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CITIZEN PETITION

Hyman, Phelps & McNamara, P. C. (Petitioner) submits this petition to request that the Commissioner of Food and Drugs not regulate as medical devices assays developed by clinical reference laboratories strictly for in-house use. The Center for Devices and Radiological Health of the Food and Drug Administration (FDA) has issued a draft Compliance Policy Guide (CPG) entitled "Commercialization of Unapproved In Vitro Diagnostic Devices Labeled for Research and Investigation." Petitioner requests that no final CPG addressing or referring to in-house assays be issued because: (1) regulation of in-house assays by FDA is inconsistent with the Clinical Laboratory Improvement Act Amendments of 1988; (2) FDA lacks the statutory authority to regulate in-house assays; and (3) FDA's regulation of in-house assays would diminish the quality of health care in

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the United States. In addition, any regulation of in-house assays by FDA can be accomplished only through notice-and comment rulemaking, rather than the issuance of a compliance policy guide.

The Petitioner is a law firm that represents clinical laboratories that would be affected by FDA regulation of assays developed or modified by clinical laboratories.

A. Action Requested

Petitioner requests that any final CPG on the distribution of research and investigational in vitro diagnostics, as well as any other CPG, exclude assays developed by clinical reference laboratories for in-house purposes, whether developed from components or from commercially available kits.

B. Statement of Grounds

On August 3, 1992, the Office of Compliance and Surveillance issued a "note" releasing a draft Compliance Policy Guide entitled "Commercialization of Unapproved In Vitro Diagnostic Devices Labeled for Research and Investigation." This "note" invited comments from interested parties.

The primary focus of the draft CPG is on the distribution of research and investigational in vitro diagnostics. However, the first paragraph on the fourth page of the CPG asserts that "laboratories have been manufacturing, 'home brew' products, either from products already on the market, or from components, and utilizing these unapproved products for diagnostic purposes."

According to the CPG, "home brew" tests are to be regulated "as any unapproved medical device." This single paragraph, if adopted in the final CPG (or in any other document issued by FDA), would have a profound impact on clinical reference laboratories in the United States. Any final CPG should omit any reference to in-house assays. Petitioner specifically requests that the CPG not assert that FDA has the authority to regulate "home-brew" assays, even if the CPG also disclaims any intent to exercise this alleged authority.

The Proposal Is Inconsistent with CLIA

With the promulgation of the final rule to implement the Clinical Laboratory Improvement Act Amendments of 1988 (42 C.F.R. Part 493), FDA assumed responsibility for determining test categorization while reviewing device marketing applications. However, the final rule clearly contemplates that there will be test systems, assays, and examinations that are not commercially

available and not subject to FDA review (Note 42 C.F.R. § 493.17(c)(2).

It is evident in the CLIA '88 final rule that those test systems, assays, or examinations that are not commercially available do not fall within FDA's jurisdiction. A process, apart from the FDA approval process and test categorization decision, was established wherein the Centers for Disease Control (CDC) would make the decision on how to categorize a test. The FDA proposal would nullify this process by requiring all tests, examinations, or assays to get FDA approval.

This attempt by FDA to expand its jurisdiction ignores the fact that the CLIA final rule provides adequate safeguards for patients for all tests, assays, or examinations, including those that are not approved or categorized by FDA. These protections begin with the categorization of a test system, assay, or examination and are reflected in the quality control (QC) provisions of 42 C.F.R. §§ 493.1201, et. seq.

The placement of a test system, assay, or examination in the waived, moderately complex, or highly complex categories is based on a number of factors. These factors, which are identified in 42 C.F.R. § 493.17, encompass: the training and experience required to perform the test; test preparation; operational characteristics; quality control; troubleshooting steps involved;

and the interpretation and judgement of the personnel performing the test. These factors are intended to protect the patient by ensuring that tests, assays, or examinations which pose a greater risk to the patient are placed in categories entailing a greater degree of scrutiny of personnel and test performance.

The steps required to comply with the QC provisions of 42 C.F.R. §§ 493.1201, et. seq., also vary with respect to the specialty or subspecialty of a test or assay and test category. Quality control encompasses facility conditions, test methods, instrumentation, reagents, materials, and supplies. Laboratories must have in place procedure manuals, be capable of establishing and verifying test performance, and ensure the proper functioning of all equipment.

