tate or local requirements are preempted only when the Food and Drug Administration has established specific counterpart regulations or there are other specific requirements applicable to a particular device under the act, thereby making any existing State or local requirements applicable to the device different from, or in addition to, the specific Food and Drug Administration requirements.” 21 CFR 808.1(d).

Several courts have interpreted the scope of preemption under § 521(a), including the Supreme Court in Medtronic v. Lohr, 116 S.Ct. 2240 (1996). In that case, the Court stated that section 521 of the Act and section 808.1 of the regulations “require a careful comparison between the allegedly preempting Federal requirement and the allegedly preempted State requirement to determine whether they fall within the intended preemptive scope of the statute and regulations.”

In addition, State laws that are not affected by an express preemption provision may nonetheless be subject to implied preemption. See Buckman Co. v. Plaintiffs Legal Committee, 121 S.Ct. 1012, 1019 (2001) (the existence of an express preemption provision does not mean that ordinary preemption principles do not apply). The general rule of implied preemption is that where the scheme of federal regulation is not so pervasive as to leave no room for State supplementation, the state requirement will still be preempted if it directly conflicts with the federal requirement making compliance with both impossible, or if the State law is an “obstacle to the accomplishment and execution of the full purposes and objectives of Congress.” See Geier v. American Honda Motor Corp., Inc., 120 S.Ct. 1913, 1921 (2000) (quoting Hines v. Davidowitz, 61 S. Ct. 399 (1941)).

III. Analysis of the PA Regulation

A. Express Preemption Under Section 521(a)

(1) Federal Requirements Applicable to Appraise

(a) In vitro diagnostic devices are presumptively OTC as a matter of law, but must meet highly specific requirements applicable to their labeling to be legally marketed OTC

Under the Act, all devices as a matter of law are presumptively available OTC, unless they are exempt prescription devices under 21 CFR § 801.109, or prescription devices as a result of a PMA order, see section 515(d)(1)(B)(ii) of the Act.³ IVDs retain their presumptive OTC status if they meet the conditions of 21 CFR § 801.119, which states that an IVD “shall be deemed to be in compliance with the requirements of this section and section 502(f)(1) of the Act if it meets the conditions of 21 CFR § 809.10” Section 809.10 sets out highly specific requirements for the labeling of IVDs. In other words, complying with section 809.10 and thus satisfying section 801.119 means that an IVD complies with section 502(f)(1) of the Act, which requires “adequate directions for use”. Specifically, the adequate directions for use required by section 502(f)(1) are directions adequate for “self-administration by a layman.” United States v. Articles of Drug, 625 F.2d 665, 673 (5th Cir. 1980). See also United States v. Two Units, More or Less, of an Article of Device, 49 F.3d at 482 (devices that do not bear adequate directions for use for a lay person are misbranded). Because adequate directions for use for a lay person cannot be written for a prescription device, such devices must meet the requirements for exemption from adequate directions for use established by FDA before they can be legally marketed. See Articles of Drug, supra.

(b) Having met the specific requirements of 21 CFR §§ 809.10 and 801.119, IVDs, including Appraise, are available OTC, unless FDA determines that an IVD may only be sold to or on the order of a practitioner licensed by law to use or order the use of such device, and otherwise must meet the exemption from adequate directions for use for prescription devices under 21 CFR § 801.109

Even though an IVD meets the requirements of sections 809.10 and 801.119, FDA may nonetheless determine that such devices meet the description of a device requiring prescription status under 21 CFR § 801.109. A device has prescription status when “because of any potential for harmful effect, or the method of its use, or the collateral measures necessary to its use, [the device] is not safe except under the supervision of a practitioner licensed by law to direct the use of such device, and hence adequate directions for use cannot be prepared” 21 CFR § 801.109. For prescription devices, the requirements for exemption include that such devices may only be sold to or on the order of a practitioner licensed by law to use or order the use of such device. See 21 CFR § 801.109(a). Therefore, in the premarket clearance or approval context, the decision that a device has prescription status represents a determination by FDA that the conditions of section 801.109 are met, *i.e.*, adequate directions for use for a lay user cannot be written and the labeling requirements for prescription devices are

³ Section 515(d)(1)(B)(ii) provides, as a condition of PMA approval, that sale and distribution of a device be restricted to the extent allowed under section 520(e) of the Act, which provides that certain devices may be restricted to prescription use only.

satisfied.⁴ However, as long as an IVD meets the requirements of section 809.10 and thus the requirements of section 801.119, and does not have prescription status under section 801.109, it retains its presumptive OTC status, notwithstanding the premarket notification process.

