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Personalized Medicine and Rescuing “Unsafe” Drugs with Pharmacogenomics: A Regulatory Perspective

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Personalized Medicine and Rescuing “Unsafe” Drugs with Pharmacogenomics: A Regulatory Perspective

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For more than a decade, we have been on the verge of a new era in medicine, but scientific hurdles, adverse market pressures and outdated regulations have blocked progress Genomics holds the promise of revolutionary advances in medicine. Hopefully Congress will soon realize the enormous potential of genomics and pass this legislation to support it.

—Senator Barack Obama¹

INTRODUCTION

The sequencing of the human genome and the revolution it caused in biomedical science created hope for a new era in the prevention and treatment of serious illnesses.² In the area of drug development, much of this hope is focused in the field of pharmacogenomics (PGx), which is the study of how individual genetic differences affect drug response.³ Many people expected advances in pharmacogenomics to lead to the rapid development of new “personalized medicines,” where drugs and dosages could be tailored specifically to a patient’s genotype.⁴ Ideally, patients could take a genetic test before taking a drug to determine whether the drug will be effective or cause a severe adverse reaction.⁵ Only those who pass the test would be prescribed the drug, and alternate therapies would be used on those who do not.⁶ Some believe that this method of treatment has the “potential to replace traditional trial-and-error medicine.”⁷

However, pharmacogenomics has largely failed to meet these expectations. The Food and Drug Administration (FDA) has only approved a handful of drugs that rely on PGx data.⁸ There is concern that the increasingly challenging and inefficient

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¹ Press Release, Senator Barack Obama, Obama Introduces Bill to Help Tap Power of Genomics to Find Cures (Aug. 9, 2006) (statements in support of the Genomics and Personalized Medicine Act) (internal introductory tags and quotation marks omitted), available at http://obama.senate.gov/press/060809-obama_introduce_9/index.php.

² See FDA, INNOVATION OR STAGNATION?: CHALLENGE AND OPPORTUNITY ON THE CRITICAL PATH TO NEW MEDICAL PRODUCTS, at i (2004) [hereinafter FDA, INNOVATION OR STAGNATION]; Friend, Tim, *Genome Projects Complete Sequence; Unraveling of DNA Code is a Blueprint for the Future of Medicine*, USA TODAY (June 23, 2000) at A1.

³ DEP’T OF HEALTH & HUMAN SERVICES, SECRETARY’S ADVISORY COMM. ON GENETICS, HEALTH & SOC’Y, REALIZING THE POTENTIAL OF PHARMACOGENOMICS 1 (2008) [hereinafter SACGHS PHARMACOGENOMICS REPORT]; Roses, Allen D., *Pharmacogenetics and the Practice of Medicine*, 405 NATURE 857, 857 (2000).

⁴ See Binzak, Barbara Ann, *How Pharmacogenomics Will Impact the Federal Regulation of Clinical Trials and the New Drug Approval Process*, 58 FOOD & DRUG L.J. 103, 103 (2003); SACGHS PHARMACOGENOMICS REPORT, *supra* note 3, at 1-2. While the term “personalized medicine” is sometimes broadly defined as tailoring a medical treatment based on a patient’s susceptibility to a disease or response to a specific treatment, this article uses the term more narrowly to refer to the tailoring of a medical treatment based on a patient’s genotype.

⁵ See Woodcock, Janet, *FDA Policy on Pharmacogenomic Data in Drug Development*, 66 LA. L. REV. 91, 98-99 (2005).

⁶ See Lesko, Lawrence J. et al., *Pharmacogenetics and Pharmacogenomics in Drug Development and Regulatory Decision Making*, 43 J. CLINICAL PHARMACOLOGY 342, 351 (2003).

⁷ Dunn, Kathleen, *Personalized Medicines: Implications for Pharma*, PHARM. EXEC. (Dec. 1, 2009).

⁸ See FDA, Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels (Sept. 10, 2008) [hereinafter FDA, Table of Valid Genomic Biomarkers 2008], http://www.fda.gov/cder/genomics/genomic_biomarkers_table.htm (last visited Mar. 11, 2009); SACGHS PHARMACOGENOMICS REPORT, *supra* note 3, at 1.

regulatory regime, combined with an ever more costly drug development process, is preventing pharmaceutical pioneers from fully realizing the benefits of many scientific discoveries made in recent years.⁹ Since peaking in 1996, when FDA approved 53 new drugs, the annual number of new drugs approved for marketing has steadily declined.¹⁰ In 2009, only 24 new drugs were approved.¹¹ This declining product pipeline can be partially attributed to increased regulatory caution caused by recent high-profile safety issues.¹² As a result of the heightened bar to obtain FDA approval, drug manufacturers have been plagued by a dearth of new product flow.¹³

At the same time that the number of new drug approvals is declining, research and development (R&D) costs continue to rise. Since 1996, research and development spending by pharmaceutical manufacturers has increased 187 percent, from \$16.9 billion to \$48.5 billion. Recent estimates calculate that average R&D costs are now \$1.32 billion per new molecule approved by FDA.¹⁴ Overall, this means that more money is being spent on a product pipeline that brings fewer therapies to patients.

The new era of treatment promised by pharmacogenomics has not yet arrived. FDA acknowledges that there is a “pipeline problem,” and that instead of the expected acceleration in the development of innovative medical therapies, such therapies are reaching patients more slowly.¹⁵ It is clear that the medical product development process has been unable to keep pace with scientific innovation.¹⁶

However, pharmacogenomics can still offer a solution to the industry’s pipeline problem. The problem can be alleviated by using PGx to “rescue” drugs in development that would otherwise fail to obtain FDA marketing approval. Fewer than 20 percent of drugs that begin human clinical trials are approved for marketing by FDA.¹⁷ The remaining 80-plus percent usually fail to demonstrate adequate safety and efficacy in the general patient population.¹⁸ Pharmacogenomics can

⁹ See FDA, INNOVATION OR STAGNATION, *supra* note 2, at i.

¹⁰ BURRILL & CO., BIOTECH 2008 LIFE SCIENCES: A 20/20 VISION TO 2030, at 43 (2008).

¹¹ In 2009, FDA approved seventeen new molecular entities (NMEs) and seven biological license applications (BLAs). Arnold, Matthew, *FDA BLA Approvals Rose in 2009 While NMEs Stumbled*, MED. MARKETING & MEDIA, (Dec. 31, 2009), <http://www.mmm-online.com/fda-bla-approvals-rose-in-2009-while-nmes-stumbled/article/160496/>. Interestingly, the number of applications filed to investigate new drugs (INDs) has varied little since 1996, with approximately 1700 INDs filed per year. FDA, *Number of INDs Received: Calendar Years 1986-2006*, <http://www.fda.gov/cder/rdmt/Cyindrec.htm>. However, over the same period, the number of applications filed to market new molecular entities and biologics (i.e., NDAs and BLAs for NMEs) dropped almost 50 percent. FDA, INNOVATION OR STAGNATION, *supra* note 2, at 2 fig.2.

¹² Hughes, Bethan, *2007 FDA Drug Approvals: A Year of Flux*, 7 NATURE REV. DRUG DISCOVERY 107, 107 (2008); see also PETER BARTON HUTT ET AL., FOOD AND DRUG LAW: CASES AND MATERIALS 714 (3d ed. 2007). In the past decade, the pharmaceutical industry has found that FDA is “requesting more nonclinical studies and more clinical trials, of longer duration, with more subjects, containing more arms for additional dosage levels, with more diverse subjects, and longer follow up. The result [is] a significant reduction in NDAs submitted to the agency and an approximate doubling of the average cost of an NDA.” *Id.*

¹³ FDA, INNOVATION OR STAGNATION, *supra* note 2, at 3.

¹⁴ See DiMasi, Joseph A. & Grabowski, Henry G., *The Cost of Biopharmaceutical R&D: Is Biotech Different?*, 28 MANAGERIAL & DECISION ECON. 469, 477 (2007).

¹⁵ FDA, INNOVATION OR STAGNATION, *supra* note 2, at i.

¹⁶ See Binzak, *supra* note 4, at 104; FDA, INNOVATION OR STAGNATION, *supra* note 2, at ii.

¹⁷ TUFTS CENTER FOR THE STUDY OF DRUG DEVELOPMENT, IMPACT REPORT 2009: LARGE PHARMA SUCCESS RATE FOR DRUGS ENTERING CLINICAL TRIALS IN 1993-04; 16% (K.I. Kaitin ed., 2009); HUTT ET AL., *supra* note 12, at 624.

¹⁸ Lesko, Lawrence J. & Woodcock, Janet, *Translation of Pharmacogenomics and Pharmacogenetics: A Regulatory Perspective*, 3 NATURE REV. DRUG DISCOVERY 763, 764 (2004); HUTT ET AL., *supra* note 12, at 624. In addition to safety and efficacy, a drug candidate might fail to make it to market because of commercialization issues. Lesko & Woodcock, *supra*. Note that this article uses “efficacy” and “effectiveness” interchangeably, though the author acknowledges that “effectiveness” is the preferred term of art. Interview with Peter Barton Hutt, Senior Counsel, Covington & Burling LLP, in Wash., DC. (Feb. 13, 2009); see also SACGHS PHARMACOGENOMICS REPORT, *supra* note 3, at 34 n.234 (“[T]he term ‘effectiveness’ is used as a measure of how well the test performs in ‘real-world’ clinical settings, and ‘efficacy’ is used for outcomes seen in controlled research settings.”).

be used to convert an otherwise “unsafe” drug into a “safe” drug by identifying either those patients likely to respond to the drug or those likely to have an adverse reaction to the drug, thereby ensuring that the drug is only given those whom will benefit most.¹⁹ But developers of PGx-based drugs face two major regulatory challenges. First, these drugs are regulated by an FDA framework largely fashioned before the field of pharmacogenomics ever existed.²⁰ Consequently, sponsors are hesitant to generate PGx data because it is not clear how FDA will regulate its use.²¹ Second, the way the agency currently regulates PGx-based drugs discourages the development of such drugs by requiring sponsors to conduct additional clinical trials if they want to rely on PGx data. In fact, many personalized medicines fail to receive marketing approval because of FDA’s hostile approach to regulating the use of pharmacogenomic data. These drugs will continue to fail unless the regulatory pathway is modified to encourage the development of personalized medicine.

This article shows how FDA regulations and economic factors combine to discourage the development of personalized medicine, and how modest changes to the current regulatory regime could have a dramatic impact on encouraging sponsors to develop these drugs. Part 1 of this article provides a brief overview of pharmacogenomics, personalized medicine, and the regulatory and economic factors that deter the development of PGx-based drugs. Part 2 briefly reviews FDA regulation of traditional drugs and medical devices. Part 3 then analyzes how FDA has applied its regulations when PGx data is generated during clinical trials and relied on for a grant of market clearance. The analysis shows how current regulations are inadequate for addressing the challenges of developing personalized medicine, and how FDA discourages such development by forcing sponsors to conduct additional expensive clinical trials to validate pharmacogenomic biomarkers. Finally, Part 4 proposes modifying the current regulatory regime to encourage development of personalized medicine by either: 1) allowing PGx-based drugs to be approved with unvalidated biomarkers if the sponsor commits to Phase IV studies; or 2) using the Orphan Drug Act to provide economic incentives for developing PGx-based drugs.²²

¹⁹ See BOSTON CONSULTING GROUP, A REVOLUTION IN R&D: HOW GENOMICS AND GENETICS ARE TRANSFORMING THE BIOPHARMACEUTICAL INDUSTRY, at 12 (2001) (estimating that drug companies could rescue two new drugs per year using PGx technology), available at http://www.bcg.com/publications/files/eng_genomic-sgenetics_rep_11_01.pdf. For the sake of simplicity, this paper will categorize patients into three categories: “Positive responders,” or simply “responders,” are those patients who have an efficacious response to the drug. “Non-responders” are those patients for whom the drug fails to demonstrate any benefit. Finally, “adverse responders” are those patients who suffer severe adverse reactions from taking the drug.

²⁰ See Crews, Margaret, Comment, *Pharmacogenomics: Tailoring the Drug Approval Process for Designer Drugs*, 24 J. CONTEMP. HEALTH L. & POL’Y 363, 364 (2008).

²¹ Woodcock, *supra* note 5, at 95.

²² It is beyond the scope of this article to analyze the following issues related to pharmacogenomics and personalized medicine: 1) cross-labeling issues where a third party device manufacturer independently develops a pharmacogenomic diagnostic device to be used in combination with a sponsor’s approved drug; 2) the use of pharmacogenomic data in postmarketing studies; 3) ethical issues related to stratifying patient populations by race, ethnicity, genetics or other factors; 4) the use of genetic data in predicting disease susceptibility. For a discussion of cross-labeling issues, see generally Sasjack, Scott, *Demanding Individually Safe Drugs Today: Overcoming the Cross-labeling Legal Hurdle to Pharmacogenomics*, 34 AM. J. L. MED. 7 (2008). For a discussion of race-based medicine, compare Cohn, Jay N., *The Use of Race and Ethnicity in Medicine: Lessons from the African-American Heart Failure Trial*, 34 J.L. MED. & ETHICS 552 (2006) and Hoffman, Sharon, “Racially-Tailored” Medicine Unraveled, 55 AM. U.L. REV. 395 (2005). For a discussion of using genetic information to predict disease susceptibility, see generally Roses, *supra* note 3, at 863-865 and Wade, Nicholas, *Genes Show Limited Value in Predicting Diseases*, N.Y. TIMES, (Apr. 16, 2009).

