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## **THE WARFARIN REVISED PACKAGE INSERT: IS THE INFORMATION IN THE LABEL "TOO THIN"?**

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## I. INTRODUCTION

Each and every drug has unique effects on the individual patients using them, with some drugs proving to be safer or more effective for some patients than for others. Until very recently, however, it has not been possible to proactively identify specific groups of patients in a way that allowed physicians to more accurately determine which drugs to give what patients and in what specific dose.

With the sequencing of the human genome in 2003, the pharmaceutical and biotechnology industries have been better able to define specific groups of patients for whom drugs are safer or more effective by identification of genetic polymorphisms.<sup>1</sup> Where possible, these industries are developing these genetic differences, or biomarkers, into companion diagnostic tests to guide prescribing decisions.

This approach to drug development, termed "personalized medicine," has gained momentum in the few years since the human genome was sequenced. There are already approximately fifteen such drugs on the market<sup>2</sup> with another wave of targeted therapies expected to be launched by 2010.<sup>3</sup> One highly anticipated benefit of

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<sup>1</sup> Certainly, there is a much wider array of testing available to distinguish patients than just genetic testing, including proteomic, metabolomic, and a variety of other molecular entities. For purposes of this paper, as the testing for warfarin is genetic in nature, I will only focus on genetic testing.

<sup>2</sup> While there are many more than fifteen therapies currently on the market that contain pharmacogenetic information in the label, at present there are only fifteen that either require or recommend use of a test in advance of prescribing. The Personalized Medicine Coalition, "*The Case for Personalized Medicine*", at 11, 18-19, May 2009, available at [http://www.personalizedmedicinecoalition.org/communications/TheCaseforPersonalizedMedicine\\_5\\_5\\_09.pdf](http://www.personalizedmedicinecoalition.org/communications/TheCaseforPersonalizedMedicine_5_5_09.pdf).

<sup>3</sup> It has also been estimated that "[i]n 10 years, about 20 to 25 percent of new [therapeutic] products in the pipeline will depend to some degree on a related test." LULU PICKERING, COMPARING DIAGNOSTICS: ENABLING PERSONALIZED MEDICINE IN CANCER (Spectrum

personalized medicine is the potential to use tests to “retrofit” already available drugs that have significant adverse event profiles to make them safer. These tests would identify those individual patients most likely to experience adverse events and either exclude them from being prescribed the drug or regulate dosing guidelines.

In fact, pursuant to the regulations governing the Food and Drug Administration (FDA) in Title 21 of the Code of Federal Regulations (CFR), Section 201.57, “where evidence is available to support better safety or efficacy of the drug in selected subgroups of the larger population,” the drug label should *describe the evidence* and identify *the specific tests* needed for selection of those patients.<sup>4</sup> This practice clearly reflects the FDA’s stated mission of supporting new technologies, such as pharmacogenomics, that speed innovation and make medicines safer and more effective.

In recognition of this requirement, in the summer of 2007, the FDA changed the package insert for the anticoagulant Warfarin to reflect the fact that genetic differences in two different genes are responsible for nearly forty percent of the observed differences in tolerability and sensitivity of the drug.<sup>5</sup> The FDA describes the evidence for selection of patients, as required by CFR 201.57, by including genomic information in the label that explains in general terms how a patient’s specific differences in two particular genes could affect dosing. However, the revised package insert does not mention a test, either generically or specifically.

This is not the first time that the FDA has revised a drug label with information pertaining to how genomic differences affect dosing. In 2003, the FDA revised the label for mercaptopurine, a drug used to treat a form of childhood leukemia. Although mercaptopurine (6MP) has a very similar profile to Warfarin, the revised label not only described the available evidence, but also mentioned generically that tests were available -even though none of

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Reports, Biomarkers and Diagnostics 2006).

<sup>4</sup> 21 C.F.R. § 201.57 (2000). While a drug label and a package insert are, in reality, two different objects, in the vernacular of talking about FDA updates they are often used interchangeably, and are used that way in this paper.

<sup>5</sup> Press Release, U.S. Food and Drug Administration, *FDA Approves Updated Warfarin (Coumadin) Prescribing Information* (Aug. 16, 2007).

the tests were FDA approved at the time.<sup>6</sup>

With so much emphasis placed on the ability to better prescribe drugs based on genetic differences, and the regulatory requirement that the FDA describe the evidence and mention specific tests necessary to identify subpopulations for whom drugs are safer or more efficacious, it is not entirely clear what the FDA's rationale was in choosing not to mention the availability of tests in the updated Warfarin package insert. The pharmacogenomic information provided references to genetic differences affecting dosing that only obliquely suggests to physicians that genetic testing should be done in advance of prescribing.

While there are a number of possible reasons for not mentioning a test specifically, the primary concern with the FDA not following its own regulations is that by failing to implement a standardized approach to relabeling package inserts in this area, the FDA is potentially creating confusion for the pharmaceutical and diagnostics industries. Such confusion over regulatory requirements could potentially stifle new innovations rather than encourage their development. Furthermore, the lack of a standardized approach to when and how the FDA will include mention of available tests in package inserts may create confusion in the minds of physicians, increase their liability and deter, rather than encourage use of these new technologies.

It is possible that the lack of evidence demonstrating clinical utility of the test to guide Warfarin dosing was the reason the FDA chose not to mention the availability of a test in the revised label. Perhaps the ten years of clinical data supporting the use of tests in prescribing 6MP was the reason the FDA chose to mention the availability of tests when it revised the label for 6MP. If this was the rationale, although the FDA is still to be commended for its efforts in promoting personalized medicine through the Warfarin label revision, perhaps the revision would have been more appropriately delayed until such clinical evidence was available. It is possible that the revision was "too thin" to accomplish the FDA's stated mission of supporting new technologies that speed innovation and make medicines more effective and safer.

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<sup>6</sup> See U.S. FOOD AND DRUG ADMIN., *infra* note 30.

While future label revisions will certainly be initiated by the FDA, as the effort to revise the Warfarin label was, one can imagine the numerous cases likely to occur where a drug manufacturer (and possibly its diagnostic partner) will seek inclusion of a test in the drug label.<sup>7</sup> This possibility leads to broader and more significant concerns related to when the FDA might include mention of a specific test in a drug label.

First, the issue of the quantity and quality of evidence the FDA requires to include mention of a specific test in a drug label is as yet unresolved. Even assuming sufficient evidence is available to provide the FDA enough certainty to mention that test(s) are available, either generically or specifically; it is still not entirely clear whether the FDA may only reference an FDA approved test in a label. Finally, if drug or test manufacturers will be required to shoulder the burden and expense of conducting clinical trials to obtain FDA approval so that tests used to guide dosing could be mentioned in a drug label, then it is unclear how the FDA can continue to justify allowing the use of non-FDA approved, laboratory developed tests (LDTs), which are specifically designed to measure the same biomarkers as the FDA approved tests. In doing so, the FDA permits laboratories to benefit from the burden already shouldered by manufacturers seeking FDA approval, providing a significant disincentive to seek FDA approval on new tests.