(c) OTC status is a separate legal determination from a finding of substantial equivalence and results in its own specific regulatory requirements for IVDs.

Importantly, an FDA determination of prescription or OTC status for a device subject to premarket review is the imposition of a federal requirement that is separate from a finding of substantial equivalence (or premarket approval). Indeed, there are devices within the same type that cleared for marketing, yet have both prescription and OTC designations under section 520(e) of the Act. Even restricted devices remain presumptively OTC unless FDA, by regulation, affirmatively designates prescription status as one of the restrictions. Compare, e.g., 21 CFR § 809.40 (placing restrictions on the test laboratories to which the samples can be sent and imposing additional labeling requirements for OTC test kits for drugs of abuse, but not requiring physician intervention) to 21 CFR § 809.30 (restricting the use of in house tests using analyte specific reagents to the order of a physician or other person authorized by applicable state law). Therefore, for purposes of preemption, OTC status should be analyzed separately from substantial equivalence findings because OTC status has its own statutory and regulatory requirements and thus its own specific regulatory consequences.

For example, when reviewing an IVD that a manufacturer intends to market OTC, the agency makes an individualized, data-driven determination about the OTC requirements for the device under review that is separate from the more generic conclusion about substantial equivalence. Indeed, OTC status results in a number of specific labeling and other requirements for IVD home use devices like Appraise. See FDA's "Assessing the Safety and Effectiveness of Home-Use In Vitro Diagnostic Devices (IVDs): Draft Points to Consider Regarding Labeling and Premarket Submissions" (October 1988) ("IVD home use guidance") at 4-5 (setting forth labeling considerations for home use devices, including those involving mail-in specimens, to meet the criteria for adequate directions for use under section 502(f)(1) of the Act and 21 CFR § 801.5). Moreover, under section 801.119, highly specific requirements for labeling are applicable to IVDs like Appraise under section 809.10 of FDA's regulations in order that such devices bear adequate directions for use. See 21 CFR 801.119; IVD home use guidance at 5-6 (elaborating on the means of complying with 809.10 for such IVDs).

⁴ Notably, satisfaction of the prescription labeling requirements would not, due to the level of technical information required, see sections 801.109(c) and (d), satisfy adequate directions for use for a lay user under section 502(f)(1) of the Act. Cf. United States v. Evers, 643 F.2d 1043, 1051 (5th Cir. 1981) ("neither prescription drugs nor non-prescription drugs can meet the terms of the statute by providing such adequate directions for use as are required for the other type of drug."). Therefore, State prescription requirements for OTC devices would create the need for additional labeling.

Compliance with all these requirements resulted in particularized instructions and conditions for use for Appraise. To receive Appraise, a customer calls Matria Healthcare's 800 number. Matria enrolls the patient in its diabetes supply management program and ships them Appraise. After receiving Appraise, a patient performs sample collection at home according to the instructions for use. The patient then mails the sample in a prepaid preaddressed envelope through regular U.S. mail to a designated CLIA approved laboratory for analysis. The test report is sent to the patient, and also to the patient's physician, upon the patient's request. The results are presented on a form that reports the patient's hemoglobin A1c level numerically and rates the patient's level in a "diabetic control" reference range of "optimal", "sub-optimal", and "poor", as well as providing the American Diabetes Association's recommended numerical target level. The report also depicts in a simple graph format a hemoglobin A1c trend analysis for the patient over time. Directly under the graph, the form states: "Test results should be reviewed with your physician."