1. *The Promise of Pharmacogenomics and Personalized Medicine*

1.1. *Genetics, Pharmacogenomics, and Medicine*

The completion of the mapping of the human genome has catalyzed research in many fields, including genomics, proteomics, and metabolomics.²³ Research in these areas has led to the development and commercialization of gene chips, which allow an individual's genes to be analyzed for variations and mutations.²⁴ Gene chips and other gene sequencing technologies have enabled researchers to discover genetic biomarkers that correlate to specific disease states.²⁵ The same technology can enable doctors to tailor the selection of drugs or drug doses to a patient's specific genetic profile.²⁶

Pharmacogenomics is the science of using genetic information from an individual or a population for the purpose of: 1) explaining inter-individual differences in the metabolism of a drug (pharmacokinetics) and the physiological response to a drug (pharmacodynamics); 2) identifying likely responders and non-responders to a drug; and 3) predicting the efficacy or toxicity of a drug on individuals.²⁷ Differences in drug response may occur because of inter-individual genetic differences, such as variations in DNA sequence, gene expression, and gene copy number.²⁸ These genetic variations can affect the metabolism, transport, distribution, absorption, and excretion of a drug.²⁹

Inter-individual variations in drug response make it difficult to predict whether a drug will work on a specific patient. Consequently, treatment for many diseases is done in a trial-and-error fashion—physicians begin with the first line drug, and proceed to second and third line drugs until they find something that works.³⁰ One study found that efficacy rates for most drugs range between 50 and 75 percent.³¹

²³ See Lesko, L.J., *Personalized Medicine: Elusive Dream or Imminent Reality?*, 81 CLINICAL PHARMACOLOGY & THERAPEUTICS 807, 809 (2007); see also, Dep't of Energy, Office of Sci., Human Genome Program, Pharmacogenomics, http://www.ornl.gov/sci/techresources/Human_Genome/medicine/pharma.shtml.

²⁴ Lesko, *supra* note 23, at 809.

²⁵ See Grant, Denis M., *Pharmacogenomics and the Changing Face of Clinical Pharmacology*, 6 CAN. J. CLINICAL PHARMACOLOGY 131, 131 (1999); Lesko, *supra* note 23, at 809.

²⁶ Lesko, *supra* note 23, at 809.

²⁷ Lesko, L.J. & Woodcock, J., *Pharmacogenomic-Guided Drug Development: Regulatory Perspective*, 2 PHARMACOGENOMICS J. 20, 20-21 (2002); Roses, *supra* note 3, at 858. Pharmacogenetics is a scientific subset of pharmacogenomics that studies how genetic variations in individuals and populations result in different systemic drug exposure patterns to drug doses and dosing regimens. Lesko & Woodcock, *supra*, at 21; Roses, *supra* note 3, at 858. Similarly, toxicogenomics is a subset of pharmacogenomics that applies genomic concepts to the study of drug toxicity. Lesko et al., *supra* note 6, at 346. References in this article to pharmacogenomics are intended to include pharmacogenetics, toxicogenomics, and similar sub-disciplines.

²⁸ SACGHS PHARMACOGENOMICS REPORT, *supra* note 3, at 9. Of course, variations may occur because of other intrinsic factors, such as the individual's age, race, or sex. Variability can also be attributed to extrinsic factors, such as the individual's diet, consumption of alcohol or tobacco, or concurrent use of other drug therapies. Huang, S.-M. & Temple, R., *Is This the Drug or Dose for You?: Impact and Consideration of Ethnic Factors in Global Drug Development, Regulatory Review, and Clinical Practice*, 84 CLINICAL PHARMACOLOGY & THERAPEUTICS 287, 287 (2008).

²⁹ See THE ROYAL SOCIETY, *PERSONALISED MEDICINES: HOPES AND REALITIES* (2005), available at <http://royalsociety.org/displaypagedoc.asp?id=15874>.

³⁰ See, e.g., Agarwal, Amit, *Overlooked Opportunities*, PHARM. EXEC. (Jan. 1, 2009) (discussing the typical trial-and-error treatment of multiple sclerosis).

³¹ See Spear, B.B. et al., *Clinical Application of Pharmacogenetics*, 7 TRENDS MOLECULAR. MED. 201 (2001). For example, treatments for osteoporosis, arthritis, and migraines fail to show effect almost 50 percent of the time. See Agarwal, *supra* note 30; see also Khan, Arif et al., *Are Placebo Controls Necessary to Test New Antidepressants and Anxiolytics?*, 5 INT'L J. NEUROPSYCHOPHARMACOLOGY 193, 195-196 (2002); see also Roses, Allen D., *Pharmacogenetics and Drug Development: The Path to Safer and More Effective Drugs*, 5 NATURE REV. GENETICS 645, 648 (2004) (stating that many drugs are approved with as little as 30 percent efficacy among the general patient population).

Certain classes of drugs are even more unpredictable. For example, cancer drugs are effective for only 25 percent of cancer patients on average.³² The large non-responder populations of most drugs means that numerous patients are wasting their money and being unnecessarily exposed to side effects by taking drugs that will not actually work on them.³³ But what if it were possible to take a test to determine if a specific drug would be effective on you before you take it? For cancer drugs, this could reduce wasteful and ineffective prescriptions by up to 75 percent.

There is also great variability in inter-individual responses to specific doses of a given drug. One patient may only need half as much of a drug to achieve the same response as another patient. Similarly, a normal dose in one patient may be toxic in another. Notwithstanding this variability, most drugs still use a simple “one size fits all” dosing paradigm.³⁴ Sometimes doses are adjusted before administration to account for patient characteristics (e.g., age, weight) that are known or suspected to change the exposure profile of the drug.³⁵ Also, doses are frequently adjusted after the first administration following observation of the patient’s initial response.³⁶ But even with these adjustments, the “one size fits all” approach often fails to provide effective treatment, especially for drugs with narrow therapeutic indexes.³⁷ Consequently, new approaches are needed to ensure that patients get the right dose.

There are two types of inter-individual variabilities that must be considered—variability in efficacy and variability in toxicity.³⁸ Drug selection generally is based on the average response of the patient population.³⁹ Drugs, however, are often erroneously classified as ineffective because only a small patient population responds to treatment.⁴⁰ In fact, some patients may respond very well, notwithstanding a poor response from most of the population.⁴¹ Similarly, improper conclusions may be drawn about a drug’s toxicity because a small portion of patients have severe adverse reactions.⁴² But the drug may in fact be completely safe for the vast majority of patients.⁴³

These flawed conclusions would be eliminated if doctors could tailor prescriptions to individual patients by testing for genetic variations associated with specific drug reactions.⁴⁴ But this requires researchers to first identify genotype-response associations and then to develop diagnostic tests to identify those genotypes. Few drug labels contain any pharmacogenomic information that would allow physicians to predict whether their patient will respond to a drug or suffer an ill effect.⁴⁵ But many physicians

³² See Garrison, L.P., Jr. & Austin, M.J., *Linking Pharmacogenetics-based Diagnostics and Drugs for Personalized Medicine*, 25 HEALTH AFFAIRS 1281 (2006).

³³ Pollack, Andrew, *Patient’s DNA May Be Signal to Tailor Medication*, NY TIMES, (Dec. 30, 2008); Goldstein, Jacob, *The Next Step in Cancer Drugs: Who Should NOT Get Them*, WALL ST. J. HEALTH BLOG (Jan. 14, 2009), <http://blogs.wsj.com/health/2009/01/14/the-next-step-in-cancer-drugs-who-should-not-get-them/>; see also Roses, *supra* note 3, at 863.

³⁴ Xie, Hong-Guang & Frueh, Felix W., *Pharmacogenomics Steps Toward Personalized Medicine*, 2 PERSONALIZED MED. 325, 325-326 (2005); Lesko, *supra* note 23, at 808.

³⁵ Lesko, *supra* note 23, at 808.

³⁶ *Id.*

³⁷ Roses, *supra* note 3, at 862; Lesko, *supra* note 23, at 808.

³⁸ Woodcock, *supra* note 5, at 91.

³⁹ *Id.* at 93.

⁴⁰ *Id.* at 91.

⁴¹ *Id.*

⁴² See *id.* at 92. For example, a drug candidate that is safe and effective in 99 percent of the population may fail to receive FDA approval because the remaining 1 percent experiences a potentially fatal side effect.

⁴³ See *id.*

⁴⁴ Sasjack, *supra* note 22, at 9; see also Roses, *supra* note 3, at 863.

⁴⁵ See FDA, Table of Valid Genomic Biomarkers 2008, *supra* note 8; Lesko & Woodcock, *supra* note 27, at 20.

hope that one day they will be able to truly individualize therapy for each patient, maximizing the benefit and minimizing the toxicity of every drug used.⁴⁶

1.2. *A Tale of Two Personalized Medicines*

It has been over 10 years since the first personalized medicine, Herceptin, received FDA approval. In that time, only three other PGx-based drugs have entered the market.⁴⁷ More recently, FDA rejected marketing approval for Advexin, a promising PGx-based drug. Comparing the stories of these two drugs illustrates the challenges sponsors face in bringing personalized medicine to the market.

Herceptin (trastuzumab), a breast cancer therapy marketed by Genentech, was the first drug approved by FDA to truly take advantage of pharmacogenomics. In approximately 30 percent of breast cancer patients, the HER2 gene is over-expressed, causing an over-expression of the HER2 receptor protein.⁴⁸ Herceptin targets the HER2 receptor protein and, during early-stage clinical trials, Genentech learned that its drug was ineffective on patients who did not over-express HER2.⁴⁹ During Phase III clinical trials, Genentech and FDA agreed that appropriate treatment with Herceptin would require identification of HER2-positive individuals.⁵⁰ Genentech collaborated with Dako Corporation to develop an immunohistochemistry test that measured the level of expression of the HER2 protein in tumors.⁵¹ Genentech and Dako then filed applications for coordinated use of the drug and the companion diagnostic in 1998.⁵² When FDA approved the application, Herceptin became the first drug to be co-marketed with a diagnostic test.⁵³

The approved labeling for Herceptin specifies that it is only to be used on patients with metastatic breast cancer whose tumors over-express the HER2 protein.⁵⁴ Before taking Herceptin, patients must take a test to determine if their tumor over-expresses HER2, and patients who do not show HER2 over-expression are not given the drug.⁵⁵ The patients who do not over-express HER2 avoid risking their health and wasting their time and money on a drug that would be ineffective on them.⁵⁶ FDA officials commented that Herceptin probably would not have been approved without the accompanying diagnostic test to determine likely responders.⁵⁷

⁴⁶ Lesko & Woodcock, *supra* note 27, at 20. Considering the current political focus on healthcare reform, an arguably more important result is that personalized medicine would allow physicians to lower overall healthcare costs by avoiding wasteful prescriptions to non-responders and adverse responders. *See id.* at 21.

⁴⁷ FDA has only approved four drugs with labeling that require a physician to administer a genetic test prior to prescribing the drug. *See* FDA, Table of Valid Genomic Biomarkers 2008, *supra* note 8. They are Herceptin (trastuzumab), Selzentry (maraviroc), Erbitux (cetuximab), and Sprycel (dasatinib). *Id.*

⁴⁸ Xie & Frueh, *supra* note 34, at 329; Lesko & Woodcock, *supra* note 27, at 23.

⁴⁹ Harries, M. & Smith, I., *The Development and Clinical Use of trastuzumab (Herceptin)*, 9 ENDOCRINE-RELATED CANCER 75, 78-79 (2002); Xie & Frueh, *supra* note 34, at 329.

⁵⁰ SACGHS PHARMACOGENOMICS REPORT, *supra* note 3, at 26.

⁵¹ *Id.*

⁵² *Id.*

⁵³ *See* Roses, *supra* note 31, at 648.

⁵⁴ GENENTECH, HERCEPTIN FINAL DRAFT LABEL, U.S. BLA SUPPLEMENT, available at <http://www.fda.gov/cder/foi/label/2002/trasgen082802LB.pdf>; Lesko & Woodcock, *supra* note 27, at 23.

⁵⁵ Lesko & Woodcock, *supra* note 27, at 23.

⁵⁶ This is a significant savings, since Herceptin costs approximately \$40,000 to \$60,000 per patient per year. *See* Neyt, M. et al., *An Economic Evaluation of Herceptin in Adjuvant Setting*, 17 ANN. ONCOL-OGY 381 (2006).

⁵⁷ Lesko & Woodcock, *supra* note 27, at 23.

Herceptin is the classic example of a successful personalized medicine. In contrast, Advexin serves as an illustration of the regulatory and economic factors that deter the development of more personalized medicines. Advexin is a therapy for head and neck cancer developed by Introgen Therapeutics, an emerging Texas-based biotech company. Advexin targets the p53 tumor suppressor function, which is associated with cancer. Phase III clinical trials showed that Advexin was basically ineffective on the general patient population. However, the Phase II trial data showed both that Advexin was effective on the subgroup of patients with the abnormal p53 tumor suppressor gene and that this same subgroup of patients was less likely to benefit from existing treatments.⁵⁸ This correlation between Advexin's efficacy and the p53 gene was discovered during a *post hoc* analysis of Phase II trial data conducted after the Phase III trial had begun but before the trial was unblinded.⁵⁹ In June 2008, Introgen submitted its application for market approval to FDA and relied on data from patients with the abnormal p53 gene to demonstrate efficacy.⁶⁰ But FDA refused to file the application on the grounds that, even though the p53 gene subgroup analysis was specified prior to breaking the blind on the Phase III trial, the subgroup was not specified prior to the start of the Phase III trial.⁶¹ The agency said it would require an additional Phase III trial to prospectively demonstrate Advexin's efficacy in patients with the abnormal p53 gene. However, Introgen could not afford spending millions of dollars on another Phase III trial and it was forced to stop development and file for bankruptcy.⁶²

1.3. *The Economics of Developing Personalized Medicine*

On its face, developing personalized medicine appears to be against the interests of pharmaceutical companies. Most drugs are approved to treat the general patient population. But if a company uses pharmacogenomics to identify likely responders, this may limit the use of its drug to a fraction of the overall patient population. Drugs that can only be sold to a small subgroup of the patient population are clearly less attractive investments.⁶³ Ironically, the commercial incentives to develop personalized medicine are weakest precisely with the drugs that pharmacogenomics would most benefit, since a company developing a drug with a high level of non-responders has the most to lose by using pharmacogenomics.⁶⁴ Pioneers could

⁵⁸ *Introgen Advexin Clinical Biomarker Data Demonstrate Recurrent Head and Neck Cancer Patients Likely to Have a Survival Benefit From Advexin*, REUTERS (Jan. 22, 2007) ("Tumor disease control was observed in 75 percent of patients with the abnormal p53 biomarker compared to 18% of patients without the p53 biomarker."), <http://www.reuters.com/article/idUSIN20070122134705INGN20070122>.