Indeed, § 492.1213(b)(2) explicitly contemplates that not all test systems, assays, or examinations will receive FDA approval. This provision directly addresses the QC requirements for tests that are not FDA approved, or have been approved by FDA and are modified by the laboratory. The final CLIA '88 rule sets forth more detailed QC provisions for those tests and for tests where the manufacturer's instructions do not encompass all of the quality control requirements. These provisions protect the patient and ensure that accurate and reliable test results are produced by clinical laboratories. It would have made no sense

to include these provisions if all in-house assays need FDA approval.

Moreover, there are serious concerns regarding the ability of the FDA to process all of the section 510(k) premarket notifications and premarket approval applications (PMA) that would need to be submitted as a result of these provisions. The preamble to the CLIA '88 final rule estimates that a total of 3,000 to 9,000 "QC Clearance" applications are expected to be submitted, primarily during the first two years, along with the normal 1,000 applications received annually. 57 Fed. Reg. 7002, 7758. The preamble indicates that FDA is concerned about its ability to process these applications, stating that "there are practical limits on the number of additional technical staff that can be hired and trained within a short period of time, particularly when the need for these staff is temporary." Id. at p. 7759.

This concern is well-founded. At a public meeting last spring, the Division of Clinical and Laboratory Devices (DCLD) promised that it would soon issue guidelines concerning the requirements for QC clearance submissions under CLIA. Despite the arrival of the September 1, 1992 date for initial submission of QC clearance filings, DCLD has not yet released draft guidelines. Presumably, the delay in issuing the guidelines

stems at least in part from the already large workload of DCLD and the complexity of implementing CLIA.

These workload difficulties would only intensify if every "home brew" diagnostic test or in-house assay had to be submitted to the FDA for approval. FDA's difficulties in handling 510(k) premarket notification and PMA applications would be exacerbated by the expansion of FDA authority to "home brew" diagnostic tests or in-house assays.

Patient care is threatened if FDA cannot promptly process the existing 510(k) premarket notifications and PMA applications. Tests that would be potentially beneficial to patient face the prospect of significant delays in becoming commercially available if FDA cannot complete its evaluation process in a timely fashion. This problem would be greatly magnified if FDA authority is expanded to include "home brew" diagnostic tests or in-house assays.

FDA Lacks the Statutory Authority to Regulate In-House Assays

Second, the draft CPG assumes that FDA has the statutory authority over assays developed in-house. This assumption is not well-founded.

The CPG appears to state that laboratories with in-house assays will need to obtain FDA marketing clearance. The approval requirements, however, apply only to devices that are placed into commercial distribution. That is not the case here; the in-house assays do not enter commercial distribution.

The need for this type of shipment to trigger FDA enforcement is underscored by page 4 of the CPG. Under the heading of "Regulatory Action Guidance," FDA's districts are advised not to take action against "manufacturers" if certain conditions are present -- the manufacturer agrees not to "commercially market the device" or the manufacturer "will not distribute the device for investigational or research use," and the manufacturer will "recall or correct any device(s) in the marketplace." Each of those conditions presupposes that the manufacturer has actually distributed the device in question. But because in-house assays are not distributed, none of the three conditions will apply here. The "Regulatory Action Guidance" assumes, and correctly so, that commercial distribution is a prerequisite to FDA jurisdiction. See 21 C.F.R. § 807.20(a). That prerequisite is missing with in-house assays developed by reference or academic laboratories.

In addition, because in-house assays do not enter commercial distribution, registration of the laboratories is not required. Id. This means that 510(k) premarket notifications would not be

necessary. See 21 U.S.C. § 360(k) and 21 C.F.R. § 807.81(a). Similarly, PMAs are not needed unless a device enters commercial distribution. 21 U.S.C. § 360c(f) and 21 C.F.R. § 814.1(c)(1).

Moreover, it is far from clear that an in-house assay system or method is actually a medical device within the meaning of the Federal Food, Drug, and Cosmetic Act (FDC Act). Rather, they are services. The FDA's authority does not extend to test methods, protocols, or services. And even if these in-house protocols were construed as devices and were somehow within FDA's jurisdiction, their use would not constitute a prohibited act under the FDC Act.