## II. REGULATORY BACKGROUND

### A. Drug Regulation

Drugs, and concerns about their safety, were not always a priority in the United States. It was not until the late nineteenth

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<sup>7</sup> There are significant and complex legal and policy issues in the related but substantially different case where a test manufacturer seeks to cross-label a drug post-approval by including mention of its test completely independent from the manufacturer of that drug. That issue is beyond the scope of the present paper, but for an excellent discussion of those issues see, Barbara J. Evans, *What Will it Take to Reap the Clinical Benefits of Pharmacogenomics?* 61 FOOD & DRUG L.J. 753, 780-87 (2006); see also, Scott Sasjack, *Demanding Individually Safe Drugs Today: Overcoming the Cross-Labeling Legal Hurdle to Pharmacogenomics*, 34 AM. J.L. & MED. 7 (2008).

century that drug regulation was initiated in response to increasing numbers of "patent" medicines being sold that not only failed to provide the curative relief they advertised, but also caused significant sickness and death.<sup>8</sup> Federal regulation of drugs began with enactment of the Pure Food and Drugs Act of 1906 (PFDA),<sup>9</sup> which was actually enacted in response to Upton Sinclair's unintended exposé of animal husbandry practices in his book *The Jungle*.<sup>10</sup> The primary intent of the PFDA was to ensure accurate food labeling,<sup>11</sup> although it also made illegal the adulteration and "knowing" misbranding of drugs.<sup>12</sup> A drug manufacturer could make implausible claims for the drugs' properties and abilities, as long as they had a good faith belief that the statements being made were true.

In 1938, the Food, Drug, and Cosmetics Act (FDCA), which still serves as the cornerstone of drug regulation today, replaced the PFDA. The FDCA was enacted in direct response to the "Elixir Sulfanilamide tragedy," in which a liquid sulfa drug containing a highly toxic variant of antifreeze resulted in the deaths of over 100 people.<sup>13</sup> The FDCA introduced mandatory pre-market approval for new drugs, requiring for the first time that drug manufacturers demonstrate to the FDA that a new drug was safe before it could be sold to the public.<sup>14</sup> Perhaps surprisingly, drug manufacturers were

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<sup>8</sup> Mark T. Law, History of Food and Drug Regulation in the United States, EH.NET ENCYCLOPEDIA (Robert Whaples, ed. 2004), available at <http://eh.net/encyclopedia/article/Law.Food.and.Drug.Regulation>.

<sup>9</sup> *Id.*

<sup>10</sup> Sinclair's motivation in writing *The Jungle* was not to obtain legislation to ensure the safety of food, but rather, ironically, to provoke public outrage over industrial working conditions: "I aimed at the public's heart," he later wrote, "and by accident I hit it in the stomach." GABRIEL KOLKO, THE TRIUMPH OF CONSERVATISM: A REINTERPRETATION OF AMERICAN HISTORY 103 (MacMillan 1967).

<sup>11</sup> See Mark T. Law, *supra* note 8.

<sup>12</sup> *Id.*

<sup>13</sup> U.S. Food and Drug Administration, *History of the FDA: The 1938 Food, Drug and Cosmetic Act*, available at <http://www.fda.gov/aboutFDA/WhatWeDo/History/origin/ucm054826.htm>; See JAMES H. YOUNG, THE MEDICAL MESSIAHS: A SOCIAL HISTORY OF QUACKERY IN TWENTIETH CENTURY AMERICA, Princeton University Press (1967).

<sup>14</sup> *Id.*

not actually required to demonstrate that their new drugs were effective for the ailments they treated until the 1962 Kefauver-Harris Amendments to the FDCA, enacted in response to the thalidomide tragedy.<sup>15</sup>

The FDCA has been enforced by a number of different agencies since it was first enacted, but the government agency responsible for enforcing it at present is the Food and Drug Administration (FDA). Although it went through a number of iterations and homes through the years, the FDA was originally created by the PFDA.<sup>16</sup> The FDA's mission today is, in relevant part:

to protect the public health by assuring the safety, efficacy, and security of human drugs and biological products and to advance the public health by helping to speed innovations that make medicines more effective, safer, and more affordable.<sup>17</sup>

However, the FDA is neither tasked with, nor allowed to regulate the practice of medicine, which becomes an important question when considering whether or not a drug label should include reference to a test.<sup>18</sup>

## B. Drug Labeling

The 1938 version of the FDCA was the first time that the FDA was granted the power to regulate the therapeutic claims drug manufacturers printed on their product labels.<sup>19</sup> The historic requirements of the Act did not obligate the FDA to monitor and approve what was placed in the label; rather it was simply illegal for the manufacturer to include any false or misleading information.

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<sup>15</sup> *Id.*

<sup>16</sup> Mark T. Law, *supra* note 8. The Bureau of Chemistry (BC), a division of the USDA, was the agency originally tasked with enforcing the new laws. The BC was renamed the Food, Drug, and Insecticide Administration in 1927 which was then shortened to the current title, the Food and Drug Administration (FDA) in 1931. Nine years later, the FDA was transferred from the United States Department of Agriculture to the Federal Security Agency, which was subsequently renamed the Department of Health, Education and Welfare in 1953. *Id.*

<sup>17</sup> FDA's Mission Statement, available at <http://www.fda.gov/aboutFDA/WhatWeDo/History/origin/ucm054826.htm>.

<sup>18</sup> Shane M. Ward, *The First Amendment Inquiry of the Food and Drug Administration's Regulation of Off-Label Drug Use Information on the Internet*, 56 FOOD & DRUG L.J. 41 (2001).

<sup>19</sup> *Id.*

Today, the specific requirements on the content and format of labels for human prescription products are laid out in Title 21 of the Code of Federal Regulations, Section 201.57. The iteration of these regulations in place at the time the FDA revised the Warfarin package insert (PI) directed the FDA to include specific information in the label about available tests when differences in pharmacogenomic subgroups showed clinically relevant responses in safety or efficacy:

If evidence is available to support the safety and effectiveness of the drug only in selected subgroups of the larger population with a disease, syndrome, or symptom under consideration, e.g., patients with mild disease or patients in a special age group, the labeling *shall* describe the available evidence and state the limitations of usefulness of the drug. The labeling *shall* also identify *specific tests* needed for selection or monitoring of the patients who need the drug, e.g., microbe susceptibility tests.<sup>20</sup> (emphasis added)

It is important to note that the regulations do not draw any distinction between identifying subgroups for the purpose of avoiding therapy entirely due to potentially severe or fatal adverse reactions and identifying subgroups for which changes in dosing are merely necessary. In utilizing the broad language that the label should “state the limitations of usefulness” for the specific subgroups, the regulations allow the FDA significant latitude in defining what constitutes a subpopulation for whom the drug is safer and/or more effective. The regulations do clearly state, however, that for any such subgroup there should be mention of a “specific test” in the label used to identify that group.

### III. PERSONALIZED MEDICINE

The practice of medicine, as any physician will tell you, has always been “personalized” – your physician inquires about your personal health and symptoms and that of your family in an effort to “tailor” treatment to your most likely conditions. Today, however, the phrase “personalized medicine” is an umbrella term encompassing the idea that now information about a specific

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<sup>20</sup> 21 C.F.R § 201.57(e)(3)(1).

patient's genotype or gene expression profile may be used to even more closely tailor medical care to an individual's needs. Such information can be used to help stratify disease status, select between different medications, and tailor their dosage or provide a specific therapy for an individual's specific disease.

One of the subfields of research included under the umbrella term personalized medicine is pharmacogenetics (PGx), which is the specific study of genetically determined variability in drug metabolism and responses to drugs, including adverse events and desired effects. Different patients have always had different reactions to the same drugs - some people have no adverse effects from a drug while others experience many of the side effect listed in the drug's label; or some patients' diseases respond rapidly to a drug while others receive almost no benefit. Historically, these differences have been addressed at the phenotypic level with physicians altering doses or choosing among competing drugs based on variables such as age, weight, concurrent drugs, co-morbidities and family histories.

With the sequencing of the human genome in 2003, however, researchers discovered that some of the differences in how patients respond to drugs could be determined at the molecular or genetic level. This variability between patients can occur because of either variation in DNA, polymorphisms, in either a single gene or limited sets of multiple genes, or differences in gene sequences that influence enzyme or receptor activity.<sup>21</sup> Researchers have begun incorporating these genetic differences, or biomarkers, into tests called companion diagnostics, to be used in advance of prescribing to better guide prescribing decisions.