⁵⁹ E-mail from Peter Barton Hutt, Senior Counsel, Covington & Burling LLP, to author (Feb. 23, 2009, 13:42:08 PST) (on file with author).

⁶⁰ Young, Donna, *Introgen Takes a Hit on FDA's Refusal to Review Gene Therapy*, BIO WORLD TODAY (Sept. 3, 2008).

⁶¹ E-mail from Peter Barton Hutt, *supra* note 59.

⁶² *Introgen Files for Bankruptcy, Sees Exit in 2009*, REUTERS (Dec. 3, 2006), <http://www.reuters.com/article/idUSN0343564920081203>.

⁶³ Reeder, C.E. & Dickson, W. Michael, *Economic Implications of Pharmacogenomics*, in PHARMACOGENOMICS: SOCIAL, ETHICAL AND CLINICAL DIMENSIONS 229, 232 (Mark. A. Rothstein ed., 2003). But see Keeling, Peter & Roth, Mollie, *Getting Personal(ized)*, PHARM. EXEC. (Oct. 1, 2008) (arguing that a sponsor can actually increase sales by coupling its drug with a companion diagnostic test because "prescribers are more likely to use a drug that comes with a test—at a rate of 70–90 percent more than other more traditional drugs—because the test provides greater evidence of likely positive patient outcome"). Furthermore, if PGx data is only used to exclude a small group of likely adverse responders, it may be a substantially more attractive investment.

⁶⁴ Evans, Barbara J. et al., *Creating Incentives for Genomic Research to Improve Targeting of Therapies*, 10 NATURE MED. 1289, 1289 (2004).

increase the prices for personalized medicines that are limited to small markets in order to recoup their research and development costs, but this might be infeasible where cheaper alternative therapies for the same disease state already exist or where third-party payers have fixed reimbursement rates for treating that disease state.⁶⁵

Besides possibly reducing their market size, drug manufacturers are further disincentivized from generating pharmacogenomic data because incorporating PGx testing into clinical trials will make the trials more expensive. In addition to standard clinical trial expenses, the developers of personalized medicines will have to pay for the cost of gathering and analyzing pharmacogenomic data and developing and obtaining approval for a companion diagnostic test.⁶⁶ Also, clinical trials may need to be redesigned and additional trials may be needed to fully utilize pharmacogenomic data discovered during the clinical trials.⁶⁷ For example, a greater number of subjects may be needed in early-phase clinical trials to identify relevant PGx biomarkers.⁶⁸ Similarly, larger trials may be needed to identify likely adverse responders since adverse drug reactions generally occur infrequently.⁶⁹

Pharmaceutical companies, however, have some incentives to develop personalized medicine.⁷⁰ The drug discovery process has a high failure rate,⁷¹ and enormous costs are associated with the identification, development, and testing of new drug candidates.⁷² Approximately 50 percent of drugs in Phase III clinical trials fail to obtain FDA marketing approval,⁷³ and in most cases the trials fail because the drugs have some safety or efficacy issue.⁷⁴ Pharmacogenomics has the potential to reduce drug candidate attrition during clinical trials by using biomarkers to enrich trials with likely responders and to exclude those at risk for serious adverse events.⁷⁵ But this also suggests that pharmaceutical companies would only use pharmacogenomic data to “rescue” drugs that FDA would not otherwise approve for the general

⁶⁵ See SACGHS PHARMACOGENOMICS REPORT, *supra* note 3, at 2. Also note that the incentive to develop and use pharmacogenomic-based diagnostic tests is further impeded by the refusal of most health insurers to cover the cost of such tests. In fact, Medicare is statutorily prohibited from reimbursing the costs of most PGx tests. *Id.* at 3, 60. It is also interesting to note that the cost of a PGx test is easier to justify for more expensive therapies. *Id.* at 25; Flowers, C.R. & Veenstra, D., *The Role of Cost-Effectiveness Analysis in the Era of Pharmacogenomics*, 22 PHARMACOECONOMICS 481 (2004). It is, however, beyond the scope of this article to explore the problems associated with third-party payers.

⁶⁶ Spice, Byron, *Pharmacogenomics: One Day, it May Allow Doctors to Tailor Drugs to Individuals*, PITTSBURGH POST-GAZETTE (July 9, 2000), at AO, available at <http://www.post-gazette.com/healthscience/20000709pharmacogenomics.asp>; see also Keeling & Roth, *supra* note 63.

⁶⁷ See Evans et al., *supra* note 64, at 759.

⁶⁸ See SACGHS PHARMACOGENOMICS REPORT, *supra* note 3, at 22.

⁶⁹ See NUFFIELD COUNCIL ON BIOETHICS, PHARMACOGENETICS: ETHICAL ISSUES (2003), available at http://www.nuffieldbioethics.org/fileLibrary/pdf/pharmacogenetics_report.pdf; SACGHS PHARMACOGENOMICS REPORT, *supra* note 3, at 22; Roses, *supra* note 3, at 862. But see Emilien, G. et al., *Impact of Genomics on Drug Discovery and Clinical Medicine*, 93 Q. J. MED. 391, 394 (2000) (arguing that clinical trials that include PGx testing may be more efficient because they will improve the use of inclusion and exclusion criteria for the trial); Bonnie, A. et al., *Clinical Trials in the Genomic Era: Effects of Protective Genotypes on Sample Size and Duration of Trial*, 21 CONTROLLED CLIN. TRIALS 7 (2000) (same); BOSTON CONSULTING GROUP, *supra* note 19 (estimating that genomic technology could save drug companies an average of \$300 million as a result of increased efficiency).

⁷⁰ See, e.g., Agarwal, *supra* note 30.

⁷¹ See Pritchard, J.F. et al., *Making Better Drugs: Decision Gates in Non-Clinical Drug Development*, 2 NATURE REV. DRUG DISCOVERY 542, 542 (2003) (describing failure risks associated with drug discovery).

⁷² See *supra* text accompanying note 14.

⁷³ Lesko & Woodcock, *supra* note 18, at 764.

⁷⁴ Lesko, *supra* note 23, at 810.

⁷⁵ See *id.*; Lesko & Woodcock, *supra* note 27, at 21.

population.⁷⁶ However, pharmacogenomic data is almost never used in this manner because FDA would likely require an additional clinical trial to demonstrate safety and efficacy in the responding subgroup.⁷⁷ The cost of these extra clinical trials, which can be tens to hundreds of millions of dollars,⁷⁸ is probably the primary economic deterrent to developing personalized medicine.

1.4. *The Challenges to Bringing Personalized Medicine to Consumers*

Currently, few companies actively gather pharmacogenomic data during clinical trials.⁷⁹ The development of personalized medicine is stymied primarily by two factors: 1) a lack of economic incentives to develop PGx-based drugs; and 2) uncertainty over how the current regulatory regime will be applied to pharmacogenomic data. This article assumes that pharmaceutical companies, as profit-maximizing entities, will always first seek to get a new drug approved for treating the general patient population.⁸⁰ Consequently, sponsors will only have an economic incentive to use pharmacogenomics when a drug candidate would otherwise fail in clinical trials.⁸¹ Working from this assumption, this article will focus on analyzing the regulatory problems related to using pharmacogenomic data to rescue drugs that possess limited positive responder populations or substantial adverse responder populations.

2. *FDA Regulation of Drugs and Medical Devices*

2.1. *Introduction*

In order to market a new prescription drug or medical device, the pharmaceutical sponsor must first obtain regulatory approval from FDA.⁸² Drugs and devices, however, are regulated in completely separate ways. Consequently, seeking regulatory approval for personalized medicine is complicated by the need to get FDA approval to market both the drug and the companion diagnostic device.

2.2. *Regulation of Drugs*

A new drug cannot be marketed until FDA approves the drug as safe, effective, and properly labeled.⁸³ To obtain FDA marketing approval, the sponsoring pharmaceutical company must perform extensive testing and analysis on the new drug in order to provide FDA with data on the drug's safety, efficacy, pharmacology,

⁷⁶ Reeder & Dickson, *supra* note 63, at 231-232.

⁷⁷ See Evans et al., *supra* note 64, at 758-759.

⁷⁸ See Li, Gen, *Site Activation: The Key to More Efficient Clinical Trials*, PHARM. EXEC. (Dec. 12, 2008) (reporting that single clinical trial can involve up to 50,000 patients, last five years or longer, and cost up to \$500 million).

⁷⁹ See Woodcock, *supra* note 5, at 93.

⁸⁰ In fact, as a matter of practice, a sponsor will almost always abandon a drug in the middle of clinical trials if it only demonstrates efficacy in a small subgroup. See Roses, *supra* note 31, at 648.

⁸¹ The motive to use PGx to rescue a failing drug may be greater where no alternative treatment exists for the target disease state. See NUFFIELD COUNCIL ON BIOETHICS, *supra* note 69.

⁸² See, e.g., 21 U.S.C. § 355(a) ("No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application ... is effective with respect to such drug.").

⁸³ See 21 U.S.C. § 355(d).

and toxicology.⁸⁴ With this data, the sponsor must demonstrate: 1) that the drug is safe and effective for the use in the proposed labeling; and 2) that the benefits of the drug outweigh its risks.⁸⁵

Before human clinical testing can begin on a drug candidate, the sponsor must complete substantial preclinical testing, which involves laboratory and animal tests.⁸⁶ After pre-clinical testing is complete, the sponsor must proceed through the IND process. During the IND process, the sponsor must conduct human clinical studies designed to demonstrate that the drug is safe and effective.⁸⁷ The process usually begins with Phase I clinical studies,⁸⁸ which are generally conducted in 20-80 healthy volunteer subjects.⁸⁹ These studies are designed primarily to evaluate the safety of the drug,⁹⁰ though the sponsor must also obtain sufficient data about the drug's pharmacokinetic and pharmacological effects to permit the design of Phase II studies.⁹¹ In Phase II clinical studies, the drug is generally tested on several hundred patients with the disease.⁹² Phase II studies are conducted to obtain preliminary data on the drug's effectiveness.⁹³ If the preliminary evidence from the Phase II trials suggests the drug is effective, the sponsor may proceed to Phase III trials.⁹⁴ Finally, the pivotal Phase III trials are conducted to gather sufficient information about the drug's safety and efficacy to extrapolate the results to the general population.⁹⁵ Phase III studies are the most important and expensive trials, generally involving several thousand patients with the disease and costing hundreds of millions of dollars.⁹⁶

⁸⁴ 21 C.F.R. § 312.23.

⁸⁵ FDA, CENTER FOR DRUG EVALUATION AND RESEARCH (CDER), THE CDER HANDBOOK 7 (1998) [hereinafter FDA, CDER HANDBOOK], available at <http://www.fda.gov/cder/handbook/handbook.pdf>.

⁸⁶ During pre-clinical testing, the sponsor must obtain toxicological and pharmacological information on the drugs. See 21 C.F.R. 312.23(a)(8); FDA, CDER HANDBOOK, *supra* note 85, at 5. In practice, however, most investigational new drug (IND) applicants only submit toxicology data. Interview with Peter Barton Hutt, *supra* note 18. While FDA does not directly regulate preclinical testing, the agency indirectly regulates how preclinical testing is conducted because it uses the results of these tests to determine whether to allow human clinical trials. Consequently, as part of preclinical testing, the sponsor must develop a "pharmacological profile" of the new drug to allow FDA to determine whether "it is reasonably safe to proceed with human trials of the drug." FDA, CDER HANDBOOK, *supra* note 85, at 5, 7.

⁸⁷ See 21 U.S.C. § 355(d); 21 C.F.R. § 312.23.

⁸⁸ Alternatively, the IND process can begin with exploratory IND studies (so-called "Phase Zero" studies), which involve administering the drug to a very limited number of healthy human volunteers for a limited duration (e.g., one week). Phase Zero studies are optional, and generally used to gather preliminary pharmacokinetic and pharmacodynamics data on multiple drug candidates to identify the best compound(s) to advance to full-scale clinical trials. Draft Guidance for Industry, Investigators, and Reviewers: Exploratory IND Studies, 70 Fed. Reg. 19,764 (Apr. 14, 2005).

⁸⁹ FDA, CDER HANDBOOK, *supra* note 85. Phase I studies are sometimes divided into Phase IA and Phase IB, where Phase IA tests the drug in healthy volunteers and Phase IB tests the drug in patients with the disease.

⁹⁰ See 21 C.F.R. § 312.21(a) (stating that Phase I studies are "designed to determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. ... Phase I studies also include studies of drug metabolism, structure-activity relationships, and mechanism of action in humans, as well as studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes); HUTT ET AL., *supra* note 12, at 630.