Importantly, although the Supreme Court in Lohr found that clearance of a 510(k) and general labeling requirements were not the type of Federal requirements that would preempt the State common law claims at issue in that case, the Court distinguished such requirements from "the case in which the Federal government has weighed the competing interests relevant to the particular requirement in question, reached an unambiguous conclusion about how those competing requirements should be resolved in a particular case or set of cases, and implemented that conclusion via a specific mandate on manufacturers or producers". Lohr, 116 S. Ct. at 2258. Here, FDA has done just that. Under section 809.10, FDA promulgated specific requirements with respect to the type of device at issue here, an in vitro diagnostic. Further, with regard to an even more specific subset of such devices, home-use IVDs, CDRH has devoted close attention to the role of lay users, licensed practitioners, and other professionals in the use of OTC IVDs, and reached conclusions about the appropriate role of each for particular devices. Those conclusions are reflected in the requirements imposed upon each type of device in order for it to have an OTC status and bear adequate directions for use.

For Appraise, the requirements of OTC status resulted in an easy to administer test, a dedicated laboratory to which the results are to be sent for analysis and reporting, and a non-technical report form that provides results both numerically and in a simple graphical format, and describes their meaning within an easy to understand reference range. Compliance with these specifications makes the device available for purchase and use by lay users, and permits lay users to request and receive results from the test directly from the laboratory designated on the preaddressed envelope provided in the kit for mailing the sample in for analysis. Thus, the labeling requirements applicable to Appraise should be understood not as the generic labeling requirements FDA applies to all devices, cf. Lohr, 116 S. Ct. at 2258, but as a set of instructions, precautions, indications, and conditions for use and other statements that uniquely assure appropriate use of the IVD in the hands of lay users. Thus, OTC status, and the labeling requirements for OTC blood sample collection kits like Appraise, amount to "specific counterpart[s]" to the PA regulation that ultimately limits the use of such devices to licensed practitioners.

(2) The PA Regulation is a State Requirement Applicable to a Device

Significantly, as discussed above, the agency has already found that laws in New York and California that are substantively identical to the PA regulation at issue here were preempted as applied to the HIV-1 Home Access Test Kit. FDA found that because the FDA approved test protocol instructed patients to mail samples to a laboratory in a preaddressed envelope, the state “requirements [requiring a physician’s or other health care provider’s referral of samples to laboratories], as applied to the Home Access test system are different from the requirements in FDA’s approval order.” Home Access advisory opinion at 2 (emphasis added). Thus, FDA’s opinion held that a restriction on who can order tests from a clinical laboratory is a requirement applicable to test kits like Appraise. Indeed, FDA’s opinion found that even more attenuated licensing requirements affecting the permitting of laboratories and certification of personnel to be requirements “with respect to the Home Access test kit” and were also preempted. See id. at 3.

Nonetheless, PaDOH argues that the PA regulation, which has the admitted purpose of limiting the conditions under which an in vitro diagnostic sample may be tested, and is “designed to ensure that the health care consumer is properly informed and counseled about the significance of laboratory test results of specimens collected from that consumer”, see PaDOH Request for Advisory Opinion at 4, does not affect the safety and effectiveness of the device, and thus is not a requirement applicable to a device. In fact, PaDOH argues, the regulation does not address or regulate medical devices at all. See id. Therefore, according to PaDOH, its regulation “is not the type of regulation that is preempted under the Medical Device Amendments.” Id. The argument is without merit. Although the PA regulation appears in clinical laboratory provisions of the state health code, as FDA found in the Home Access opinion, the regulation nonetheless creates requirements applicable to diagnostic devices that provide specimens for laboratory evaluation.

Indeed, the federally determined indications for use and labeling for Appraise belie Pennsylvania’s position that the purpose of its regulation, appropriate patient counseling, is not directly related to safety and effectiveness considerations. The federal labeling requirements are specifically tailored to address the same concerns. First, Appraise is not indicated for the diagnosis of diabetes. See Appraise indications for use, quoted supra, page 2. Were Appraise indicated for diagnosing the condition, FDA may well have found Appraise to be a prescription device. Instead, Appraise is indicated for monitoring an already diagnosed diabetes patient’s condition over a 10-12 week period. Id. Second, the report form provides not only the most recent results, but a trend over time on a straightforward graph that simply describes reference points to provide context for the lay person receiving the results. Third, the indications for use state that the results “are to be evaluated by the patient and their physician”, id., and patients are given the option to have their test results sent directly to their physicians. The report form advises “[t]est results should be reviewed with your physician.” Thus, the admitted purpose of the PA regulation relates directly to federally considered safety and effectiveness concerns regarding Appraise. Further, the effect of the PA regulation is to modify the

federally determined OTC status of the device by imposing a different or additional requirement concerning who may request results from a blood sample collection kit, thus interfering with the balance struck between the risk of patient misuse or misunderstanding and the health benefits of convenience by the federal OTC labeling requirements for the specific type of device.