#### **A. FDA: Push For Personalized Medicine**

As part of its 2003 strategic plan, the FDA developed standards designed to effectuate the efficient and rapid translation of new emerging technologies and scientific developments into therapies to better enable the development of safe and effective medical products.<sup>22</sup> This plan directly furthers the FDA's mission to advance

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<sup>21</sup> *Id.*

<sup>22</sup> The Food and Drug Administration's Strategic Action Plan Protecting and Advancing America's Health: Responding to New Challenges and Opportunities (August 2003)

public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable and to assure that the approved products are relatively safe in terms of risk and effect.<sup>23</sup>

The FDA has identified PGx as one of the fields it believes has the potential to significantly influence the safety and efficacy of new and existing products by its ability to translate the research on genetic variability into regulatory actions to provide for greater drug safety. A recent meta-analysis of adverse event studies clearly demonstrates that 59 percent of drugs causing adverse events (AEs) are metabolized by polymorphic enzymes, while only 7 to 22 percent of other randomly selected drugs are thus metabolized.<sup>24</sup> Furthermore, it is estimated that adverse drug events result in over 750,000 injuries and deaths each year.<sup>25</sup> These results suggest that dosing based on individuals' metabolizing genotype may significantly reduce the risk of AEs with certain drugs.

In pursuit of this improved safety goal, the FDA has specifically made the integration of PGx into drug development an agency-wide initiative. On April 13, 2003, Mark McClellan, M.D., then Commissioner of the FDA, stated in Washington Drug Letter, that:

Certain new therapies will be developed along with genetic or phenotypic tests that can identify an appropriate treatment population and detect patients who need different doses or are prone to certain toxic effects. *Development of these test and therapy combinations must be facilitated because they have the potential to maximize drug benefits while minimizing toxicity.*<sup>26</sup> (emphasis added).

Similarly, the Center for Drug, Evaluation and Research at the

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available at  
<http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/StrategicActionPlan/default.htm>.

<sup>23</sup> *Id.*

<sup>24</sup> K.A Phillips, et al., *Potential Role of Pharmacogenomics in Reducing Adverse Drug Reactions: A Systematic Review*, 286 JAMA 2270 (2001).

<sup>25</sup> Bates, et al, *The costs of adverse drug events in hospitalized patients: Adverse Drug Events Study Group*, 277(4) JAMA 307-311 (2007).

<sup>26</sup> Lawrence J. Lesko, FDA Pediatric Oncology Subcommittee meeting, *Powerpoint Presentation: Updating information in the approval label for 6-Mercaptopurine* (July 15, 2003) available at [http://www.fda.gov/ohrms/dockets/AC/03/slides/3971S1\\_03\\_Lesko.ppt](http://www.fda.gov/ohrms/dockets/AC/03/slides/3971S1_03_Lesko.ppt).

FDA, or CDER, has also shifted its focus onto PGx, in both new and existing drugs, thereby making its integration into mainstream drug development a priority.<sup>27</sup>

As part of these ongoing efforts, the FDA has been seeking a high profile drug example that would provide the opportunity to demonstrate the utility and value of such drug development approaches.

### **B. The Test Case: Mercaptopurine (6MP)**

Although it predates the mainstream awareness of PGx technologies that arose in the wake of the sequencing of the human genome, the FDA's approach to revising the label for this chemotherapy agent used in the treatment of a fatal form of childhood leukemia is instructive.

In the summer of 2003, the FDA considered whether or not to relabel mercaptopurine (6MP), a chemotherapy drug used in the treatment of acute lymphoblastic leukemia (ALL), based on genotypic differences in dosing. ALL is a severe and often fatal form of childhood cancer of the white blood cells brought about by the continuous multiplication of malignant, immature white blood cells in the bone marrow. ALL results in severe organ damage and death as a result of the exclusion of normal white blood cells through the overproduction of malignant cells and by the eventual spread of the cancer to other organs. ALL typically occurs at 3-4 years of age and has a current overall cure rate in children of 85% with about 50% of treated adults having long-term, disease free survival.<sup>28</sup>

Chemotherapy is the initial treatment of choice for ALL, which typically uses multiple anti-leukemic drugs in various combinations to induce remission. 6MP, one of the most effective treatments for ALL, is an immunosuppressive drug that works by suppressing the production of both red and white blood cells. 6MP also has some

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<sup>27</sup> *Id.* (quoting Janet Woodcock, M.D., then Director of CDER, in an FDA Science Board Meeting on April 9, 2003, that “[g]enetic contributions to variability in toxicity include differences in metabolism, e.g., thiopurine methyltransferase, and use of genetic tests for metabolizer status to predict dosing.”)

<sup>28</sup> Dan L. Longo, *Malignancies of Lymphoid Cells*, in HARRISON'S PRINCIPLES OF INTERNAL MEDICINE 687, 687-99 (Anthony S. Fauci et al. eds., 17<sup>th</sup> ed. 2008).

serious AEs, however, including myelosuppression, or suppression of white blood cell production. PGx research demonstrated that the patients most likely to develop this dangerous side effect are those with a specific gene mediated enzyme deficiency called thiopurine methyltransferase (TPMT). In such patients it may be possible to continue using 6MP, but a lower dose is required to avoid myelosuppression.

### C. The Decision to Relabel 6MP

On July 15, 2003, the Pediatric Oncology Subcommittee ("Subcommittee") of the Oncologic Drugs Advisory Committee to the FDA convened to discuss, among other issues, a "proposed change in the product package insert for [6MP] to include pharmacogenetic screening recommendation."<sup>29</sup> The Subcommittee recognized that the effect of the TPMT polymorphism was well documented in the literature with a direct causal link between it and the risk of increased myelosuppression for roughly 10% of the population (depending on whether there was reduced or no enzyme activity). At the time, PGx tests were readily available and feasible for use in identifying those patients with the polymorphism in order to better guide dosing. None of the available tests, however, were FDA approved.<sup>30</sup>

At the time the FDA was considering making this revision, the label for 6MP already contained a statement in the "Warnings" section regarding genotypic differences in dosing that was very similar to the revision ultimately added to the Warfarin label, discussed below. The 6MP label current at the time the Subcommittee was considering the revision stated that "[t]here are individuals with an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) who may be unusually sensitive to the myelosuppressive effects of mercaptopurine" and that "[s]ubstantial dose reductions may be required to avoid the development of life-threatening bone marrow suppression in these patients."<sup>31</sup>

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<sup>29</sup> U.S. FOOD AND DRUG ADMIN., CTR. FOR DRUG EVALUATION & RES., MEETING OF THE PEDIATRIC SUBCOMMITTEE OF THE ONCOLOGIC DRUGS ADVISORY COMMITTEE 16, 16-7 (2003), <http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3971T1.pdf>.

<sup>30</sup> *Id.* at 126-27.

<sup>31</sup> *Id.* at 18.

The Subcommittee heard from a number of researchers, clinicians and FDA staff including Dr. Larry Lesko, Director of the Office of Clinical Pharmacology and Biopharmaceutics in the Center for Drug Evaluation and Research (CDER) at the FDA. Dr. Lesko noted that the FDA's broad goals for pediatric therapeutics, as in other therapeutic areas, were to:

. . . improve the quality of therapeutics related to the use of already-marketed drugs . . . , to update product labels where new data is relevant to the safe and effective use of the drug, and to place information in product labels as a mechanism to disseminate important information about the drug's use.<sup>32</sup>

Dr. Lesko went on to note that these goals were consistent and in accord with the label regulations under which the FDA operated and that:

[t]his is part of the label regulations from the CFR that [where] evidence is available to support the safety and effectiveness of the drug only in a selected subgroup of the larger population with the disease, and that subgroup can be defined by many different intrinsic or extrinsic factors. The labeling shall describe the evidence and identify specific tests needed for selection or monitoring of patients who need the drug.