⁹¹ FDA, CDER HANDBOOK, *supra* note 85, at 8.

⁹² *Id.*

⁹³ *Id.*; see also 21 C.F.R. § 312.21(b). Phase II studies are sometimes divided into Phase IIA and Phase IIB. Phase IIA is designed to assess dosing requirements and Phase IIB is designed to study efficacy.

⁹⁴ FDA, CDER HANDBOOK, *supra* note 85, at 8.

⁹⁵ *Id.*; see also 21 C.F.R. § 312.21(c).

⁹⁶ See Li, *supra* note 78, CDER HANDBOOK, *supra* note 85, at 9.

Phase II and III studies are usually double-blinded and placebo-controlled, with various fixed doses administered to random patients.⁹⁷ This randomized fixed-dose design allows researchers to study the patients' responses to the various doses.⁹⁸ The problem with this dose-response study, however, is that it only gives information about the general patient population, and possibly about certain subsets within that population (e.g., age, sex, race) that are defined at the beginning of the trial.⁹⁹ Because each patient only receives a single fixed dose, the trial yields no information about each patient's individual response to different doses.¹⁰⁰

Once human clinical trials are complete, the sponsor may file a New Drug Application (NDA),¹⁰¹ which requires the sponsor to provide detailed reports of all prior animal and human studies.¹⁰² FDA then reviews the application to determine if the drug is "safe and effective" to treat the targeted disease state.¹⁰³ If the agency approves the NDA, the sponsor may begin commercially marketing its new drug immediately.¹⁰⁴

All drugs must include labeling, which is printed material accompanying the drug that describes, among other things, information concerning dosages, directions for administration, conditions for which the drug is effective, contraindications, and warnings about known or suspected side effects and adverse reactions.¹⁰⁵ The sponsor must include proposed labeling for the drug with the NDA, and the agency will reject the application if it finds the proposed labeling is in any way false or misleading.¹⁰⁶ For PGx-based drugs, the "Indications and Usage" section of the labeling would inform clinicians that there is a companion diagnostic test that may have to be performed prior to administering the drug.¹⁰⁷

⁹⁷ Huang, S.-M. & Temple, R., *Is This the Drug or Dose for You?: Impact and Consideration of Ethnic Factors in Global Drug Development, Regulatory Review, and Clinical Practice*, 84 CLINICAL PHARMACOLOGY & THERAPEUTICS 287, 288 (2008); see also 21 C.F.R. § 314.126. Placebo-controlled means that there is also a patient population that randomly receives a placebo, which serves as a control against which safety and efficacy in the active group can be determined. Double-blind means that neither the physicians nor the patients know who is receiving placebos—only the researchers overseeing the study know which patients are receiving actual treatment.

⁹⁸ Huang & Temple, *supra* note 97, at 288.

⁹⁹ See 21 C.F.R. § 314.50; Huang & Temple, *supra* note 97, at 288.

¹⁰⁰ Huang & Temple, *supra* note 97, at 288 ("What this means is that we have reasonably good data on group safety and effectiveness dose-response relationships but cannot determine whether individuals differ in important ways in their responses If such differences were predicted by a demographic feature, they might be detected by standard subset analyses, but if they reflect unrecognized genetic or physiologic pharmacodynamic (PD) differences, they would not.").

¹⁰¹ This article refers to NDAs. Developers of biological products file Biologicals License Applications (BLAs) rather than NDAs. For purposes of this article, any discussion of NDAs is also applicable to BLAs.

¹⁰² Landen, Pennington Parker, *Federal Preemption and the Drug Industry: Can Courts Co-Regulate?*, 43 FOOD DRUG COSM. L.J. 85, 100 (1988); see also 21 U.S.C. § 355(a)-(b). In general, the NDA should contain reports on the following: 1) chemistry, manufacturing, and control; 2) nonclinical pharmacology and toxicology; 3) human pharmacokinetics and bioavailability; 4) clinical efficacy and safety data (both generally and by sex, age and race). See 21 C.F.R. § 314.50; see also FDA, CDER HANDBOOK, *supra* note 85, at 21.

¹⁰³ See 21 U.S.C. § 355(d). After reviewing the application, FDA may take one of three actions: 1) send a "not approvable" letter stating that the drug cannot be approved; 2) send an "approvable" letter indicating that the drug could be approved if certain changes are made; or 3) send an "approval" letter stating that the drug is approved as it stands. See FDA, CDER HANDBOOK, *supra* note 85, at 24; see also 21 C.F.R. §§ 314.105, 314.110, 314.120.

¹⁰⁴ See 21 U.S.C. § 355(a).

¹⁰⁵ See 21 U.S.C. §§ 321(m), 352(f)(1)-(2); Merrill, Richard A., *Compensation for Prescription Drug Injuries*, 59 VA. L. REV. 1 (1973).

¹⁰⁶ 21 U.S.C. § 355(b)(1)(F), (d)(7).

¹⁰⁷ See Lesko et al., *supra* note 6, at 351.

2.3. Regulation of Medical Devices

To effectively use PGx-based drugs, some form of companion diagnostic test is needed to identify likely responders and adverse responders.¹⁰⁸ Pharmacogenomic tests generally use high-throughput technologies, such as gene chips, to identify specific genes or biomarkers that correlate to drug activity.¹⁰⁹ These genetic tests can then be used by physicians to help them decide whether to use a particular drug and at what dosage.¹¹⁰ Most PGx testing is performed by clinical laboratory services using so-called “laboratory-developed tests” (LDTs).¹¹¹ Some genetic tests, however, are also performed using individually marketed in vitro diagnostic (IVD) test kits.¹¹²

Regulation of In Vitro Diagnostic Assays

FDA regulates IVDs as medical devices. First, depending on the safety risks posed by a device, FDA classifies devices as Class I, II, or III, with increasing levels of regulatory control for each class.¹¹³ For IVDs, safety is measured by the impact that the assay has on patient management (e.g., potential harm from false-positive or false-negative results).¹¹⁴

Class I devices present minimal safety risks and are generally exempt from premarket review and subject only to “general controls” that require the manufacturer to register the device with FDA, manufacture it in accordance with Good Manufacturing Practices (GMPs), and provide proper labeling for the device.¹¹⁵ General controls do not require the sponsor to submit any clinical data related to safety and efficacy.

Class II devices present moderate risk and typically require submission of a so-called “510(k) premarket notification,”¹¹⁶ which requires the sponsor to show that the device is “substantially equivalent” to an approved predicate device.¹¹⁷ A predicate device is basically any device that has already been approved by FDA.¹¹⁸ In addition to general controls, FDA can subject Class II devices to “special controls,” which may include special labeling requirements, mandatory performance standards, and postmarket surveillance.¹¹⁹

¹⁰⁸ See SACGHS PHARMACOGENOMICS REPORT, *supra* note 3, at 25.

¹⁰⁹ *Id.* at 10.

¹¹⁰ *Id.* at 25.

¹¹¹ *Id.*

¹¹² *Id.*

¹¹³ See 21 U.S.C. § 360c(a)(1); SACGHS PHARMACOGENOMICS REPORT, *supra* note 3, at 52; Gibbs, Jeffrey N., *Personalized Medicine: Panacea or Pipedream?*, FDLI UPDATE (Sept./Oct. 2008), at 6, 8.

¹¹⁴ SACGHS PHARMACOGENOMICS REPORT, *supra* note 3, at 52.

¹¹⁵ See FDA, Device Classes, <http://www.fda.gov/CDRH/DEVADVICE/3132.html>; 21 U.S.C. §§ 351, 352, 360, 360f, 360h, 360i, 360j; see also 21 C.F.R. §§ 801, 809, 820.

¹¹⁶ Note that general controls require submission of a 510(k) premarket notification for both Class I and II devices. See 21 U.S.C. §§ 360(k), 360c(i). However, by regulation, almost all Class I and many Class II devices are exempt from the 510(k) submission requirement. See 21 C.F.R. §§ 862-892; FDA, Class I/II Exemptions, <http://www.fda.gov/CDRH/DEVADVICE/3133.html>.

¹¹⁷ See 21 U.S.C. §§ 360(k), 360c(i).

¹¹⁸ See FDA PREMARKET NOTIFICATION 510(k), <http://www.fda.gov/CDRH/DEVADVICE/314.html>; SACGHS PHARMACOGENOMICS REPORT, *supra* note 3, at 52.

¹¹⁹ See 21 U.S.C. § 360c(a)(1)(B).

Class III devices are those that may present serious safety risks to the patient.¹²⁰ In addition to complying with general and special controls, sponsors of Class III devices must submit a premarket approval (PMA) application that includes data showing that the device is safe and effective for its intended use.¹²¹ The PMA must be approved by FDA before the sponsor can commercially market the device.¹²²

If an IVD assay is intended for use with a specific branded drug, FDA requires that the drug and IVD have mutually conforming labels.¹²³

Regulation of Laboratory-Developed Tests

Diagnostic tests manufactured and used internally by a laboratory service are classified as “laboratory-developed tests” (LDTs).¹²⁴ Under the current laws, FDA has authority to regulate LDTs.¹²⁵ FDA, however, has elected not to exercise this authority.¹²⁶ Instead, LDTs are regulated by the Center for Medicare and Medicaid Services (CMS) under the Clinical Laboratory Improvement Amendments of 1988.¹²⁷ Under these Amendments, CMS requires the laboratory service to demonstrate analytical validity for the LDT.¹²⁸ However, no showing of clinical utility or validity is required.¹²⁹

3. FDA Regulation of Personalized Medicine & Pharmacogenomics

FDA has highlighted the potential of pharmacogenomic testing to create personalized drugs and the agency aims to encourage both the public and private sectors

¹²⁰ See *id.* § 360c(a)(1)(C)(ii); SACGHS PHARMACOGENOMICS REPORT, *supra* note 3, at 52. Note that devices with no equivalent predicate are classified as Class III devices by default, regardless of their safety. Consequently, sponsors of these devices can request a down-classification to either a Class I or II device if they can show the device presents only a low or moderate risk. *Id.* If FDA approves the down-classification, the device can be marketed without obtaining a PMA. See FDA, CENTER FOR DEVICES & RADIOLOGICAL HEALTH (CDRH), NEW SECTION 513(F)(2)—EVALUATION OF AUTOMATIC CLASS III DESIGNATION, GUIDANCE FOR INDUSTRY AND CDRH STAFF (1998), available at <http://www.fda.gov/cdrh/modact/clasiii.pdf>.

¹²¹ See 21 U.S.C. § 360c(a)(1)(C); SACGHS PHARMACOGENOMICS REPORT, *supra* note 3, at 52. However, sponsors of Class III devices with no equivalent predicate device can request a down-classification to either a Class I or II device if the device is of low or moderate risk. See 21 U.S.C. § 360c(f)(3). If FDA approves the down-classification, the device can be marketed without obtaining a PMA. See FDA, *Supra* note 120.

¹²² 21 U.S.C. § 360e.

¹²³ FDA, INTERCENTER AGREEMENT BETWEEN THE CENTER FOR DRUG EVALUATION AND RESEARCH (CDER) AND THE CENTER FOR DEVICES AND RADIOLOGICAL HEALTH (CDRH), at VII.A.1(a)iii., VII.B (2006), available at <http://www.fda.gov/oc/ombudsman/drug-dev.htm>.

¹²⁴ SACGHS PHARMACOGENOMICS REPORT, *supra* note 3, at 51.

¹²⁵ See Medical Device Amendments of 1976, Pub. L. No. 94-295, 90 Stat. 539 (May 28, 1976) (codified as amended in scattered sections of 21 U.S.C.); Safe Medical Devices Act of 1990, Pub. L. No. 101-629, § 16, 104 Stat. 4511 (codified at 21 U.S.C. § 353(g)).

¹²⁶ SACGHS PHARMACOGENOMICS REPORT, *supra* note 3, at 53-54.

¹²⁷ See Clinical Laboratory Improvements Amendments of 1988, Pub. L. No. 100-578, 102 Stat. 2903 (codified at 42 U.S.C. § 263a); Prebula, *supra* note 130, at 16.

¹²⁸ See Bouchie, Aaron, *MDx: A Murky Brew*, BioCENTURY (Jan. 26, 2009), at A1, A2. Analytical validity is a measure of how accurately and consistently the test detects the presence of a specific genotype. SACGHS PHARMACOGENOMICS REPORT, *supra* note 3, at 32; Gwinn, M. & Khoury, M.J., *Epidemiologic Approach to Genetic Tests: Population-Based Data for Preventive Medicine*, in HUMAN GENOME EPIDEMIOLOGY (M.J. Khoury & J. Little eds., 2003).

¹²⁹ See Bouchie, *supra* note 128, at A2. Clinical utility refers to the device’s ability to inform clinical decision making and predict clinical outcomes. Grosse, S.D. & Khoury, M.J., *What is the Clinical Utility of Genetic Testing?*, 8 GENETIC MEDICINE 448 (2006). Clinical validity means how well the test predicts a given phenotype (i.e., clinical disorder or outcome). SACGHS PHARMACOGENOMICS REPORT, *supra* note 3, at 32; Gwinn & Khoury, *supra* note 128.

to develop PGx products.¹³⁰ Pharmaceutical companies have reacted by integrating pharmacogenomic research into their drug development programs with increasing frequency.¹³¹ But it is not clear from current regulations how PGx data fits into the regulatory framework or how FDA will use this data.¹³² Pharmaceutical companies have been particularly concerned that FDA would use pharmacogenomic data against them by requesting additional clinical trials, putting trials on hold, or limiting a drug's indication to certain subgroups.¹³³ Consequently, sponsors are hesitant to use PGx data because "[d]rug development is already a long, arduous, expensive and very uncertain process, and sponsors expressed reluctance to add any additional uncertainty to the process."¹³⁴ Specifically, sponsors have raised the following questions about using pharmacogenomics to develop personalized medicine:¹³⁵

- What are the regulatory implications of screening a patient's genetic profile during investigational drug therapy?
- Can a PGx test be used to stratify patients entering into a clinical trial? If so, will the labeling for that drug be limited to certain subgroups? Will the labeling require a PGx diagnostic test?
- Would FDA require the sponsor of a PGx-based drug to seek concurrent approval for the PGx diagnostic test?
- Would FDA allow a *post hoc* subset analysis based on PGx data in a clinical trial that either failed to demonstrate efficacy in the general patient population or had an unacceptably high rate of adverse events?