PaDOH relies for its argument upon 21 CFR 808.1(d)(3), which exempts from preemption "[s]tate or local permits, licensing, registration, certification, or other requirements relating to the approval or sanction of the practice of medicine, . . . pharmacy, nursing, . . . or any other of the healing arts or . . . related professions or occupations that administer, dispense, or sell devices" because they are not regarded by FDA as "requirements applicable to a device" within the meaning of section 521(a) of the Act. There is little, if any, interpretative guidance on the scope of this exemption, however, a fair interpretation is that the exemption means only that FDA sought to preserve the traditional role of States in determining the appropriate occupational backgrounds for individuals licensed to administer or provide prescription devices and thus to protect the public from incompetence or fraud, typical state police power prerogatives. On the other hand, it is a stretch to argue, as PaDOH does, that the provision supports the interpretation that State requirements "with respect to" devices are valid so long as they appear as part of a laboratory licensing scheme, or that FDA sought to permit States to override Federal determinations concerning whether a device should be available by prescription or over-the-counter. Importantly, FDA came to the same conclusion in the Home Access advisory opinion, stating that 21 CFR § 808.1(d)(3) does not bar preemption of State licensing requirements that "impose requirements on a particular device that are different from or in addition to specific counterpart requirements." See Home Access advisory opinion at 3.

(3) The PA Regulation is a Different or Additional Requirement that Directly Conflicts with the Federal OTC Status of Appraise

PaDOH argues that because its regulations "do not prevent or regulate the over-the-counter sale" of Appraise, or prevent the user from collecting the sample, there is no conflict with federal law. See Request for Advisory Opinion at 2-4. The argument is unacceptable on its face. Obviously, consumers do not believe that purchasing the kit and collecting a sample is an end in itself. The whole purpose of OTC availability is the convenience and savings resulting from the ability of users independently to request and receive results from use of the kits. Here, Pennsylvania is asking to apply a regulation adopted in 1962 (which when promulgated did not likely consider home use diagnostic test kits) to override FDA's judgment that lay persons may order and receive results for certain home-use IVDs, like Appraise, that require the use of a clinical laboratory to ensure accurate results. The fact that the prescription device requirements of 21 CFR § 801.109 are inapplicable to Appraise means that Pennsylvania's regulation is clearly in conflict with FDA's similar authority for limiting the conditions under which a device may be used. When a state imposes requirements on a device that FDA found unnecessary, FDA's expert determination should govern. See Commonwealth of Mass. v. Hayes, 691 F.2d 57, 64 (1st Cir. 1982) (holding that because FDA specifically considered a mandatory audiological testing requirement and rejected it as unnecessary

for the sale of hearing aids, and the state had presented no new evidence to support the desirability of such a requirement after the agency's original decision, the agency's decision governed the preemption analysis). PaDOH presents no evidence questioning FDA's determination that the device is reasonably safe and effective without mandatory intervention of a licensed practitioner. Thus, FDA's decision that physician or other professional intervention is unnecessary should govern and preempt the PA regulation to the extent it conflicts with the OTC use of Appraise. See id.

Moreover, where the risk is low (as with an OTC device), interstate commerce issues of affordability and availability should weigh significantly in the preemption analysis. See Hayes, 691 F.2d at 61. Avoiding burdens on commerce was a fundamental reason for enacting section 521 of the Act. See H.R. Rep. No. 94-853 at 45 (1976) (stating that "if a substantial number of differing requirements applicable to a medical device are imposed by jurisdictions other than the federal government, interstate commerce would be unduly burdened"). FDA's own regulations on exemption from preemption state that the Secretary may not grant an exemption if the Commissioner determines that it would not be in the best interest of the public health, taking into account the potential burden on interstate commerce." See § 808.25(g)(3). The best interest of the public health includes consideration of how the state regulation will affect cost to the consumer, as well as availability of needed products. See 43 Fed. Reg. 18661, 18664 (May 2, 1978). Here, the PA regulation increases cost and decreases convenience for the lay user, directly affecting commerce by conflicting with and undermining the statutory OTC presumption as well as FDA's specific labeling requirements for IVDs.