Because the test assays are created and used on site, the prohibited acts set forth in 21 U.S.C. § 331(a), (b), (c), and (d) are all plainly inapplicable. The only prohibited act subsection with any conceivable relevance is 331(k). However, even if a laboratory uses a component or device that has traveled in interstate commerce, a section 331(k) charge is not viable against the laboratory.

FDA acknowledged as much in Chaney v. Heckler, 714 F.2d 1174 (D.C. Cir. 1984), rev'd on other grounds, 470 U.S. 821 (1985). Chaney involved FDA's decision not to take action against states that wished to administer lethal doses of approved drugs to execute prisoners. As one of its defenses, FDA directly asserted

that the "unapproved use of drugs for lethal injection is outside the general jurisdictional provisions of the [FDC] Act." Id. at 1179. FDA argued that § 331(k) simply did not apply to drugs that were lawfully shipped and then used for some other purpose after completing their journey in interstate commerce.

FDA's position was supported by then-judge (now Justice) Scalia. Justice Scalia stated that:

> Even if one adopts the extraordinary notion that a person causes an article to be misbranded by simply using it for the purpose not stated in the label, § 331(k) would still not apply, since -- in accordance with the [FDC] Act's focus upon sale and distribution rather than . . . use -- it requires the misbranding occur "while such article is held for sale (whether or not the first sale) after shipment in interstate commerce." Here the drugs are in the possession of the states' penal authorities. Under no conceivable interpretation of the English language could they be deemed "held for sale."

718 F.2d at 1192 (emphasis added). The same analysis applies to laboratories that develop in-house assays that neither leave the facility nor are sold to others.

The interpretation adopted by Justice Scalia and espoused by FDA in Chaney was consistent with the ruling in United States v. Evers, 643 F.2d 1043 (5th Cir. 1981). FDA alleged that Dr. Evers had violated the FDC Act when he "promoted and administered a drug for a use that is not approved by the [FDA], without providing adequate directions for use to his patients." The court disagreed, and held that § 331(k) did not apply. It found that [FDA's] interpretation of the [FDC] Act breaks down over its use of the phrase 'held for sale after shipment in interstate commerce.'" Id. at 1053.

The structure of CLIA and the implementing regulations further undercut FDA's implicit assertion of jurisdiction. Under CLIA, the task of regulating in-house laboratory services, such as clinical assays, falls upon the Health Care Financing Administration, not FDA. Moreover, nowhere in the legislative history of CLIA, the voluminous proposed implementing regulation, or the final regulation is there a suggestion that FDA has the statutory authority to regulate these laboratory services. In fact, as noted above, the CLIA '88 regulations establish a separate test categorization process within CDC for these assays which are not subject to FDA regulations. See 42 C.F.R. § 493.1213(b)(2).

The CPG Would Violate the Administrative Procedure Act

For the reasons stated above, FDA does not have the legal authority to regulate in-house laboratory assays. Even if FDA did have this authority, however, the initiation of this regulation through the issuance of a CPG would violate the notice-and-comment rulemaking provisions of the Administrative Procedure Act. 5 U.S.C. § 553.

The APA requires that agencies proceed through notice-and-comment rulemaking prior to issuing a substantive rule. While FDA might try to denominate the paragraph in the CPG as merely being an interpretation of agency position, that is not the case. Rather, taking the position that laboratories must obtain FDA approval for in-house assays would represent a substantive change and therefore be subject to the APA's rulemaking requirements.

As part of the services they provide physicians and patients, laboratories have been developing their own assay systems and methods for decades. Many laboratories across the United States are now using assay methods that they devised themselves. Other assay systems and methods for in-house use are currently under development. Yet, to the best of our knowledge, FDA has never required, stated, or even implied that each assay system be approved by FDA prior to use. Moreover, we are aware of no instance in which a laboratory that has used an assay

solely for internal purposes has submitted a marketing application to FDA. Nor are we are aware of a single instance in which FDA has directed a laboratory to submit such a marketing application for its in-house assay. Thus, the imposition of "the same regulatory requirements" to laboratories' in-house assays as to a new AFP or CEA test kit sold by a manufacturer would result in imposing new substantive requirements upon laboratories.