In response to these questions, FDA has created several guidance documents that attempt to explain how the agency plans to use pharmacogenomic data within the current regulatory scheme.¹³⁶ The agency, however, has not changed any regulations—it has simply provided suggestions on how to fit pharmacogenomic data into existing laws and regulations.¹³⁷ Consequently, it is still not obvious how FDA will actually regulate the use of PGx data and sponsors continue to seek direction from the agency.¹³⁸ Parts 3.1 through 3.5, *infra*, attempt to clarify the current state of FDA's regulatory approach by analyzing FDA's guidance documents and regulations and directly answering the questions above. In answering these questions, this article also shows how the agency's current approach to regulating personalized medicine is inadequate and discourages sponsors from using pharmacogenomics during the development process.

3.1. *Validation of Biomarkers*

A biomarker is a "characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic

¹³⁰ See FDA, CRITICAL PATH OPPORTUNITIES REPORT AND LIST, at R-10 (2006), available at http://www.fda.gov/oc/initiatives/criticalpath/reports/opp_report.pdf; Dooren, Jennifer Corbett, *Consortium to Study Genetics, Drug Safety*, WALL ST. J. (Sept. 27, 2007); Prebula, Randy, *The Ever-Evolving Role of "Companion Diagnostics"*, FDLI UPDATE, (Sept./Oct. 2008), at 14, 14.

¹³¹ See Lesko et al., *supra* note 6, at 348.

¹³² See Woodcock, *supra* note 5, at 95.

¹³³ FDA, GUIDANCE FOR INDUSTRY, PHARMACOGENOMIC DATA SUBMISSIONS 14 (2005) [hereinafter FDA, GUIDANCE ON PHARMACOGENOMIC DATA SUBMISSIONS], available at <http://www.fda.gov/cber/gdlns/pharmdtasub.pdf>; Lesko & Woodcock, *supra* note 18, at 766.

¹³⁴ Woodcock, *supra* note 5, at 95.

¹³⁵ See Lesko & Woodcock, *supra* note 27, at 22.

¹³⁶ Woodcock, *supra* note 5, at 95.

¹³⁷ *Id.*

¹³⁸ SACGHS PHARMACOGENOMICS REPORT, *supra* note 3, at 96.

responses to a therapeutic intervention.”¹³⁹ In the pharmacogenomic context, a biomarker would be a specific genetic variation that correlates with drug response.¹⁴⁰

FDA classifies biomarkers as either “exploratory,” “probable valid,” or “valid.”¹⁴¹ FDA will only allow a PGx biomarker to be included in drug labeling if it is “valid,” meaning the biomarker is one that is known and accepted by the biomedical community.¹⁴² A biomarker is valid if: 1) the biomarker “is measured in an analytical test system with well-established performance characteristics”; and 2) “there is an established scientific framework or body of evidence that elucidates the physiologic, pharmacologic, toxicologic, or clinical significance of the test results.”¹⁴³ A “probable valid biomarker” is one that is not widely accepted, but the sponsor has “data sufficient to establish a significant association between a pharmacogenomic test result and clinical outcomes.”¹⁴⁴ An “exploratory biomarker” is one where the sponsor does not yet have sufficient data to establish such an association.¹⁴⁵

In most cases, pharmacogenomic biomarkers discovered during clinical trials will be classified as either exploratory or probably valid, since the sponsor will lack the necessary “body of evidence” regarding its clinical significance.¹⁴⁶ FDA will review clinical data on unvalidated biomarkers, but the sponsor cannot rely on this data to support claims of safety or efficacy.¹⁴⁷ Only data on validated biomarkers can support such claims.¹⁴⁸

The agency has not provided guidance on exactly what a sponsor must show to validate a biomarker.¹⁴⁹ FDA, however, has established a pilot program for validating biomarkers through its Interdisciplinary Pharmacogenomic Review Group.¹⁵⁰ The review group will work with a sponsor to design studies and clinical trials for validating a biomarker, and will then review the results to either accept or reject the biomarker for its intended use.¹⁵¹ While FDA’s assistance to individual sponsors is helpful, a guidance document laying out the preferred process for biomarker validation is needed.

3.2. Pharmacogenomic Data Submission Requirements

When a sponsor generates pharmacogenomic data that is used in clinical trial design or drug labeling, FDA regulations clearly require the sponsor to submit the

¹³⁹ Biomarkers Definitions Working Group, *Biomarkers and Surrogate Endpoints: Preferred Definitions and Conceptual Framework*, 69 CLINICAL PHARMACOLOGY & THERAPEUTICS 89, 91 (2001); see also HUTT ET AL., *supra* note 12, at 640.

¹⁴⁰ For example, the HER2 gene is a biomarker for Herceptin efficacy. See *supra* notes 48-49 and accompanying text.

¹⁴¹ FDA, GUIDANCE ON PHARMACOGENOMIC DATA SUBMISSIONS, *supra* note 133, at 4, 24.

¹⁴² *Id.* at 4, 17.

¹⁴³ *Id.* at 4.

¹⁴⁴ *Id.* at 5, 17.

¹⁴⁵ *Id.* at 4.

¹⁴⁶ *Id.*

¹⁴⁷ See *infra* notes 171-172 and accompanying text.

¹⁴⁸ *Id.*

¹⁴⁹ See Goodsaid, Federico & Frueh, Felix W., *Implementing the U.S. FDA Guidance on Pharmacogenomic Data Submissions*, 48 ENVTL. MOL. MUTAGENESIS 354, 355 (2007).

¹⁵⁰ See Goodsaid, Federico & Frueh, Felix W., *Biomarker Qualification Pilot Process at the US Food and Drug Administration*, 9 AAPS J. E105, E106 (2007).

¹⁵¹ See Goodsaid & Frueh, *supra* note 150, at E106-07. It is likely that a prospective Phase III trial would be sufficient for validation. However, the huge cost of running these trials is a major roadblock to validating biomarkers. See Roses, *supra* note 3, at 859.

PGx data as part of its IND and NDA.¹⁵² But if the PGx data is not used in the trials or in labeling, the regulations are not clear regarding whether exploratory PGx data must be submitted, and if so, how FDA will use this data. Many pharmaceutical companies were concerned that FDA would require them to submit any PGx data they generated and then use that data against them when evaluating INDs and NDAs.¹⁵³ In response to these concerns, FDA published guidelines that clarify when submission is required and establish a process for voluntary submission of exploratory data.¹⁵⁴ Furthermore, the guidelines state that FDA will not use voluntarily submitted PGx data when making decisions regarding drug approval.¹⁵⁵

As part of the IND application, the sponsor must submit PGx data from pre-clinical studies if: 1) the data is being used to make decisions about a clinical trial (e.g., the results will affect dose and dose schedule selection, entry criteria into a clinical trial, safety monitoring, or patient stratification); 2) the data is being used to support arguments regarding the dosing, safety, or efficacy of the drug; or 3) the data concerns a known valid biomarker.¹⁵⁶ In other situations, submission of PGx data is merely voluntary.¹⁵⁷

During the NDA phase, sponsors must submit PGx data generated during Phase I, II, and III clinical trials if: 1) the sponsor intends to use the data in the drug labeling; 2) the sponsor intends to use the data to support scientific arguments about drug dosing, safety, patient selection or monitoring; 3) a PGx test is essential to achieving the dosing, safety, or effectiveness described in the labeling; 4) the data concerns a known valid biomarker; 5) the data concerns a probable valid biomarker.¹⁵⁸ As with the IND, submission of PGx data in other situations is voluntary.¹⁵⁹ FDA, however, does recommend submission of a synopsis of exploratory data.¹⁶⁰ Finally, after an NDA is approved, the sponsor must submit any newly-generated data concerning known or probable valid biomarkers.¹⁶¹

3.3. *Use of Pharmacogenomic Data During Clinical Trials*

Patient Stratification Based on a Pharmacogenomic Test

A standard clinical trial uses an “all-comers” approach, where any patient who meets relatively general inclusion criteria can enroll.¹⁶² However, when a drug fails to show an adequate safety or efficacy profile in all-comers, the sponsor may want to narrow the enrollment criteria and enrich the clinical trial with likely responders (or similarly exclude likely adverse responders). Using PGx data during a clinical trial can enable the sponsor to run a smaller trial by only targeting patients who are likely

¹⁵² See 21 C.F.R. §§ 312, 314, 601.

¹⁵³ See Lesko & Woodcock, *supra* note 73, at 766.

¹⁵⁴ FDA, GUIDANCE ON PHARMACOGENOMIC DATA SUBMISSIONS, *supra* note 141, at 7.

¹⁵⁵ *Id.* at 14-15.

¹⁵⁶ *Id.* at 5, 8-9 (interpreting 21 C.F.R. § 312.23(a)); see also 21 C.F.R. §§ 312.30(b), 312.31; Prebula, *supra* note 130, at 15.

¹⁵⁷ FDA, GUIDANCE ON PHARMACOGENOMIC DATA SUBMISSIONS, *supra* note 141, at 9.

¹⁵⁸ *Id.* at 6, 10-11 (interpreting 21 C.F.R. §§ 314.50, 601.2); see also Prebula, *supra* note 130, at 15. Basically, PGx data must be submitted with the NDA unless it concerns an exploratory biomarker.

¹⁵⁹ FDA, GUIDANCE ON PHARMACOGENOMIC DATA SUBMISSIONS, *supra* note 141, at 10-11 (interpreting 21 C.F.R. § 314.50).

¹⁶⁰ *Id.* (interpreting 21 C.F.R. § 314.50).

¹⁶¹ *Id.* at 11 (interpreting 21 C.F.R. § 314.81(b)(2)). This data must be submitted in the NDA holder's annual report as synopses or abbreviated reports. *Id.*

¹⁶² HUTT ET AL., *supra* note 12, at 633.

to benefit from the drug based on their genotype.¹⁶³ Thus, pharmacogenomics may be a means for applying more precise and effective inclusion and exclusion criteria in clinical trials, resulting in human studies that are safer and more efficient.¹⁶⁴

But enriching patient populations in clinical trials is not always permissible. FDA will clearly allow stratification based on a valid biomarker.¹⁶⁵ Similarly, FDA officials have stated that it would be unacceptable to use an exploratory biomarker as a criterion for excluding patients from a clinical trial.¹⁶⁶ It is not clear, however, whether a probable valid biomarker could be used to stratify patients *a priori*, though the same FDA officials suggested that excluding patients based on a probable valid biomarker would not be acceptable.¹⁶⁷ Consequently, since sponsors are unlikely to validate a biomarker prior to Phase III trials, it is effectively impossible to stratify patient populations based on a PGx biomarker discovered during early-stage trials. However, if a sponsor gathers PGx data during Phase I and II trials and discovers a correlation between a genotype and a drug response, this probable valid biomarker can be validated in Phase III trials. But it is likely that the trial will still have to be performed on all-comers.¹⁶⁸

Post Hoc Subset Analysis Based on Pharmacogenomic Data

In general, FDA requires clinical trials to be prospective studies, designed to confirm a scientific hypothesis.¹⁶⁹ However, if PGx data is gathered during a clinical trial, analysis of that data after the trial is complete may show a correlation between a drug response and a genotype in a subset of patients. Particularly if this correlation is discovered during a failed Phase III trial, a sponsor may want to use the PGx data to rescue the drug by limiting the drug labeling to a patient subset.

¹⁶³ Roses, *supra* note 3, at 862.

¹⁶⁴ See PRICEWATERHOUSECOOPERS, PERSONALIZED MEDICINE: THE EMERGING PHARMACOGENOMICS REVOLUTION (2005), available at <http://www.pwc.com/techforecast/pdfs/pharmaco-wb-x.pdf>; Sadee, W., *Pharmacogenomics: The Implementation Phase*, AAPS PHARMSci, Vol. 4, Issue 2, at E5 (2002).

¹⁶⁵ For example, this was done during the Herceptin Phase III trials. Lesko et al., *supra* note 6, at 356 (“A well-known example of enrichment is the enrollment of women with breast cancer who overexpress the HER-2 protein in clinical trials of [Herceptin].”). In that case, the sponsor knew that likely responders would have HER2-overexpression. However, like Herceptin, if patients are included or excluded from a clinical trial based upon a PGx biomarker, that PGx data must be included in the drug labeling, and the label will probably be restricted to a subset of patients. See discussion *infra* Part 3.5.

¹⁶⁶ Lesko et al., *supra* note 6, at 350 (“[T]here is a need to have some confirmation and/or validation before using pharmacogenetics and pharmacogenomics as inclusion/exclusion criteria or for stratification.”). Notwithstanding FDA’s guidance, sponsors in fact use exploratory biomarkers as a criterion for stratifying patients in clinical trials. Letter from Peter Barton Hutt, Senior Counsel, Covington & Burling LLP, to author (Jan. 10, 2009) (on file with author).