Contrary to PaDOH's assertion that the PA regulation is not "the type of regulation that is preempted under the Medical Device Amendments", see PaDOH Request for Advisory Opinion at 4, it is exactly the type of conflicting state requirement that was a primary reason for enactment of section 521. See Lohr, 116 S. Ct. at 2252 (stating that conflicting positive enactments of state law are a primary concern behind section 521). State statutes imposing prescription requirements on OTC blood sample collection kits do more than regulate laboratories; they contradict Federal law related to the use of medical devices like Appraise. To accept PaDOH's argument and allow the PA regulation to escape preemption because it appears in a code related primarily to clinical laboratories and does not prohibit the sale of the device or collection of the sample, would elevate form over substance, and deny the burden imposed by the PA regulation on the Federal system of device regulation and interstate commerce.

B. Implied Preemption—if not Expressly Preempted, the PA Regulation is Impliedly Preempted because it Conflicts with the Federally Determined OTC Status of Appraise and Similar Devices, and Frustrates the Federal Scheme for Regulation of such Devices

"[N]either an express preemption provision nor a saving clause 'bars the ordinary working of conflict preemption principles.'" Buckman, supra, 121 S. Ct. at 1019 (quoting Geier, supra, 120 S. Ct. 1913 (2000)). The Supreme Court recently applied this principle to find that the Federal scheme for policing fraud in submissions to FDA

preempted State common law “Fraud on the FDA” claims. See Buckman, 121 S. Ct. at 1017.

The Supreme Court defines implied or conflict preemption as occurring whenever “under the circumstances of th[e] particular case . . . [State law] stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress” and includes both “‘conflicts’ that prevent or frustrate the accomplishment of a Federal objective and ‘conflicts’ that make it ‘impossible’ for private parties to comply with both State and Federal law.” Geier at 1921 (citations omitted). Under the doctrine of implied preemption, “both forms of conflicting State laws are ‘nullified’ by the Supremacy Clause” of the Constitution. Id.

Applying this doctrine in a device context, the Court in Buckman held state claims of fraud on the FDA are preempted, finding the State law requirements skew the “somewhat delicate balance” of statutory objectives sought by the agency in policing fraud. Id. at 1017. The Court noted that such claims could both deter manufacturers from submitting 510(k)s for fear of liability when the cleared device was used for an off-label use, and compel manufacturers that did submit 510(k)s to “deluge” the agency with information to protect themselves from charges of fraud based on having withheld information from the FDA. Id. at 1018-1019. The state law claims thus conflicted with enforcement of the Federal scheme and therefore were impliedly preempted.

Similarly, state laws requiring prescription orders and similar restrictions affecting Federally determined OTC status for devices skew the delicate balance achieved by FDA. The agency’s determination that the presumptive OTC status of an IVD should be retained, and the requirements for proper labeling under section 801.5, and specific labeling for OTC IVDs under sections 801.119 and 809.10, represent a weighing of risks, benefits, and regulatory priorities as applied to a particular device. Hence, the conflict exists in both ways described by the court: for a device to have OTC and prescription status at the same time is an impossibility; further, the state requirements frustrate the marketing and labeling scheme designed by FDA for these types of devices.

As discussed above, to satisfy FDA that an IVD may be marketed OTC, sponsors must develop labeling to assure that laypersons will be able to use the test and understand the results. State requirements that federally designated OTC devices can be used only by or on the order of certain professionals would create the need for different labeling than required by FDA and the Act, see United States v. Evers, 643 F.2d at 1051 (the same adequate directions for use cannot be written for a prescription versus a non-prescription product), and clearly a different means of device distribution and use. Thus, under the law, a manufacturer of a blood sample collection kit like Appraise could only ensure adequate instructions for lay and professional users by developing two sets of labeling. Therefore, failing to preempt the PA regulation would burden device manufacturers by requiring compliance “with the FDA’s detailed regulatory scheme in the shadow of 50 States’ [laws],” Buckman, supra, at 1018, and burden FDA, which must review labeling for all uses. Further, the PA regulation interferes with the balance struck by the federal OTC labeling requirements for the specific type of device between the risk of patient

participation of a state sanctioned health practitioner, *i.e.*, a licensed practitioner, a status that literally defines prescription status under FDA's regulations. See 21 CFR § 801.109. In sum, PaDOH's petition misconstrues FDA law and disregards the specific federal requirements that make Appraise available OTC.