Clearly, as early as 1993, the FDA was fully aware of the regulations under which it was supposed to operate with regard to the label content of prescription therapies and the requirement that tests be specifically mentioned in the label if they are available to identify a subgroup for which a drug is safer or more effective. In fact, Dr. Lesko later suggested that the Committee might consider including a statement in the label for 6MP that "laboratory tests are now available to determine the TPMT status of patients if the physician so chooses and some information regarding the use of these tests."<sup>33</sup>

In discussing the evidence available to support a label revision for 6MP, Dr. Lesko noted that 6MP was a drug with a narrow therapeutic index and that dose titration was a major determinant of

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<sup>32</sup> *Id.* at 36.

<sup>33</sup> *Id.* at 42.

long-term, event-free use.<sup>34</sup> In that regard, the therapeutic footprint for 6MP was very similar to that of Warfarin, which also has a narrow therapeutic index and requires testing to determine proper dosing.<sup>35</sup> Also like the Warfarin situation, none of the tests available to be used in conjunction with 6MP available at the time of the hearing were FDA approved.<sup>36</sup>

Notably different between the case of 6MP and Warfarin, however, was the quantity of scientific data regarding the clinical utility of the test for TPMT status that was available at the time the FDA was considering the relabeling. Dr. Lesko noted that there existed a body of scientific literature reaching back almost ten years that clearly documented the clinical utility of the test in terms of recommendations for dose adjustments.<sup>37</sup> Furthermore, at the time of the Subcommittee hearing, TPMT tests were already in use in several academic centers where they were used in conjunction with phenotypic data and clinical outcome monitoring to determine total blood counts.<sup>38</sup> While the Mayo Clinic had begun using tests in conjunction with Warfarin testing at the time the label was revised,<sup>39</sup> there was no significant body of evidence that clearly supported the clinical utility of the tests.

One of the researchers who presented to the Subcommittee, Dr. Howard McLeod of the Washington University School of Medicine, noted that the most important point in the consideration of whether

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<sup>34</sup> *Id.* at 39.

<sup>35</sup> D. Voora, et al., *The pharmacogenetics of coumadin therapy*, 6 *FUTURE MED.* 503, 503-13 (2005).

<sup>36</sup> See U.S. FOOD AND DRUG ADMIN., *supra* note 29.

<sup>37</sup> U.S. FOOD AND DRUG ADMIN., *supra* note 29 at 39. The clinical utility of a genetic test defines the elements that need to be considered when evaluating the risks and benefits associated with introduction of the test into routine practice, including but not limited to such considerations as, 1) the natural history of the specific disorder so that optimal age for testing might be taken into account, 2) the availability and effectiveness of interventions aimed at avoiding adverse clinical consequences, 3) the performance of testing under real-world conditions, and 4) possible consequences of testing in individuals with either positive or negative test results. Centers for Disease Control, National Office of Public Health Genomics, ACCE Project, <http://www.cdc.gov/genomics/gTesting/ACCE.htm>.

<sup>38</sup> *Id.* at 40.

<sup>39</sup> North Carolina State Health Plan, *Warfarin/Genetic Testing*, available at <http://new.statehealthplan.state.nc.us/new/board-materials/November-2008/warfarin-genetic-testing.pdf>.

to relabel 6MP was the need to get clear information into the package insert so as to better inform patients.<sup>40</sup> While acknowledging that multiple prospective cohort studies had not yet been conducted to clearly delineate dosing monograms for 6MP, Dr. McLeod opined that the one study that had been conducted certainly gave physicians a starting point from which to determine dosing.<sup>41</sup> However, based on this paucity of data, Dr. McLeod did not advocate putting dosing guidelines into the package insert<sup>42</sup> but felt that there was sufficient data in the medical literature that many physicians already used the test to guide 6MP dosing.<sup>43</sup> Dr. McLeod was of the opinion that:

. . . the context in which we're operating now is that we know there is an event, in this case a genetic variant, that predisposes patients to risk of toxicity. Not acting on it at all or at least not informing patients of its presence is really not adequate and not optimal medical care.<sup>44</sup>

Ultimately, the Committee agreed to revise the 6MP package insert to include a statement that laboratory tests are available to determine the TPMT status of pediatric patients but not to include dosage adjustment recommendations.<sup>45</sup> The current label for 6MP, under the section titled "Warnings," states:

Individuals who are homozygous for an inherited defect in the TPMT (thiopurine-S-methyltransferase) gene are unusually sensitive to the myelosuppressive effects of mercaptopurine and prone to developing rapid bone marrow suppression following the initiation of treatment. *Laboratory tests are available, both genotypic and phenotypic, to determine the TPMT status.* Substantial dose reductions are generally required for homozygous-TPMT deficiency patients (two non functional alleles) to avoid the development of life threatening bone marrow suppression.<sup>46</sup> (emphasis added)

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<sup>40</sup> U.S. FOOD AND DRUG ADMIN., *supra* note 29 at 77.

<sup>41</sup> *Id.*

<sup>42</sup> *Id.* at 78.

<sup>43</sup> *Id.* at 76-7.

<sup>44</sup> *Id.*

<sup>45</sup> U.S. FOOD AND DRUG ADMIN., CTR. FOR DRUG EVALUATION AND RES., SUMMARY MINUTES OF THE PEDIATRIC ONCOLOGY SUBCOMMITTEE OF THE ONCOLOGIC DRUGS ADVISORY COMMITTEE (2003), <http://www.fda.gov/ohrms/dockets/ac/03/minutes/3971M1.htm> at 4.

<sup>46</sup> DailyMed, Mercaptopurine Tablet, *Warnings*, last accessed June 7, 2009, at [http://dailymed.nlm.nih.gov/dailymed/drug\\_info.cfm?id=7276](http://dailymed.nlm.nih.gov/dailymed/drug_info.cfm?id=7276).

It is interesting, even more so in light of the revision to the Warfarin label, that the FDA made the above change to the 6MP label in spite of the fact that there were no FDA-approved tests for TPMT detection, there was a lack of prospective cohort data relating to how TPMT status relates to changes in dosing<sup>47</sup>, and there were available alternate means to measure appropriate dosing levels. The notable difference between 6MP and Warfarin is, of course, the lack of data supporting the clinical utility of tests to guide Warfarin dosing, which will be discussed further below.

#### IV. WARFARIN: A RISKY DRUG IN SPITE OF THE BENEFITS

Warfarin (generic name coumadin) has been on the market as a stand-alone drug for almost half a century. First discovered in 1948 at the University of Wisconsin, Warfarin was originally patented as a rat poison in 1952. Its anticoagulant properties in humans were realized only after it was used in an attempted suicide by an Army inductee during the Korean War.<sup>47</sup> Since then it has become the most extensively used, oral anticoagulant in the world. In 2006, approximately thirty million prescriptions were written for its use in the United States alone.<sup>48</sup>

In spite of its broad and successful use as an anticoagulant, Warfarin has a very difficult dosing profile, with a narrow therapeutic range and significant AE potential.<sup>49</sup> To date, physicians have used a number of broadly applicable, individual risk characteristics and behaviors to determine the appropriate Warfarin dose, including age, weight, gender and other co-morbidities. Still, physicians have long recognized, based solely on empirical evidence collected through long experience with the drug, that approximately one-third of patients receiving Warfarin metabolize it quite

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<sup>47</sup> Anna Wilde Matthews, *In Milestone, FDA Pushes Genetic Test Tied to Drug*, WALL ST. J., August 16, 2007.