Significantly, in litigation within the past year, FDA repeatedly declined to state that it regulated in-house protocols. In Clinical Reference Laboratory v. Sullivan, Civ. No. 91-2313-L (D. Kans.) the plaintiff laboratory contended that FDA's regulation of specimen collection cups interfered with the laboratory's ability to utilize test protocols developed at the laboratory. That is, the laboratory defended itself by saying that FDA was acting improperly by seeking to regulate a laboratory service, or, in FDA's new terminology, a "home brew" assay. If laboratories were required to obtain FDA approval for in-house assays, FDA presumably would have replied simply by saying that "home brew" assays were indeed regulated. It did not. This, too, shows that the CPG would impose new regulatory requirements.

The CPG shifts laboratory assays from services, which are unregulated by FDA, 21 C.F.R. § 807.65(i), to the status of "unapproved medical device[s]." This clearly would have a

substantive impact on laboratories. Assays would be subjected to the premarket approval application and 510(k) requirements. Labeling regulations would suddenly apply. See 21 C.F.R. Part 801. Presumably, FDA would insist that the production of the assay systems conform to the good manufacturing practice regulations. See 21 C.F.R. Part 820. In other words, laboratories would suddenly be held to the same binding requirements as companies manufacturing catheters and pacemakers. This type of change is a substantive rule.

Assuming that FDA attempts to introduce this requirement through a CPG, the CPG will be invalid. A legislative rule that is issued without notice-and-comment rulemaking is void, no matter how FDA characterizes the rule. E.g., State of Alaska v. United States Department of Transportation, 868 F.2d 441 (D.C. Cir. 1989); Community Nutrition Institute v. Young, 818 F.2d 943 (D.C. Cir. 1987); Bellarno Int'L Ltd. v. FDA, 678 F. Supp. 410 (E.D.N.Y. 1988); Pharmaceutical Mfrs. Ass'n v. Finch, 307 F. Supp. 858 (D. Del. 1970). See Thompson, The Food and Drug Administration's New Rules for Investigational and Research IVDs, 4 Regulatory Affairs 305 (1992) (FDA's new regulations of IVDs violates the APA).

The injury caused by the failure to comply with the APA was only exacerbated by the manner in which "notice" to affected parties was provided. First, regardless of the number of

responses received, the highly informal nature of the "note" sent by the Office of Compliance and Surveillance was not calculated to solicit maximum public participation or involvement. FDA mailed the "note" to a relatively small number of individuals and organizations. This casual, ad hoc dissemination of "notes" is no substitute for the formal publication in the Federal Register required by the Administrative Procedure Act.[1/]

Moreover, laboratories were given only an abbreviated period in which to respond. The Medical Device Amendments require that FDA allow no less than sixty days for comments for any notice published in the Federal Register. 21 U.S.C. § 360j(d). Frequently, the comment period is then extended at the request of some interested party. Twenty-eight days from the date of the "note" was simply too short a comment period for a regulatory action that would, if implemented, significantly affect numerous laboratories and millions of patients. It is also paradoxical that interested parties are given more time to comment on a routine notice that a PMA has been approved than on a proposed regulatory change that would impose new regulations on clinical laboratories.

1/ The need for rulemaking is underscored by the ambiguities found in the proposal. The draft CPG uses the term "home brew," but that term is undefined. Moreover, laboratories cannot discern the FDA's intent in imposing this requirement, since the draft CPG includes no rationale for this new requirement.

The APA is designed to achieve multiple goals. One goal is fairness; another is to enable the agency to receive "valuable information concerning the various issues involved." National Ass'n of Home Health Agencies v. Schweiker, 690 F.2d at 950. Regardless of the number of comments submitted, the release of this draft CPG was inadequate to accomplish either objective.

In addition to being extensive, the new regulatory requirements would be expensive. Imposing the product approval and GMP requirements on laboratories would cost laboratories tens of millions of dollars. The proposed CPG does not state that FDA has performed a threshold assessment to determine whether a regulatory impact analysis, see Executive Order 12291, or regulatory flexibility analysis, see Pub. L. 96-354, is necessary. Unless these analyses are performed, FDA has not acted in accordance with Executive Order 12291 or the Regulatory Flexibility Act.