¹⁶⁷ Lesko et al., *supra* note 6, at 350 (“Even after one or two Phase I studies show that a variant in the drug target may affect drug response, there may not be enough information to exclude a population from Phase II studies, unless more is understood about the functional consequences of the genetic variants.”).

¹⁶⁸ FDA, however, has been inconsistent on this point. The agency has allowed unvalidated biomarkers to be used for patient stratification, though it is not clear when this practice is acceptable. Interview with Peter Barton Hutt, *supra* note 18.

¹⁶⁹ FDA, International Conference on Harmonization; Guidance on General Considerations for Clinical Trials, 62 Fed. Reg. 66,113, 66,118 (Dec. 17, 1997) [hereinafter FDA, Guidance on Clinical Trials] (“The results of a clinical trial should be analyzed in accordance with the plan prospectively stated in the protocol”); see also Mandrekars, S.J. et al., *Clinical Trial Designs for Prospective Validation of Biomarkers*, 5 AM. J. PHARMACOGENOMICS 317 (2005); Evans, Barbara J., *What Will it Take to Reap the Clinical Benefits of Pharmacogenomics?*, 61 FOOD & DRUG L.J. 753, 759 (2006). For example, the traditional clinical trial is designed to confirm that a drug candidate is safe and effective in the general population, where efficacy is determined by measuring predefined clinical endpoints.

But "FDA discourages such practices," and one agency official has stated that findings from retrospective studies are often full of "spurious and false" claims.¹⁷⁰ Accordingly, FDA officials have unambiguously stated that any PGx biomarker discovered during clinical trials must be validated with a prospective clinical trial if the sponsor intends to include the biomarker in the drug label.¹⁷¹ Relying on PGx biomarkers discovered during *post hoc* analysis is not permitted.¹⁷²

In order to use PGx data to rescue a drug that previously failed in clinical trials, the sponsor must run a new trial to confirm the hypothetical relationship between the unvalidated biomarker and clinical outcome discovered during the *post hoc* analysis.¹⁷³ FDA officials, however, have suggested that a subsequent confirmatory trial might not be necessary if there are "strong mechanistic bases for the correlation" between the PGx test and the safety or efficacy results observed.¹⁷⁴ This likely means that additional trials are not necessary for valid biomarkers, but they are necessary for exploratory and probable valid biomarkers. Consequently, since sponsors cannot rescue drugs with *post hoc* PGx data of unvalidated biomarkers, sponsors should begin gathering PGx data related to safety and efficacy in early-stage clinical trials.¹⁷⁵ If they can validate a biomarker by the end of Phase II trials, they can properly incorporate the biomarker into their pivotal Phase III trial and rescue the drug if it fails to demonstrate sufficient safety and efficacy in the general population.¹⁷⁶

Though FDA normally rejects *post hoc* analysis, the agency's position may be shifting. In December 2008, FDA's Oncologic Drug Advisory Committee agreed that Amgen and ImClone could use retrospective studies to support PGx data on the labels of Vectibix and Erbitux, respectively.¹⁷⁷ The committee also suggested that it would generally accept retrospective studies to validate pharmacogenomic biomarkers.¹⁷⁸ The committee would allow a sponsor to use retrospective studies to validate a biomarker where it had data from two well-conducted studies with similar endpoints, large patient populations, replicated outcomes, and high rates

¹⁷⁰ Young, Donna, *FDA Panel Wrestles with Biomarker Label Concerns*, BIO WORLD TODAY (Dec. 17, 2008) (quoting Richard Pazdur, Director, FDA Office of Drug Products) (internal quotation marks omitted), available at http://www.bioworld.com/servlet/com.accumedia.web.Dispatcher?forceid=49565&next=bioworldtoday_article&search=1&prodID=4&htsid=8&htmax=178.

¹⁷¹ Woodcock, *supra* note 5, at 100-101 ("[A]ny initial finding in a subset of people, no matter how exciting, must be approached as a hypothesis-generating event that must be confirmed."); Lesko et al., *supra* note 6, at 354 ("[T]he confirmation of identified genetic associations is mandatory if pharmacogenetic biomarkers are to be included in drug labeling.").

¹⁷² FDA, Guidance on Clinical Trials, *supra* note 169; see also Lesko et al., *supra* note 6, at 356 ("Associations between genotypes and clinical outcomes can also be explored retrospectively . . . but these are mainly exploratory and would need confirmation in a clinical trial prospectively."); Kulynych, Jennifer, *Will FDA Relinquish the "Gold Standard" for New Drug Approval? Redefining "Substantial Evidence" in the FDA Modernization Act of 1997*, 54 FOOD & DRUG L.J. 127, 141-142 (1999) (discussing FDA's reluctance to using "post hoc subgroup analysis").

¹⁷³ See Emilien et al., *supra* note 69, at 394-395; Binzak, *supra* note 4, at 113.

¹⁷⁴ Amur, Shashi et al., *Integration and Use of Biomarkers in Drug Development, Regulator and Clinical Practice*, 2 BIOMARKERS MED. 305, 310 (2008); see also FDA, DRUG-DIAGNOSTIC CO-DEVELOPMENT CONCEPT PAPER 18 (2005) [hereinafter FDA, DRUG-DIAGNOSTIC CO-DEVELOPMENT] (Stating that in clinical trials for diagnostic assays, "where the analyte is stable and where collection bias . . . can be carefully characterized and addressed, prospectively designed retrospective clinical utility studies may be possible."), available at <http://www.fda.gov/cder/genomics/pharmacoconceptfn.pdf>.

¹⁷⁵ Amur, *supra* note 174, at 309.

¹⁷⁶ See *id.*; Roses, *supra* note 3, at 862.

¹⁷⁷ Smith, Lauren, *Committee OKs Retrospective Studies, But With Caveats*, PINK SHEET (Dec. 22, 2008), at 27, 27.

¹⁷⁸ *Id.*

of tissue ascertainment.¹⁷⁹ However, a prospective study would be needed if the results cannot be replicated between two studies.¹⁸⁰ The committee indicated that, although FDA was still wary of retrospective studies, it recognized that there are legitimate reasons why PGx biomarkers cannot be studied prospectively.¹⁸¹ Following the advice of the committee, in July 2009, FDA approved labeling changes for Vectibix and Erbitux that reflected the sponsors' *post hoc* studies.¹⁸² The labels now include PGx data indicating that patients with a certain gene mutation should not take the drugs.¹⁸³ While the decision of the Oncologic Drug Advisory Committee and FDA in this case is not binding on future decisions, the acceptance of retrospective studies in this case is a dramatic shift from FDA's prior policy. The decision indicates that the agency may allow *post hoc* analysis in the future, which would create a pathway for sponsors to use pharmacogenomics to rescue drugs that fail "all-comers" trials.

3.4. *Approval of a Companion Diagnostic Test*

Co-Development of the Pharmacogenomic Diagnostic Test

If the labeling of a drug will refer to a PGx test, FDA "recommends" co-development of the drug and the companion PGx test.¹⁸⁴ Co-development means simultaneous development of the drug candidate and a companion diagnostic test, where unvalidated biomarkers identified by the test are used in the drug study.¹⁸⁵ But this recommendation is effectively a requirement, since FDA also states that it "would be unable to approve a drug for which the risk or benefit was predicated on a pharmacogenomic test that was unavailable."¹⁸⁶

FDA has traditionally reviewed drugs and devices in isolation.¹⁸⁷ But the need to cross-label PGx drugs and companion diagnostics requires coordinated review by the respective FDA review centers. However, developing a drug and diagnostic concurrently and obtaining coordinated review is not a simple task.¹⁸⁸ Where the sponsor intends to include pharmacogenomic data or a reference to a diagnostic test in the drug's labeling, FDA has provided the following idealized timeline for how a drug and companion diagnostic could be developed concurrently:¹⁸⁹

¹⁷⁹ *Id.*

¹⁸⁰ *Id.* at 28.

¹⁸¹ *See id.* at 27.

¹⁸² Wang, Shirley S., *Erbitux, Vectibix Label Change Approved for KRAS Gene*, WALL ST. J. HEALTH BLOG (July 20, 2009), <http://blogs.wsj.com/health/2009/07/20/erbitux-vectibix-label-change-approved-for-kras-gene/>.

¹⁸³ *Id.*

¹⁸⁴ This assumes that the PGx test is not already available (e.g., using a commercially available gene chip from a third party). *See* FDA, GUIDANCE ON PHARMACOGENOMIC DATA SUBMISSIONS, *supra* note 141, at 6.

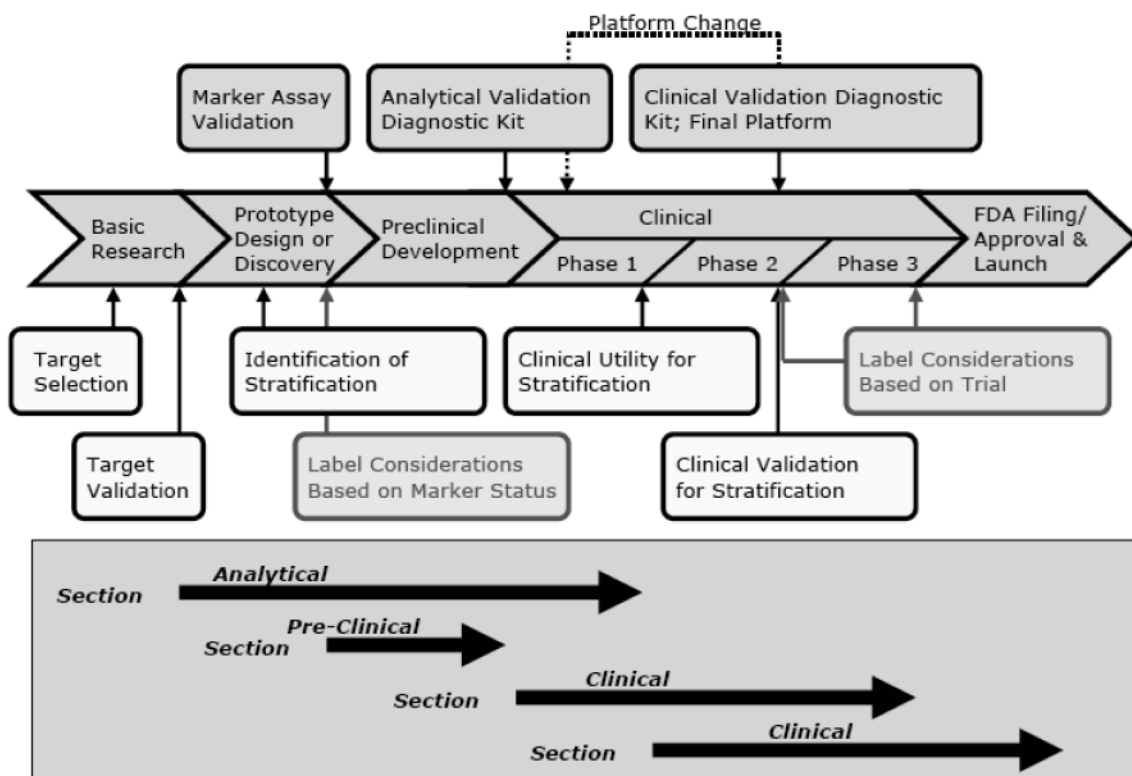
¹⁸⁵ Prebula, *supra* note 130, at 15.

¹⁸⁶ FDA, GUIDANCE ON PHARMACOGENOMIC DATA SUBMISSIONS, *supra* note 141, at 15.

¹⁸⁷ Gibbs, *supra* note 113, at 8; Dunn, *supra* note 7.

¹⁸⁸ Gibbs, *supra* note 113, at 8 ("A company that intends to commercialize an assay for personalized medicine would be well-advised to meet with the Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD) well before beginning clinical studies.").

¹⁸⁹ FDA, DRUG-DIAGNOSTIC CO-DEVELOPMENT, *supra* note 174, at 3.



This idealized timeline suggests that the sponsor study and analytically validate a new diagnostic in parallel with early drug development (Phase I or II trials), allowing for clinical utility and validation during late Phase II or Phase III studies.¹⁹⁰ This approach, however, is unrealistic since PGx biomarkers are often not identified until late-stage clinical trials, and the diagnostic assay will likely be modified in response.¹⁹¹ In general, any PGx data gathered through Phase I will be considered exploratory, and therefore not confirmatory.¹⁹² In the best case scenario, a biomarker could be validated as early as Phase II trials. As discussed previously, however, it is more likely that a PGx biomarker will not be discovered until Phase III trials.¹⁹³ In this case, the final test configuration of the companion diagnostic may not even be available after the Phase III trial is completed.¹⁹⁴ This means that it normally would be impossible to develop a drug and a companion diagnostic

¹⁹⁰ FDA, GUIDANCE ON PHARMACOGENOMIC DATA SUBMISSIONS, *supra* note 141, at 6, 15. For definitions of analytical validity, clinical utility, and clinical validity, see *supra* notes 128-129.

¹⁹¹ See Prebula, *supra* note 130, at 16; see also SACGHS PHARMACOGENOMICS REPORT, *supra* note 3, at 34 (“Not only is it difficult to generate evidence of clinical validity and clinical utility for a PGx test, but also there is little motivation to do so and considerable confusion about what constitutes a demonstration of clinical validity and clinical utility. FDA, for example, does not evaluate clinical validity or clinical utility per se but rather assesses the safety and effectiveness of a device. These parameters generally are tied to an assessment of the analytical and clinical performance of the device.”).

¹⁹² See Lesko et al., *supra* note 6, at 349.