<sup>48</sup> *Id.* (citing IMS Health). See also Laurie, G. Jacobs, *Warfarin Pharmacology, Clinical Management, and Evaluation of Hemorrhagic Risk for the Elderly*, 26 *CARDIOLOGY CLINICS* 157-67 (2008).

<sup>49</sup> D. Vora, et al., *supra* note 35.

differently than expected. The optimal Warfarin dose varies greatly from person to person;<sup>50</sup> if the dose is too strong, the risk of serious bleeding increases and, if the dose is too weak, the risk of stroke increases. It is estimated that major bleeding episodes due to overdosing result in 2.7 out of every 100 patient years and clots due to under-dosing occur in 0.8 out of every 100 patient years.<sup>51</sup> Warfarin was in the top ten drugs with the largest number of serious AE reports submitted to the FDA from 1990 thru 2000, and in the five-year period from 1999 thru 2003, Warfarin was associated with approximately 29,000 hospital visits for bleeding complications per year.<sup>52</sup>

The result of this difficult dosing profile and significant rate of adverse events is a substantial drain on the resources of the healthcare system. Proper dosing of Warfarin often requires multiple doctor visits with associated lost work, travel and co-pay costs to the patients; decreased physician time to devote to other patients; and potentially significant resources invested in hospital visits due to under or overdosing. One study estimates the average healthcare costs arising from just the most serious AE alone – gastrointestinal hemorrhage – to be roughly \$11,000 per occurrence.<sup>53</sup> Another study estimates that incorporating routine genetic testing into Warfarin therapy for only one of the genes affecting dosing could potentially avoid 85,000 serious bleeding events and 17,000 strokes, thereby resulting in a cost savings to the healthcare system of approximately \$1.1 billion annually.<sup>54</sup> These potential and significant costs to the healthcare system of prescribing Warfarin as a whole, along with the

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<sup>50</sup> Food and Drug Administration, FDA Drug Safety Initiative Fact Sheet, 2006, <http://www.fda.gov/oc/factsheets/initiative.html>.

<sup>51</sup> Marieke Torn, et al., *Lowering the Intensity of Oral Anticoagulant Therapy. Effects on the Risk of Hemorrhage and Thromboembolism*, 164(6) ARCH INTERN MED. 668-73 (2004).

<sup>52</sup> Diane K. Wysowski et al., *Bleeding Complications with Warfarin Use: A Prevalent Adverse Effect Resulting in Regulatory Action*, 167(13) ARCH INTERN MED. 1414-1419 (2007), available at <http://archinte.ama-assn.org/cgi/content/full/167/13/1414>.

<sup>53</sup> H.S. You Joyce, et al., *The Potential Clinical and Economic outcomes of Pharmacogenetics-Oriented Management of Warfarin Therapy – A Decision Analysis*, 92 THROMB HAEMOST 590, 592 (2004).

<sup>54</sup> Andrew McWilliam et al., AEI-Brookings Joint Center for Regulatory Studies, Working Paper 06-23: *Health Care Savings from Personalizing Medicine Using Genetic Testing: The Case of Warfarin 1-6*, (2006).

associated AE's, made it a prime candidate to retrofit with a test that could ostensibly reduce these initial complications.

### A. Personalized Medicine Test Case: Warfarin

Although the FDA revised the 6MP label to reflect the need for genotypic testing, with all the newly focused attention being placed on personalized medicine and pharmacogenomics in the wake of the sequencing of the human genome, the FDA was still looking for a high profile drug example it could use to demonstrate how effective genetic testing could be in making already available drugs safer. The FDA was aware that recent research conducted on the genetic differences between individual patient responses to Warfarin demonstrated that at least part of the unexpected response was dependent on a patient's variants of the genes CYP2C9 and VKORC1.<sup>55</sup> Thus, the incorporation of genetic testing could potentially result in significant reductions in the healthcare costs associated with the use of the drug.<sup>56</sup> In the summer of 2007, the FDA chose Warfarin as the new "poster child" drug for personalized medicine.

### B. The Decision to Relabel Warfarin

In August 2007, the FDA announced that it had approved updated labeling to the package insert for Warfarin, based on analyses of recent studies that found people responded to the drug differently based, in part, on whether they had variations of certain genes.<sup>57</sup> The label was updated to include genomic information explaining how an individual's specific differences in two particular genes could affect dosing. The press release stated that:

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<sup>55</sup> FDA Press Release, *FDA Approves Updated Warfarin (Coumadin) Prescribing Information* (Aug. 16, 2007), available at <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108967.htm>.

<sup>56</sup> Tom Schalekamp et al., *CYP2C9 Genotyping in Acenocoumarol Treatment: Is it a Cost-Effective Addition to International Normalized Ratio Monitoring?* 79 *CLINICAL PHARMACOLOGY AND THERAPEUTICS* 511-19 (2006). See also Elizabeth A. Sconce et al., *The Impact of CYP2C9 and VKORC1 Genetic Polymorphism and Patient Characteristics upon Warfarin Dose Requirements: Proposal for a New Dosing Regimen*, 106 *BLOOD* 2329 (2005).

<sup>57</sup> FDA Press Release, *supra* note 55.

The labeling change highlights the opportunity for healthcare providers to use genetic tests to improve their initial estimate of what is a reasonable warfarin dose for individual patients. Testing may help optimize the use of warfarin and lower the risk of bleeding complications from the drug.<sup>58</sup>

Contrary to the FDA's own press release and the large number of commentary, articles and media generated about the updated PI, however, the label actually makes *no mention of a genomic test* at all.<sup>59</sup> Furthermore, the update does not even provide direct information to the physician as to how the information about specific genetic differences between patients could readily be used "to improve their initial estimate of what is a reasonable warfarin dose for individual patients."<sup>60</sup>

*i. What Does the Label Say?*

Under a section titled "pharmacogenomics" on page 4 of the label, the updated information states that a meta-analysis of 9 studies "suggested an increased bleeding risk for patients carrying either the CYP2C9\*2 or CYP2C9\*3 alleles."<sup>61</sup> The updated label further indicates that this meta-analysis indicated that these patients required *higher* mean doses than was required for patients without those alleles.<sup>62</sup> However, no mention was made of what those mean starting doses were or how large a variation there was between individual patients in the studies.

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<sup>58</sup> *Id.*

<sup>59</sup> *Id.* See e.g., Tucker, Leslie, *Pharmacogenomics: A Primer for Policymakers*, NATIONAL HEALTH POLICY FORUM, THE GEORGE WASHINGTON UNIVERSITY 6, Jan 28, 2008 ("... a discovery that led the U.S. Food and Drug Administration (FDA) for the first time to recommend genetic testing on the label of a popular drug."); Elias, Darlene J, Topol, Eric J, *A big step forward for individualized medicine: enlightened dosing of warfarin*, EUROPEAN JOURNAL OF HUMAN GENETICS 532-33 (2008) ("... has recently moved the... (FDA) to change the labeling of warfarin... recommending genetic testing to guide warfarin dosing."); Gage, Brian F, Lesko, Larry J, *Pharmacogenomics of warfarin: regulatory, scientific, and clinical issues*, J. THROMB THROMBOLYSIS 45 (2008) ("... the FDA updated the label of warfarin to include information on pharmacogenetic testing...").

<sup>60</sup> FDA Press Release, *supra* note 55. In an unusual move, the FDA had actually initiated a study with Kaiser Permanente to determine dosing guidelines, or a nomogram, but the study was never completed. *Id.*

<sup>61</sup> Bristol-Myers Squibb Co., *Coumadin Label*, at 4 (2007).