The PA regulation is clearly intended to affect the use and safety and effectiveness of devices like Appraise; the regulation is directly tied to the kit in that it precludes the analysis of blood samples collected using Appraise, thereby completely frustrating the purpose of the device. In addition, the admitted purpose of the regulation, to ensure appropriate patient counseling, is a consideration covered by the federal requirements applicable to the device. Further, the regulation directly conflicts with the specific counterpart requirements imposed on OTC IVDs like Appraise under the Act and FDA regulations. In so doing, the regulation undermines the legal status of the device by interfering with the availability of a convenient method to measure average long-term blood glucose levels (and presumably other OTC at home tests requiring clinical laboratory analysis) for Pennsylvania consumers. Thus, the PA regulation adversely affects the OTC use and distribution of the device and burdens interstate commerce. Therefore, whether analyzed under section 521(a) of the Act, or under the law of implied preemption, FDA should find the PA regulation preempted to the extent it undermines the OTC status of devices such as Appraise.

II. Background

A. Federal Status of Appraise

Appraise was formerly known and cleared by FDA as the "HemoChek-A1c Sample Collection Kit" on December 21, 1999 (K990899), with the following indications for use:

The HemoChek-A1c Sample Collection Kit is indicated for over-the-counter sale for use in the measurement of HbA1c on blood specimens which can be collected at the patient's home or at a physician's office on filter paper and delivered to the laboratory by mail. The HbA1c test is used in the assessment of the average blood glucose over a 10-12 week period. The results are to be evaluated by the patient and their physician. The product is not indicated for the diagnosis of diabetes mellitus.

The OTC status of Appraise is not derived from a finding of substantial equivalence; it is derived from evidence that a new device, here Appraise, or its predicate can be used safely and effectively by laypersons if adequate directions for use are included with the device. Thus, Appraise is legally available OTC because it complies with regulations specific to IVDs which impose requirements that assure its safe and effective use by lay persons, see 21 CFR §§ 801.119 and 809.10, thereby satisfying the statutory requirement that a device "bears adequate directions for [lay] use", see section 502(f)(1) of the Act. See also United States v. Two Units, More or Less, of an Article of Device, 49 F.3d 479, 482 (9th Cir. 1994) (stating that a medical device is misbranded if it

does not bear adequate directions for use for a lay person). Because Appraise also does not meet the definition of a prescription device under 21 CFR § 801.109, no facts would justify exempting the device from the statutory requirements of OTC labeling.

B. Previous FDA Advisory Opinions

FDA has issued two advisory opinions in this area. On August 16, 1996, attorneys for Home Access Health Corp. requested an advisory opinion that PMA approval of the OTC Home Access HIV-1 Test Kit preempted New York and California laws with the identical requirement to Pennsylvania's, *i.e.*, that clinical laboratories may only test specimens upon the request of a physician or other licensed person.¹ In an opinion letter from William Schultz to Robert P. Brady dated December 18, 1996 ("Home Access advisory opinion"), FDA found the laws to be preempted because the requirements of the State laws differed from those imposed by FDA's OTC approval order, which allowed patients to send their samples directly to a designated lab, which FDA inspected and approved. The opinion further found California's prohibition on providing reports of results directly to the patient was preempted for the same reason. In addition, the opinion preempted other even less directly related clinical laboratory licensing provisions regarding the permitting of laboratories and certification of personnel to the extent such regulations applied to the laboratory approved by FDA for testing samples from the Home Access test.