¹⁹³ See *id.* at 352. The most realistic best case scenario is that the PGx biomarker is discovered during Phase II, and the Phase III trial is used to confirm PGx data for supporting safety, efficacy, and labeling of the drug. *Id.*

¹⁹⁴ Prebula, *supra* note 130, at 16.

concurrently.¹⁹⁵ Consequently, FDA officials have stated that the agency may allow the use of retrospective analysis for clinical validation of IVDs,¹⁹⁶ though it is not clear if such analysis is always permitted.¹⁹⁷

While parallel development is clearly optimal in theory, it is difficult to execute in practice, and very few pioneers have successfully coordinated the development of a drug product and its companion diagnostic.¹⁹⁸ Because the current guidelines are focused on parallel development, they do not adequately address the issues facing most sponsors. Consequently, FDA needs to provide further guidance for the more likely scenario where development of a companion diagnostic does not begin until late in the drug development process.¹⁹⁹

Use of In Vitro Diagnostics versus Laboratory-Developed Tests

The PGx companion diagnostic test can be either a separately marketed in vitro diagnostic test kit or a laboratory-developed test conducted by a professional laboratory service.²⁰⁰ The major problem for manufacturers of PGx tests is in receiving clear regulatory guidance, since “[t]here is no regulatory category called ‘personalized medicine.’”²⁰¹

Traditionally, FDA has not subjected genetic tests to much regulatory scrutiny. In vitro diagnostic devices have traditionally been classified as Class I-exempt, subject only to general controls and exempt from the 510(k) premarket notification requirement.²⁰² Similarly, laboratory-developed tests have not been regulated by FDA at all, and are instead regulated only by the CMS. However, recently issued

¹⁹⁵ See SACGHS PHARMACOGENOMICS REPORT, *supra* note 3, at 26. Of course, if the drug can be approved for the general population, it is always possible to later modify a drug label to include information about a subsequently developed PGx diagnostic test.

¹⁹⁶ Prebula, *supra* note 130, at 16 (“FDA has acknowledged the agency will accept as supportive data for assay approval, use of retrospective samples that are collected during the drug trial and then later used for the validation of a biomarker.”) (citing Steve Gutman, Director, FDA Office of In Vitro Diagnostic Evaluation and Safety, 2007 American Association of Clinical Chemistry Annual Meeting).

¹⁹⁷ Interview with Peter Barton Hutt, *supra* note 18.

¹⁹⁸ See Prebula, *supra* note 130, at 16. Furthermore, the difficulties of co-development are exacerbated by cultural and strategic differences between pharmaceutical and medical device manufacturers. See Keeling & Roth, *supra* note 63.

¹⁹⁹ Also note that where a PGx-based drug is distributed with an IVD assay, FDA may regulate them as a “combination product.” FDA defines a combination product as: “A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose” 21 C.F.R. § 3.2(e)(3). FDA established the Office of Combination Products (OCP) to address the challenge of reviewing products that are neither pure drugs nor pure devices. Bawa, Raj et al., *Nanopharmaceuticals: Patenting Issues and FDA Regulatory Challenges*, SCITECH LAWYER (Fall 2008), at 10, 11. The agency uses the “primary mode of action” principle to assign a combination product to the appropriate center. Primary mode of action is defined as “the single mode of action of a combination product that provides the most important therapeutic action of the combination product” and mode of action is defined as “the means by which a product achieves its intended therapeutic effect or action.” If the primary mode of action of a combination product is that of a drug, then CDER has primary jurisdiction, and if the primary mode of action is that of a device, CDRH has primary jurisdiction. See Safe Medical Devices Act of 1990, Pub. L. No. 101-629, § 16, 104 Stat. 4511 (codified at 21 U.S.C. § 353(g)); 70 Fed. Reg. 49,848 (Aug. 25, 2005); Assignment of Agency Component for Review of Premarket Applications, 56 Fed. Reg. 58,754, 58,574 (Nov. 21 1991) (codified at 21 C.F.R. pt. 3); Sasjack, *supra* note 22, at 23.

²⁰⁰ For example, Herceptin has both an IVD and a LDT companion diagnostic test that can be used to test for HER2 over-expression.

²⁰¹ Gibbs, *supra* note 113, at 8.

²⁰² See SACGHS PHARMACOGENOMICS REPORT, *supra* note 3, at 53.

guidance documents from FDA's Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD) suggest that stricter regulation will be used in the future.

In one guidance document, OIVD indicated that diagnostics that use analyte-specific reagents²⁰³ will not be exempt from the 510(k) premarket notification requirements if they are promoted with specific analytical or clinical performance claims, instructions for use in a particular test, or instructions for validation of a particular test using the analyte-specific reagent.²⁰⁴

In a separate draft guidance document, OIVD indicated that certain LDTs that combine values of multiple variables in an algorithm to generate a single result to guide diagnosis and treatment will be actively regulated by FDA as medical devices and classified according to their intended use and the level of control needed to ensure their safety and effectiveness.²⁰⁵ The guidance predicts that most of these diagnostic assays would be Class II or III devices.²⁰⁶ In December 2008, Genentech filed a citizen petition with FDA that effectively endorsed FDA's draft guidance and urged the agency to directly regulate all LDTs as Class II or III devices.²⁰⁷

Because these guidance documents conflict with FDA's prior practice, it is still not clear how PGx companion diagnostics will be regulated.²⁰⁸ Consequently, FDA should go beyond these guidance documents and issue new regulations that clarify its position in this area.²⁰⁹

3.5. Labeling Requirements

Depending on how PGx data was used during clinical trials, the drug labeling may be limited to various degrees. FDA categorizes PGx-based drugs by how the approved drug labeling references the companion diagnostic test.²¹⁰ The four broad categories are: 1) "test required," 2) "test recommended," (2a) "test for at risk populations," and 3) test for "information only."²¹¹ Currently, FDA has identi-

²⁰³ Most genetic tests use analyte-specific reagents (ASRs), such as antibodies or nucleic acid sequences, to identify and quantify substances in a patient's biological sample. S.I., Gutman, FDA's Role in the Regulation of In Vitro Diagnostic, Presentation to FDA, CDRH, Office of In Vitro Device Evaluation & Safety (May 10, 2003), available at <http://www.fda.gov/cdrh/oivd/presentations/051003-gutman-1.html>.

²⁰⁴ FDA, GUIDANCE FOR INDUSTRY AND FDA STAFF: COMMERCIALY DISTRIBUTED ANALYTE SPECIFIC REAGENTS (ASRS): FREQUENTLY ASKED QUESTIONS (2007), available at <http://www.fda.gov/cdrh/oivd/guidance/1590.pdf>.

²⁰⁵ FDA, CDRH, OFFICE OF IN VITRO DIAGNOSTIC DEVICE EVALUATION & SAFETY, DRAFT GUIDANCE FOR INDUSTRY, CLINICAL LABORATORIES, AND FDA STAFF: IN VITRO DIAGNOSTIC MULTIVARIATE INDEX ASSAYS (2007), available at <http://www.fda.gov/cdrh/oivd/guidance/1610.pdf>.

²⁰⁶ *Id.* at 8.

²⁰⁷ See Petition from Genentech, Inc. to FDA, Citizen Petition No. 2008-P-0638-0001 (Dec. 5, 2008), available at <http://www.regulations.gov/fdmspublic/component/main?main=DocumentDetail&o=09000064807d4a7e>.

²⁰⁸ See Jeffrey Gibbs, *Regulatory Pathways for Molecular Dx*, GENETIC ENGINEERING & BIOTECHNOLOGY NEWS, (Aug. 1, 2008).

²⁰⁹ See Evans, B.J., *Distinguishing Product and Practice Regulation in Personalized Medicine*, 81 CLINICAL PHARMACOLOGY & THERAPEUTICS 288 (2007); see also SACGHS PHARMACOGENOMICS REPORT, *supra* note 3, at 27.

²¹⁰ See FDA, Table of Valid Genomic Biomarkers 2008, *supra* note 8.

²¹¹ Prebula, *supra* note 130, at 15; FDA, Table of Valid Genomic Biomarkers 2008, *supra* note 8. Note that older versions of the Table of Valid Genomic Biomarkers used these four categories, however FDA has dropped this information from recent versions of the table. See FDA, Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels (Aug. 18, 2009) [hereinafter FDA, Table of Valid Genomic Biomarkers 2009], <http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm> (last visited Jan. 1, 2010).

fied at least 29 drugs with PGx information in their labels.²¹² Of these, only four drugs fall within Category 1, where the labeling indicates that a PGx test must be administered before the drug can be prescribed.²¹³

The labeling must reference the PGx test if patients in clinical trials were: 1) tested for a drug metabolism genotype and dosed according to their test results; 2) enrolled in an efficacy trial because their genotype indicated they would be likely responders; or 3) excluded from the trial because their genotype indicated they would be at high risk for an adverse event.²¹⁴ In these situations, the labeling must specify that dosage, safety or effectiveness is contingent on the performance of a PGx test (i.e., Category 1, “test required”).²¹⁵ This type of labeling is very restrictive, and may limit the PGx drug to a small patient subpopulation.²¹⁶ If PGx data was generated during clinical trials and the biomarker is validated, but patients were not stratified based on a PGx test, the labeling will likely only recommend that a PGx test be performed (Category 2 or 2a). In this case, the labeling is only moderately restricted – the drug is technically still available to the general population. Finally, where PGx data only relates to an unvalidated biomarker, it may be included in the drug labeling on an informational basis (Category 3).²¹⁷ Here, the labeling is not restricted, and the drug may be prescribed without referencing a PGx test.

Where a sponsor discovers a correlation between a PGx test and adverse events in patients, FDA suggests that a sponsor should have “great interest” in exploring this correlation.²¹⁸ However, discovery of such a correlation does not bind the sponsor, and, regardless of what pharmacogenomic data is submitted, the sponsor may elect to seek marketing approval for the general patient population rather than for a sub-population of best responders identified by the data.²¹⁹ In such cases, FDA will evaluate the safety, efficacy, and risk-benefit of the drug on the general population, and will not use PGx information that was submitted voluntarily for making decisions regarding INDs or NDAs.²²⁰

4. Using Pharmacogenomics to “Rescue” Drugs

Pharmacogenomics may provide an avenue for “rescuing” drugs that were found ineffective and/or unsafe during clinical trials.²²¹ These drugs can be further developed by narrowing the trial population from the general patient population to a subset of the population that responded well to the drug.²²² Positive responders

²¹² FDA, Table of Valid Genomic Biomarkers 2009, *supra* note 211.

²¹³ *Id.*

²¹⁴ FDA, GUIDANCE ON PHARMACOGENOMIC DATA SUBMISSION, *supra* note 141, at 6.

²¹⁵ See SACGHS PHARMACOGENOMICS REPORT, *supra* note 3, at 75.

²¹⁶ *Id.* (citing FDA, DRAFT GUIDANCE FOR INDUSTRY & FDA STAFF: PHARMACOGENETIC TESTS & GENETIC TESTS FOR HERITABLE MARKERS (2006), available at <http://www.fda.gov/cdrh/oivd/guidance/1549.pdf>).

²¹⁷ See *id.*

²¹⁸ FDA, GUIDANCE ON PHARMACOGENOMIC DATA SUBMISSIONS, *supra* note 141, at 15.

²¹⁹ *Id.*

²²⁰ *Id.* at 14-15.

²²¹ While it is beyond the scope of this article to discuss this point in detail, pharmacogenomic data could also be used to rescue drugs that have been withdrawn from the market due to serious adverse reactions. See SACGHS PHARMACOGENOMICS REPORT, *supra* note 3, at 26. Drugs withdrawn for safety issues are unlikely to be reintroduced unless PGx data show improvements in the risk-benefit ratio. See Shah, R.R., *Can Pharmacogenetics Help Rescue Drugs Withdrawn From the Market?*, 7 PHARMACOGENOMICS 889 (2006).

²²² Shah, J., *Economic and Regulatory Considerations in Pharmacogenomics for Drug Licensing and Healthcare*, 21 NATURE BIOTECHNOLOGY 747 (2003).

and/or adverse responders can be identified by doing a *post hoc* analysis of the clinical trial data, and subsequent genotyping of patients could uncover a biomarker that helps predict response.²²³ The labeling for the drug could then be limited to patients with the appropriate genotype.²²⁴

This article assumes that sponsors will resort to using pharmacogenomic data only in situations where an investigational drug has failed to demonstrate an adequate risk-benefit profile in the general patient population during initial clinical trials and the sponsor wants to use the PGx data to limit the target population and rescue the drug. As described above, however, economic and regulatory issues deter sponsors from using PGx data this way. Unless the biomarker is already validated, current regulations would require the sponsor to conduct an additional clinical trial to validate the biomarker and limit the drug labeling to responders.²²⁵ But a single clinical trial can cost up to \$500 million, and sponsors are unlikely to pay this amount for another chance at FDA approval when approval is not guaranteed.²²⁶ Parts 4.1 and 4.2, *infra*, propose two solutions to this problem.