<sup>62</sup> *Id.*

Conversely, the next paragraph in the label, on page 5 under the same heading, notes that certain polymorphisms in the VKORC1 gene have been associated with the need for *lower* mean starting doses, with 30% of the variance attributed to the VKORC1 polymorphism alone and 40% attributable to the combined result of polymorphisms in the VKORC1 and CYP2C9 genes.<sup>63</sup> Again, no mention was made of what those mean starting doses were or how large a variation there was between individual patients in the studies.

Although this information may seem unduly confusing, it merely reflects the reality that the effects of individual genetic polymorphisms in the case of Warfarin do not have simple, linear results. Differences in the CYP2C9 gene reflect how quickly an individual will metabolize Warfarin whereas differences in the VKORC1 gene reflect how sensitive an individual may be to the drug. Thus, a hypothetical Patient A may need a higher dose of Warfarin due to a specific polymorphism in the CYP2C9 gene that makes them metabolize the drug faster than the mean yet that same Patient A may also have a polymorphism of the VKORC1 gene that makes them exceedingly sensitive to Warfarin thus requiring a smaller starting dose than the mean.

Thus, although the label makes mention of the fact that a patient with different alleles of the CYP2C9 ("CYP") and VKORC1 ("VKOR") genes would likely require a different starting dose from the mean, there is no specific mention of a genetic test for those alleles, despite widespread belief to the contrary.<sup>64</sup>

## V. DISCUSSION

To date, the FDA's actions on including information about tests used to guide dosing in drug labels have not been entirely consistent. At some level, the FDA is clearly required by regulation to specifically include mention of tests in drug labels when those tests can be used to identify groups of patients for whom a drug is safer or more effective.<sup>65</sup> Clearly, the ability to properly initiate or monitor

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<sup>63</sup> *Id.*

<sup>64</sup> *Id.*

<sup>65</sup> 21 C.F.R § 201.57(e)(3)(1).

more precise dosing based on the ability to identify different subpopulations would make a drug safer and/or more effective. Furthermore, to the extent that such information is used to guide therapeutic decision-making, as arguably dosing decisions are, the test providing that information should be valid and reliable. The regulations do not contemplate the label simply indicating that a drug is safer or more effective for a certain subpopulation based on its pharmacogenetic classification.

However, the regulations on labeling laid out at 21 C.F.R. §201.57(c)(3)(1) are also not clear with regard to their requirement that a “specific test” be included in the label and whether that requires the FDA to mention a specific, branded test, or just that tests are generally available. The FDA has implemented this requirement in two different ways with regard to information placed in the drug label pertaining to the availability of tests used to guide dosing: it includes pharmacogenomic information pertaining to how an individual’s specific differences in particular genes could affect use of the drug, the Warfarin situation<sup>66</sup>; or it mentions generally that “tests” are available to determine how an individual’s specific differences in particular genes could affect use of the drug, the 6MP situation.<sup>67</sup>

The FDA has not yet had the opportunity to actually include in a drug label that a specific, branded test is available to determine how individual differences in a particular gene or genes could be used to guide dosing of the drug.<sup>68</sup> This is a situation very likely to arise as

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<sup>66</sup> Bristol-Myers Squibb Co., 4 *Coumadin Label* (2007).

<sup>67</sup> DailyMed, *supra* note 46.

<sup>68</sup> There is widespread misconception that the label for Genentech’s breast cancer drug Herceptin – the poster child for personalized medicines – makes reference to a genetic test to guide access to the drug, when in reality that is not true. In the section of the label summarizing the clinical trials, it states that the DAKO HercepTest™ was *not* directly studied for its ability to predict treatment effect, but provides information on a “bridging study” used to compare the DAKO HercepTest™ to the assay used in the clinical trials. Current label for Herceptin, last accessed on June 4, 2009, at <http://www.accessdata.fda.gov/scripts/cder/onctools/labels.cfm?GN=trastuzumab>. The closest applicable usage of information in this manner is for Erbitux and Vectibix, the labels for both of which make mention of severe infusion reactions in the Warnings but do not relate that to any specific genetic polymorphism. Current label for Erbitux, last accessed on June 4, 2009, at [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2004/1250841b1.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2004/1250841b1.pdf), at 8; current

the FDA continues to explore revisions to existing drug labels and as truly co-developed drug/test combinations are submitted to the FDA for approval.<sup>69</sup>

This third labeling possibility gives rise to several difficult issues. First, the amount and type of evidence that the FDA would require to approve and include mention of a test to guide dosing in a drug label is not yet settled. Second, it is also not at all clear whether or not a test must be FDA approved to be mentioned in a drug label. Finally, if a test must be FDA approved to be included in a drug label, it is unclear how the FDA can justify allowing other, non-FDA approved tests designed to accomplish the same therapeutic goal to be sold.

### A. How Much Evidence is Needed?

The FDA is still in the process of trying to determine how much and what type of data it requires in order to accept the validity and utility of companion tests and, perhaps for this reason, it is reluctant to mention certain genetic tests in drug labels.

In 2005, the FDA published its Drug-Diagnostic Co-Development Concept Paper which presented the Agency's preliminary thoughts on how to prospectively co-develop a drug with an *in vitro* diagnostics test intended for use in clinical decision-making regarding drug selection for patients.<sup>70</sup> The Concept Paper provided

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label for Vectibix, last accessed on June 4, 2009, at [http://www.amgen.com/pdfs/misc/vectibix\\_pi.pdf](http://www.amgen.com/pdfs/misc/vectibix_pi.pdf), at 7. Both labels then makes reference, under the Precautions section, to the fact that patients in the clinical studies were required to be tested for their EGFR status using the DakoCytomation EGFr pharmDx™ test and that “[a]ssessment for EGFR expression should be performed by laboratories with demonstrated proficiency” in running the test. There were multiple, non-FDA approved tests to determine EGFR status at the time the label was approved. There are no other drug labels that include mention of test(s) to be used to guide dosing.

<sup>69</sup> In fact, the first example of a truly co-developed drug/test personalized medicine product has been submitted to the FDA for approval. In September 2008, ARCA Biopharma announced that the FDA had accepted its New Drug Application for bucindolol, an investigational and pharmacologically unique betablocker developed for the treatment of chronic heart failure. Drugs.com, *FDA Accepts NDA for Bucindolol, available at* [http://www.drugs.com/nda/bucindolol\\_080923.htm](http://www.drugs.com/nda/bucindolol_080923.htm).

<sup>70</sup> See generally, U.S. Department of Health and Human Services, Food and Drug Administration, *Drug-Diagnostic Co-Development Concept Paper, available at* <http://www.fda.gov/downloads/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/UCM116689.pdf> (April 2005).

a framework for combination product submissions, but generated concern as it envisioned the possibility that test development would run on a schedule almost concurrent with drug development. Although it is possible that biomarkers might be identified sufficiently early in the development process such that manufacturers could build test clinical trials into the drug trials, to date the majority of biomarkers have not been identified until later in the process. This raised concern about the differences in timing between clinical development studies and diagnostic device trials.<sup>71</sup>

At the American Association of Clinical Chemistry's annual meeting in 2006, Dr. Steve Gutman, then director of the FDA's Office of In Vitro Diagnostic Device Evaluation & Safety admitted that, "The concept paper was perhaps a little idealized in that it tried to create a parallel between the phases of drug studies and the phases of diagnostic studies."<sup>72</sup> Dr. Gutman further stated that although parallel development would be optimal, the eventual Guidance that would be written would consider that samples taken during the drug trial could later be tested for biomarkers if they were saved in a stable and clearly documented manner.<sup>73</sup>

Unfortunately, no Drug-Diagnostic Co-Development Guidance has yet to be finalized and put into practice, although the FDA continues to state that doing so is a priority.<sup>74</sup> In fact, in April 2009, the FDA held a roundtable discussion with industry - both pharmaceutical and diagnostic - to discuss the challenges of drug/diagnostic co-development with the continued hope of developing a guidance document on the topic. The roundtable used two current case studies where manufacturers have requested that the labels for drugs already on the market be revised to include

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<sup>71</sup> Jon C. Meltzer, Ph.D., and David M. Johnston, Ph.D., *The commercialization of companion diagnostics*, available at <http://www.ngpharma.com/article/Issue-12/Clinical-Research/The-commercialization-of-companion-diagnostics/>.