Even if these specific dollar thresholds are not reached, FDA should carefully consider the economic consequences of this new regulatory initiative. Without direct test methods, physicians would be forced to use less specific and, therefore, less useful indirect methods. This means more tests will be necessary. The absence of these methods would also often prevent an early diagnosis and therefore increase the total costs of patient care. While Petitioner understands that FDA's primary

focus is not on financial factors, FDA should be reluctant to take steps that add to the nation's burgeoning health care costs.

The Proposed CPG Would Diminish the Quality of Health Care

Finally, FDA must consider the impact of its new regulations on public health. The agency's ultimate objective, after all, is to preserve and improve the quality of patient care. Yet the regulation of in-house laboratory assays as medical devices would have the perverse effect of diminishing public health.

As noted above, clinical reference laboratories have developed numerous in-house assays. Generally, these have been created to fill a discernible medical need.

For a variety of reasons, manufacturers do not sell assays for all analytes whose detection may be medically useful. There is always a lag between the medical community's desire to test for an analyte and a company's receiving FDA clearance to market a kit for that analyte. This gap can easily span several years. In the interim, physicians and patients may have no alternate means of securing the critical diagnostic information except through in-house assays. This has been the standard practice course for decades, and it has worked well.

Other times, scientists learn of an analyte that is found in relatively few patients, but is essential to diagnosing their condition. In that case, there may never be a commercially available assay -- the analyte may remain an "orphan" indefinitely. The unavailability of these "orphan tests" could seriously compromise patient care.

The proposal would significantly curtail the ability of reference laboratories to develop state-of-the-art esoteric assays for the medical community. The logistical and financial costs of collecting and collating a data base to obtain FDA approval would delay or prohibit the introduction of new assay methods, particularly the low volume "orphan tests" applicable to many esoteric tests with smaller potential markets. Many such tests would never be developed if they could be used only by being configured into kits and sold with FDA approval.

FDA has been proud, and justifiably so, of its strong efforts to stimulate the development of orphan drugs to treat rare diseases. Agency officials have repeatedly testified before Congress about FDA's commitment to helping individuals suffering from orphan diseases. It is difficult to reconcile FDA's commitment to accelerate the approval of drugs for rare diseases with a new regulatory initiative that would prevent those diseases from being diagnosed.

Moreover, in-house assays are utilized not only by private reference laboratories. The Centers of Disease Control and the States also operate their own reference laboratories. These governmental laboratories often heavily rely upon assays and protocols developed in-house. FDA's prohibition on in-house assays could cripple the ability of these laboratories to discharge their essential public health function.

For example, from time to time researchers will encounter a new disease. It then becomes vital to develop rapidly a method for detecting that disease. Eventually, a manufacturer may obtain a 510(k) clearance or PMA for a kit indicated for that disease. That approval, though, will lie years into the future. The CDC, States, and physicians cannot wait years, months, or even weeks to generate diagnoses. In-house assays have provided this diagnostic information. It would not be in the public interest to block laboratories from performing the in-house assays that historically have been so crucial in these public health emergencies. The proposed CPG, however, would have precisely the effect of preventing laboratories from rendering this service that they have hitherto provided.

Furthermore, this new regulation of in-house assays could have profoundly negative long-term consequences for the IVD industry. Many of the kits now in commercial distribution originated with clinical reference laboratories. If in-house

assays are prohibited, this important source of new assays will wither. United States in vitro diagnostic companies will be handicapped in developing new products if in-house laboratories in the United States are prevented from generating the pioneering clinical data.[2/]

C. Environmental Impact

Petitioner claims a categorical exclusion under 21 C.F.R. § 25.24(a)(8).

D. Economic Impact

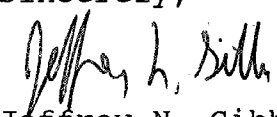
Petitioner will submit information upon request of the Commissioner. Petitioner believes that the issuance of a Compliance Policy Guide which would regulate in-house laboratory assays would result in greatly increased costs for clinical reference laboratories, and in turn cause increased health care costs.

2/ Foreign manufacturers, however, would still be able to draw upon in-house assays performed by their reference laboratories as a vehicle for learning about clinical chemistry in creating new test kits.

E. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the Petitioner which are unfavorable to the petition.

Sincerely,



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