On March 5, 1999, attorneys for Becton-Dickinson, Inc., submitted a request for an advisory opinion to FDA, requesting a determination that the 510(k) clearance for the B-D A1c At-Home Test (the "B-D test"), also an OTC blood sample collection kit,² preempted similar State requirements defining who may request and receive results of blood sample testing. In a letter dated April 5, 2000, FDA responded that it found no conflict with the State laws because the 510(k) clearance of the B-D test did not establish any specific counterpart requirement within the meaning of section 521(a) of the Act; therefore, the State requirements were not preempted as applied to the B-D test.

In declining to find preemption for the B-D test, FDA distinguished its earlier opinion solely on the basis that the Home Access test was a PMA approved device and the B-D product was not. It did not reverse its position that the State laws were requirements applicable to a device, nor that such state laws differed from an FDA order designating a device as OTC. Indeed, the advisory opinion issued concerning the B-D At-Home Test focused solely on the fact the device was subject to 510(k) clearance rather than PMA approval. Importantly, neither the request for the advisory opinion, nor the

¹ The New York statute at issue, N.Y. Comp. Codes & Regs. Tit. 10, § 58-1.7(b) (1996) provided that clinical laboratories "shall examine specimens only at the request of licensed physicians or other persons authorized by law to use the findings of laboratory examinations in their practice or the performance of their official duties." The California law, Cal. Bus. & Prof. Code § 1288 (1996), provided that "any person conducting or operating a clinical laboratory may accept assignments for tests only from and make reports only to persons licensed under the provisions of law relating to the healing arts or their representatives."

² Like the Appraise, the B-D A1c At-Home Test assesses glycated hemoglobin to determine long term average blood glucose levels.

misuse or misunderstanding and the health benefits of convenience. These burdens are precisely the sort the Supreme Court found to “exert an extraneous pull on the scheme established by Congress,” and held to be preempted in Buckman. Id. at 1020. Therefore, FDA should find the PA regulation impliedly preempted, if the agency disagrees that express preemption is present.

IV. Conclusion

In sum, in its Home Access Opinion, FDA found that substantively identical state restrictions to the PA regulation were preempted. When FDA declined in its advisory opinion on the B-D test to give preemptive effect to the B-D test’s 510(k) clearance, it distinguished the B-D test solely on the basis that the Home Access kit was a PMA approved device and the B-D test was not. The agency’s advisory opinion did not consider whether other requirements related to that device besides 510(k) clearance could preempt state requirements. Nor did FDA consider whether the state requirements were impliedly preempted because they conflicted with the federal scheme for regulating medical devices. Therefore, the B-D opinion was incorrectly decided and has no precedential weight in FDA’s consideration of this opposition.

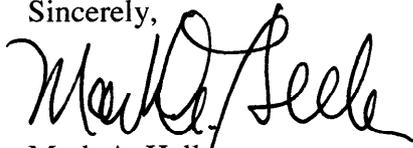
Under section 521(a) of the Act, OTC status results in specific federal requirements, unrelated to substantial equivalence determinations, that can preempt state law. IVDs retain their presumptive OTC status only if they meet the conditions of 21 CFR §§ 801.119 and 809.10, which comprise highly specific requirements for the labeling of IVDs in order that they bear adequate directions for use for a layperson. Compliance with these requirements, as tailored to the specific characteristics of an OTC blood sample collection kit, results in particularized instructions and conditions for use for Appraise. As the agency has determined in its Home Access advisory opinion, state requirements like the PA regulation “relate to” at home in vitro diagnostic kits that require clinical laboratory analysis. Further, the PA regulation adds to an FDA determination of OTC status a different state requirement for a prescription order. Therefore, the regulation is different from, and in addition to, the Federal requirements, and is expressly preempted. In addition, the PA regulation is the type of state requirement that burdens commerce and should be preempted under section 521(a).

Also, because of the direct conflict of the PA regulation with the Federal OTC status of Appraise and similar devices, and the effect of the PA regulation in frustrating the Federal scheme, the regulation is preempted by implication under the Supremacy Clause of the United States Constitution.

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For the above reasons, we ask that the agency reject PaDOH's request for an advisory opinion that the PA regulation is exempted from preemption and find the PA regulation preempted as applied to Appraise and similar OTC in vitro diagnostic kits.

Sincerely,

A handwritten signature in black ink, appearing to read "Mark A. Heller". The signature is written in a cursive, flowing style with a large initial "M".

Mark A. Heller
Melisa Moonan