<sup>72</sup> See FDA Adjusts Thinking On Drug/Diagnostic Co-Development Draft Guidance, available at <http://www.pharmpro.com/ShowPR~PUBCODE~021~ACCT~0000100~ISSUE~0609~RELTYPE~PR~PRODCODE~0000~PRODLETT~L.html>.

<sup>73</sup> *Id.*

<sup>74</sup> Remarks by Dr. Janet Woodcock, Director of the FDA's Center for Drug Evaluation and Research, *FDA-Industry IVD Companion Diagnostic Drug Roundtable*, March 24, 2009.

information about available genomic tests to be used to guide clinical decision-making to illustrate and discuss the difficulties in this area. Although FDA representatives at the meeting indicated that a Guidance on the subject should be drafted, no promises were made as to when that would occur.<sup>75</sup>

The FDA does not face an easy task in trying to create clear guidelines for the scope of evidence needed to demonstrate the clinical utility of PGx in a field that is still rapidly evolving. It is understandable then that the FDA may not yet want to commit to writing regulatory guidelines, which may well be overtaken by emerging science. However, this unclear regulatory pathway introduces additional uncertainty into the development process that might provide a chilling effect to the industry.

### **B. Must a Test be FDA Approved to be Included in a Drug Label?**

Even assuming that the issue of the amount of evidence that is required to obtain FDA approval for a test used to guide dosing is resolved, the FDA must still decide whether or not it may make reference to a non-FDA approved test to be used to guide dosing in the drug label.<sup>76</sup> When the FDA revised the label for 6MP, none of the available tests to which the FDA made general reference were FDA approved.<sup>77</sup> Therefore, if one considers the FDA's actions in the label revision of 6MP as providing some degree of precedent, it would

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<sup>75</sup> The Genetics & Public Policy Center, Johns Hopkins University, News Release, *available at* [http://www.dnapolicy.org/news.release.php?action=detail&pressrelease\\_id=130](http://www.dnapolicy.org/news.release.php?action=detail&pressrelease_id=130).

<sup>76</sup> There are currently three FDA approved tests, the Nanosphere Verigene Warfarin Metabolism Nucleic Acid Test, the Osmetech eSensor Warfarin Sensitivity Test and the Iverson Genetic Diagnostics; all three of which detect some variants of both genes used to guide Warfarin dosing. However, none of these tests were approved *after* the label for Warfarin had already been revised. See FDA Press Release, *FDA Clears Genetic Lab Test for Warfarin Sensitivity* (Sept. 2007), *available at* <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/UCM108984.htm>; *see also*, FDA Clears Osmetech's Warfarin Sensitivity Test And New ESensor® XT-8 Platform, *available at* <http://www.medicalnewstoday.com/articles/115816.php>; Iverson Genetic Diagnostics Offers FDA Cleared Warfarin Test, *available at* [http://www.redorbit.com/news/health/1282631/iverson\\_genetic\\_diagnostics\\_offers\\_fda\\_cleared\\_warfarin\\_test/index.html](http://www.redorbit.com/news/health/1282631/iverson_genetic_diagnostics_offers_fda_cleared_warfarin_test/index.html).

<sup>77</sup> See U.S. FOOD AND DRUG ADMIN., *supra* note 29.

appear that the FDA has some comfort in making general reference to non-FDA approved tests in drug labels when there is sufficient evidence of clinical utility.

While it might appear obvious, however, it has not been easy to obtain a definitive answer to the question of whether a non-FDA approved test could be mentioned in an FDA approved drug label. During a break-out session on post-market issues in personalized medicine held during the FDA/DIA PGx workshop, a group of the FDA, reviewer-level staff was asked if a non-FDA approved test could be mentioned in an FDA approved drug label. After a brief discussion, there was no consensus on what the correct answer was to that question.<sup>78</sup>

From a regulatory perspective, it is unclear how the FDA could justify making reference to a branded, non-FDA approved test to guide dosing in a regulated drug label. It is illogical for the agency tasked with regulating tests to include mention of tests it has chosen not to regulate in labels for regulated drugs. Part of the FDA's mission is to protect the public from unreliable tests that have not met rigorous standards designed to demonstrate their validity and utility. However, even making reference generally to the availability of such tests in an FDA approved drug label would seem to confer some degree of FDA approval on such tests. This might serve to provide greater confidence in these non-FDA approved tests than is warranted.

There is widespread consensus at present that the FDA needs to implement some greater level of regulatory review over genetic tests.<sup>79</sup> In 2006, the FDA indicated that it would regulate one small

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<sup>78</sup> 4th Annual FDA/DIA Industry workshop, "Biomarkers and Pharmacogenomics in Drug Development and Regulatory Decision Making," Bethesda, MD., December 10-12, 2007.

<sup>79</sup> Sean A. Johnston, Senior Vice President and General Counsel, Genentech Inc., *Citizen Petition: Regulation of In Vitro Diagnostic Tests*, December 5, 2008 (asking the FDA to regulate all *In vitro* diagnostic tests regardless of whether they are "test kits" sold to other labs or "laboratory developed tests" only to be used in-house: "In-vitro diagnostics that are used in therapeutic decision making should be held to the same regulatory standards, regardless of whether they are kits or LDTs") available at <http://aab.org/Genentech%20FDA%20Petition.pdf>; Gail H. Javitt & Kathy Hudson, *The right prescription for personalized medicine*, 4(2) PERSONALIZED MEDICINE 115-18 (2007); Francis S. Collins & Alan E. Guttmacher, *Genetics Moves Into the Medical Mainstream*, 286 JAMA 2322, 2322-24 (2001).

subset of laboratory developed tests it calls in vitro multivariate diagnostic assays, which combine the use of clinical data, a computer algorithm, and a result that requires the test developer's help to interpret.<sup>80</sup> However, very few such tests are currently in use, so the guidance does not actually affect most tests being used in clinical practice.<sup>81</sup>

The FDA should be reluctant to mention, even generally, non-FDA approved tests in labels for FDA approved drugs due to the lack of a clear regulatory scheme and the possibility of creating increased liability for manufacturers and physicians. Of even greater concern is the disincentive to test manufacturers to seek FDA approval for their tests and the disparate impact for those manufacturers who do choose to obtain FDA approval.

### C. The LDT "Gray Zone"

The FDA is currently grappling with increased pressure from industry, the public and the legislature to articulate a clear regulatory scheme for genetic tests. Although the FDA already has jurisdiction over all tests, and already regulates 'test kits'<sup>82</sup>, it has declined to step in and provide a greater measure of regulatory control over genetic laboratory developed tests or LDTs.<sup>83</sup> These are the types of tests that are currently most widely available in the pharmacogenomic space and are the types of tests that were available for use with 6MP and

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<sup>80</sup> FDA Guidance, *FDA: Draft Guidance for Industry, Clinical Laboratories, and FDA Staff: In Vitro Diagnostic Multivariate Assays* (2006), at [www.fda.gov/cdrh/oivd/guidance/1610.pdf](http://www.fda.gov/cdrh/oivd/guidance/1610.pdf).

<sup>81</sup> The first and only test approved under the FDA's draft guidance was Agendia's Mammaprint assay used to determine the likelihood of recurrence of breast cancer. Although it was approved in February 2007, Mammaprint has not yet been made available for sale in the United States. Of interest is the fact that Genomic Health's Oncotype Dx test, which is widely available for sale and is reimbursed by several insurers, is also an IVDMA but the FDA has not, as of yet, chosen to regulate it pursuant to its Draft Guidance although it has alerted Genomic Health of the need to open a dialogue.

<sup>82</sup> Test kits are all inclusive products developed and sold by laboratories to other labs or providers that contain all of the ingredients and instructions to perform the test within the "kit."

<sup>83</sup> See Steve Gutman, *Clinical Chemistry Forum: The Role of Food and Drug Administration regulation of In Vitro Diagnostic Devices - Applications to Genetics*, 45 *CLINICAL CHEMISTRY* 746 (1999).

Warfarin at the time the labels for both were revised.<sup>84</sup>

However, if the FDA continues to allow this “gray zone” where LDTs designed to detect the same biomarker as the FDA approved test contained in the label are sold with little oversight, the FDA will be creating a significant disincentive to manufacturers, and few rewards to those who do seek FDA approval. Whatever level of evidence the FDA ultimately decides is required for approval of genetic tests, the time, burden and expense required to generate that data is much less attractive to manufacturers when laboratories can create similar tests and sell them with little oversight or investment.<sup>85</sup> Furthermore, the laboratories selling the LDTs will benefit from the work done by the test and/or drug manufacturer to prepare and educate the market for use of a test with that drug.

Perhaps part of the FDA’s reluctance to close this “gray zone” stems from a hesitation to take on any further regulatory burden than they already carry in light of their consistently underfunded status and woefully inadequate staffing levels. At a time when the FDA is under significant attack for its actions in regulating the nation’s food supplies, recent post-market drug recalls due to serious adverse events and a renewed call for the FDA to take on the additional burden of regulating tobacco, this hesitation is certainly understandable.

However, while the FDA very rightly complains of the lack of resources at present to bring regulation of all LDTs under its review, the universe of LDTs that act, in essence, as “follow-on” tests in the personalized medicine arena is a significantly smaller and more manageable universe. By taking control of this small subset of LDTs, the FDA would be sending a much more compelling message about its commitment to personalized medicine and providing significant incentives to drug and test manufacturers to undertake the burden and expense of generating evidence of clinical utility knowing that any additional tests will need to go through the same process.

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<sup>84</sup> U.S. FOOD AND DRUG ADMIN, *supra* note 29.

<sup>85</sup> Genetic testing laboratories are subject to the Clinical Laboratories Improvement Amendments or CLIA guidelines but this oversight is limited and not the equivalent of FDA regulation of tests. See Gail H. Javitt & Kathy Hudson, *Federal Neglect: Regulation of genetic testing*, 2293 ISSUES SCI. TECHNOL., 59-66 (2006).

## VI. CONCLUSION

Whatever the reasons behind the FDA's decision not to specifically mention tests in the revised Warfarin label, the implications for this omission are potentially significant. It is clear that the FDA failed to follow the regulations under which it operates. Title 21 of the Code of Federal Regulations, Section 201.57, clearly states that where evidence is available to support better safety or efficacy of the drug in selected subgroups of the larger population, the drug label should describe that evidence and identify the specific tests needed for selection of those patients.<sup>86</sup> This fact, standing alone, without consideration of any other impacts, is concerning as a matter of public policy. Although a regulation is not a "law" per se, it does have the force and effect of being "a law you follow."<sup>87</sup> Congress tasks the FDA with promulgating the regulations under which it operates and if the FDA is allowed to selectively choose to follow those regulations, confidence in the system is undermined. While it is not clear that an individual could bring a lawsuit against the FDA for failing to follow its own regulations, an undertaking that would clearly be enormous with regard to the economic requirements of suing such a large government agency, it still stands to reason in such a fast developing and scrutinized area as personalized medicine that the FDA would be well advised to stick to the "letter of the regulation."

Furthermore, it is also possible that by failing to follow its own regulations and to implement a standardized approach to revising package inserts in this area, the FDA will create confusion in the minds of physicians and ultimately do the exact opposite of what it intends in this area - create a chilling effect and deter use of these tests. The FDA acknowledges that one of its traditional roles is risk management and that labeling is the primary risk management tool it has at its disposal.<sup>88</sup> However, they also readily admit that, "product

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<sup>86</sup> 21 C.F.R. § 201.57 (2000)

<sup>87</sup> Douglas J. Pisano & David S. Mantus, FDA REGULATORY AFFAIRS, A GUIDE FOR PRESCRIPTION DRUGS, MEDICAL DEVICES AND BIOLOGICS 323 (2008).

<sup>88</sup> Dr. Victor Raczkowski, Director of the Office of Drug Safety, FDA, Center for Drug Evaluation and Research, Meeting of the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee (July 15, 2003), last accessed on November 30, 2008 at

labeling has variable effectiveness in terms of its comprehension, in terms of its adherence by either: physicians, other health care providers, or patients.”<sup>89</sup> If the intent is to optimize the risk/benefit profile of a drug, the FDA clearly understands that “[a]ny risk management plan should have clear, specified rules and objectives and should have an evaluation of the effectiveness of the program.”<sup>90</sup>

The FDA is aware that to encourage the use of new technologies, and to achieve optimal risk management, it needs to implement and follow a clear and standardized approach to drug labeling. Although the FDA is not allowed to regulate the practice of medicine, its actions have a definite and potentially profound impact on how medicine is practiced. Introducing confusion into clinical settings by failing to provide physicians with relevant information they need to understand how best to use drugs can only lead to avoidance in this area. Such an outcome would certainly fail to accomplish the FDA’s stated mission of supporting new technologies that speed innovation and make medicines safer and more effective. More concerning is the potential implication with regard to liability issues, both for physicians and manufacturers, where such information is not provided in the label.

Similarly, the lack of a standardized approach to when and how the FDA will include mention of available tests in package inserts creates confusion on the part of the pharmaceutical and diagnostic industries that may have a chilling effect on these new innovations rather than encouraging their development. Given the fact that the number of therapies developed for commercialization with companion diagnostics that the FDA will have to label in the coming decade is likely to rise, there should be significant concern that the FDA has failed to follow its own regulations concerning the revised label for Warfarin. In the absence of clear, articulated and standardized approaches to regulating the approval and labeling of drugs, it is likely that the progress of personalized medicine will also

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<http://www.fda.gov/ohrms/dockets/ac/transcripts/3971T1.htm> at 25.

<sup>89</sup> *Id.*

<sup>90</sup> *Id.* at 18. The FDA is also aware of the limitations of the label. Dr. Jody Pelusi, North Arizona Hematology & Oncology Associates, in addressing the Subcommittee meeting, noted that educational programs would be necessary with regard to label changes as “many of us have read the package insert once and not necessarily do it on a regular basis.” *Id.*

be impeded as a result of manufacturers hesitating to move into this new development paradigm. While the Warfarin label revision was clearly intended to evidence the FDA's strong commitment to the advance of personalized medicine, it is possible in the long term that their inconsistent approach will only cause greater confusion and may actually be a stumbling block to the future well-being of this still nascent technology.

Finally, at a time when the FDA is under attack on all fronts and in light of President Obama's clear support for personalized medicine, the FDA should consider the impact of its actions on its own status. The pharmaceutical industry is hoping, in part, that the use of pharmacogenomic technologies will help raise its reputation in the eyes of consumers by making drugs safer, thereby avoiding the blast of media scrutiny every time a drug has to be pulled from the market due to post-market adverse events. Similarly, the FDA should also consider how embracing personalized medicine might be used to shore up its ailing reputation in the minds of the consumer.