4.1. *Conditionally Approving PGx-based Drugs and Requiring Post-Approval Phase IV Trials*

FDA can require a sponsor to commit to additional post-approval nonclinical or clinical studies as a condition of NDA approval.²²⁷ These so-called Phase IV studies are undertaken after marketing approval is granted to assure safety and/or efficacy.²²⁸ FDA can require post-market studies to assess a known serious risk related to the drug or to “identify an unexpected serious risk when available data indicates the potential for a serious risk.”²²⁹ If the sponsor fails to comply with the post-marketing requirement, FDA can deem the drug misbranded and subject the drug to seizure and condemnation.²³⁰

Required Phase IV studies could be used to rescue PGx drugs that fail to demonstrate sufficient safety and efficacy in the general population during Phase III trials. If Phase III trials conclude and the sponsor must rely on data from a probably valid PGx biomarker to show safety and/or efficacy, this article proposes that FDA “conditionally approve” the drug with a limited labeling and a requirement for a Phase IV study to validate the biomarker.²³¹ If the probable valid biomarker is being used to identify likely responders, then the drug labeling would be limited to this subgroup of patients. Similarly, if the biomarker is being used to identify likely adverse responders, then the drug labeling would specifically exclude this subgroup. In both cases, patients would be required to take the companion diagnostic test to determine whether they should take the drug.²³²

²²³ SACGHS PHARMACOGENOMICS REPORT, *supra* note 3, at 28.

²²⁴ See Lesko et al., *supra* note 6, at 351.

²²⁵ See *supra* Part 3.3.

²²⁶ See Li, *supra* note 78.

²²⁷ See 21 U.S.C. § 355(o); see also HUTT ET AL., *supra* note 12, at 727.

²²⁸ See HUTT ET AL., *supra* note 12, at 727.

²²⁹ See 21 U.S.C. § 355(o)(3); see also Schanz, Stephen J., *Pharmaceutical Postmarket Review: Fact of Fiction*, 62 FOOD & DRUG L.J. 493, 494 (2007).

²³⁰ 21 U.S.C. §§ 334, 352(a), 352(z).

²³¹ See also Roses, Allen D., *Pharmacogenetics and Future Drug Development and Delivery*, 355 LANCET 1358, 1360 (2000) (proposing that “if clinical trials were to enroll only those patients with pharmacogenetics efficacy profiles, regulatory authorities could consider a significantly enhanced surveillance system with provisional marketing approval for patients with ‘efficacy’ pharmacogenetic profiles”).

²³² This would make it a Category 1 PGx drug. See *supra* text accompanying note 211.

Under this proposed conditional approval process, if the sponsor's biomarker-response hypothesis is validated during the Phase IV trial, FDA would allow the drug to stay on the market. The sponsor would then submit a supplemental NDA to update the labeling of the drug to reflect any changes in the indication for the drug required by the Phase IV data.²³³ However, if the Phase IV trial fails to validate the biomarker, FDA would immediately deem the drug misbranded and require the sponsor to cease manufacturing and recall the drug from the market.

"Conditional approval" could be effected by two currently existing regulatory schemes. Under the Food and Drug Administration Amendments of 2007 (FDAAA),²³⁴ the agency can require the sponsor to commit to conducting a Phase IV study as a condition of NDA approval.²³⁵ Alternatively, under the regulations for "Accelerated Approval," FDA can approve an NDA on the basis of an unvalidated "surrogate endpoint" (i.e., an unvalidated biomarker) that likely predicts clinical benefit.²³⁶ The accelerated approval process is only available to drugs for "serious or life-threatening illnesses."²³⁷ Under either scheme, if the Phase IV study fails, FDA could withdraw NDA approval on the grounds that the drug is unsafe or ineffective.²³⁸

Conditional approval of a PGx drug based on an unvalidated biomarker presents the risk that patients may receive a drug that is harmful to them. The risk may be heightened because of the false security created by taking a PGx test before receiving the drug. Consequently, conditional approval may not be acceptable for drugs that fail Phase III trials due to safety reasons. Relying on an unvalidated biomarker to ensure that patients are not given a drug that may cause a severe adverse event is probably unacceptable from a public health standpoint.²³⁹ However, if the drug failed Phase III trials because it was only effective in a limited subpopulation, conditional approval does not pose as significant a threat to public health. In this case, the possible harm to the patient is limited to simply receiving an ineffective treatment, which is arguably insignificant considering the large non-responder populations of most drugs.

Another factor to consider when making conditional approvals is the presence of other therapies for treating the target disease state. If the disease state currently has no treatment, it seems clear that the benefit outweighs the risk of conditionally approving a drug based on an unvalidated biomarker. However, it may be unacceptable to conditionally approve a drug where there is already an effective therapy on the market. While there is no requirement that new therapies must be more safe and effective than existing therapies,²⁴⁰ in this scenario the risk of administering a potentially ineffective or unsafe drug is difficult to justify. But the risk may be acceptable if the PGx data shows the drug is effective on patients that do not respond to currently marketed therapies. Similarly, if the PGx drug would provide a sub-

²³³ See 21 C.F.R. § 314.70 (proposed changes to the terms and conditions specified in an approved NDA must be submitted in a supplemental NDA and approved by FDA).

²³⁴ Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-185, 121 Stat. 823 (codified as amended in scattered sections of 21 U.S.C. and 42 U.S.C.).

²³⁵ See *id.* § 901, 21 U.S.C. § 355(o).

²³⁶ See 21 C.F.R. § 314.510; see also HUTT ET AL., *supra* note 12, at 710. A "surrogate endpoint" is a clinical endpoint based on something other than morbidity. See *id.*

²³⁷ 21 C.F.R. § 314.500.

²³⁸ See 21 U.S.C. § 355(e); 21 C.F.R. § 314.530. The sponsor, however, could object and force the agency to hold a hearing before it withdraws NDA approval. See 21 U.S.C. § 371(e); 21 C.F.R. § 314.530.

²³⁹ See, e.g., Lesko et al., *supra* note 6, at 355 ("Use of genetic biomarkers to exclude individuals or populations at risk for adverse events will require rigorously validated genetic associations, especially for serious toxicity.").

²⁴⁰ See *E.R. Squibb & Sons, Inc. v. Bowen*, 870 F.2d 678 (D.C. Cir. 1989); see also HUTT ET AL., *supra* note 12, at 685-691.

stantial improvement in treatment (i.e., substantially increased safety or efficacy), even if only in a limited subgroup, it might be very desirable to allow conditional approval notwithstanding the availability of alternative therapies.

4.2. *Using the Orphan Drug Act to Cover PGx-based Drugs*

A pharmaceutical company would not normally develop a drug for a disease that affects a small population because it would be difficult to recoup its investment. However, the Orphan Drug Act of 1983 encourages pharmaceutical companies to develop drugs targeting rare diseases.²⁴¹ The Orphan Drug Act defines a rare disease as any disease that affects fewer than 200,000 individuals in the United States.²⁴² The Act encourages sponsors to develop so-called "orphan drugs" by providing multiple incentives, including seven years of exclusive marketing rights, tax credits for certain clinical testing expenses, research grants, FDA user fee waivers, and occasionally expedited FDA review for market clearance or approval.²⁴³ FDA also often provides additional assistance to sponsors of orphan drugs in developing and executing clinical trials, helping to bring the orphan drug to market as quickly as possible.²⁴⁴ This assistance means orphan drugs often get to market one to two years more quickly than non-orphan drugs.²⁴⁵ Finally, FDA may accept a lower quantity and quality of evidence to support the approval of an orphan drug, reflecting the agency's understanding that the patient population available for studying the drug is limited.²⁴⁶

A PGx-based drug that can only be used to treat a small fraction of a large patient population is similar to an orphan drug. If PGx labeling reduces the target population to less than 200,000 Americans, that drug could theoretically qualify as an orphan drug.²⁴⁷ The Act will cover a drug used to treat a "rare disease or condition," which the Act defines as "any disease or condition which affects less than 200,000 persons in the United States."²⁴⁸ It is not clear, however, whether the Act applies when a PGx-based drug is used to treat a disease state that affects over 200,000, but the effective patient population for the drug is actually less than 200,000 because the labeling limits the

²⁴¹ Orphan Drug Act, Pub. L. No. 97-414, 96 Stat. 2049 (1983) (codified as amended at 21 U.S.C. §§ 360aa-360ee).

²⁴² 21 U.S.C. § 360bb(a)(2). The Act also defines a rare disease as any disease where the sponsor has "no reasonable expectation" of recovering the costs of developing and making the drug "from sales of the drug in the United States." *Id.* However, this path to orphan drug status is almost never used because of the onerous documentation FDA requires to demonstrate the sponsor's inability to recover costs. See Karst, Kurt R., *The Rarely Used "Cost Recovery" Path to Orphan Drug Designation and Approval*, FDA LAW BLOG (Feb. 1, 2009), http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2009/02/the-rarely-used-cost-recovery-path-to-orphan-drug-designation-and-approval.html.

²⁴³ Orphan Drug Act, Pub. L. No. 97-414, 96 Stat. 2049 (1983) (codified as amended at 21 U.S.C. §§ 360aa-360ee).

²⁴⁴ See Haffner, Marlene E., *Orphan Products—Ten Years Later and Then Some*, 49 FOOD DRUG COSM. L.J. 593, 601 (1994) ("For the 70 drugs approved by the FDA in 1993, approval time averaged 33.1 months; the approval time for orphan drugs in that year averaged 12.8 months.").

²⁴⁵ See Haffner, Marlene E. & Kelsey, John V., *Evaluation of Orphan Products by the U.S. Food and Drug Administration*, 8 INT'L J. TECH. ASSESSMENT HEALTH CARE 647, 647-648 (1992).

²⁴⁶ Karst, Kurt R., *FDA Orphan Drug Designations Are On the Rise*, FDA LAW BLOG (Feb. 17, 2009), http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2009/02/fda-orphan-drug-designations-are-on-the-rise.html; see also FDA, GUIDELINE FOR INDUSTRY: THE EXTENT OF POPULATION EXPOSURE TO ASSESS CLINICAL SAFETY: FOR DRUGS INTENDED FOR LONG-TERM TREATMENT OF NON-LIFE-THREATENING CONDITIONS 4 (1995) ("In some cases, a smaller number of patients may be acceptable, for example, where the intended treatment population is small."), available at <http://www.fda.gov/cder/guidance/iche1a.pdf>.

²⁴⁷ See Loughnot, David, Note & Comment, *Potential Interactions of the Orphan Drug Act and Pharmacogenomics: A Flood of Orphan Drugs and Abuses?*, 31 AM. J. L. & MED. 365, 366 (2005).

²⁴⁸ 21 U.S.C. § 360bb(a)(1)-(2).

drug to a specific subgroup of patients.²⁴⁹ FDA will grant orphan drug status when a drug is labeled to treat a “medically plausible subset” of the patient population for a common disease or condition.²⁵⁰ Medically plausible subsets generally include “groups of patients with special requirements or characteristics that distinguish them from the larger disease grouping.”²⁵¹ FDA may recognize a medically plausible subset if the patient subpopulation demonstrates “unique pharmacological or pharmacodynamic characteristics.”²⁵² But it is not apparent if FDA will always recognize a “medically plausible subset” in this situation because the agency has declined to define the term and applies the concept on a case-by-case basis.²⁵³

Because it is not clear whether the Orphan Drug Act will apply to PGx-based drugs, this article proposes either modifying the Act so that it expressly includes PGx-based drugs or creating a *sui generis* system based on the Act to provide economic incentives to develop personalized medicine. If the Orphan Drug Act is modified to specifically include “medically plausible subsets” defined by PGx data, it will probably only apply to Category 1 PGx drugs,²⁵⁴ where a diagnostic test must be administered before the drug can be prescribed. Other categories of PGx drugs should not qualify as patient subsets because they are still available to the general population. Alternatively, a *sui generis* system could apply to all categories of PGx drugs by providing incentives to any drug that includes PGx data in its labeling.²⁵⁵ A *sui generis* system need not be limited by the “rare disease or condition” and “medically plausible subset” requirements of the Orphan Drug Act. Such a system could function purely to incentivize sponsors to generate pharmacogenomic data during clinical trials.

The Orphan Drug Act has been very successful in incentivizing pioneers to develop drugs for diseases affecting small patient populations, with over 300 orphan drugs currently approved.²⁵⁶ Similarly, when a PGx drug would not normally be classified as

²⁴⁹ SACGHS PHARMACOGENOMICS REPORT, *supra* note 3, at 31. At least two practitioners believe that the statute would cover PGx-based drugs with limited labels that reduce the target populations to under 200,000. Interview with Peter Barton Hutt, *supra* note 18; Interview with Kurt R. Karst, Hyman, Phelps & McNamara, in Wash., D.C. (Feb. 25, 2009). Erbitux (cetuximab), a cancer therapy manufactured by ImClone, is currently, the only Category 1 PGx drug that also has orphan drug status. Compare FDA, CUMULATIVE LIST OF DESIGNATED APPROVED ORPHAN PRODUCTS, available at <http://www.fda.gov/orphan/designat/allap.rtf>, with FDA, Table of Valid Genomic Biomarkers 2008, *supra* note 8. Erbitux has two indications that include PGx data. In 2004, it was originally approved as a Category 1 PGx drug for treating colorectal cancer. Press Release, FDA, FDA Approves Erbitux for Colorectal Cancer (Feb. 12, 2004), available at <http://www.fda.gov/bbs/topics/NEWS/2004/NEW01024.html>. Then in 2006, it was also approved as a Category 3 drug for head and neck cancer. Press Release, ImClone Sys. Inc., FDA Approves Erbitux (cetuximab) for Treatment of Head and Neck Cancer (Mar. 1, 2006), available at <http://phx.corporate-ir.net/phoenix.zhtml?c=97689&p=irol-newsArticle&ID=824286>. It also gained orphan drug status for this second indication. FDA, CUMULATIVE LIST OF DESIGNATED APPROVED ORPHAN PRODUCTS, *supra*. However, because head and neck cancer only affects 40,000 Americans each year, ImClone did not need to rely on labeling limited by PGx data to get orphan drug status. See Press Release, ImClone Sys. Inc., *supra*.

²⁵⁰ 21 C.F.R. § 316.20(b)(6).

²⁵¹ E-mail from Kurt R. Karst, Hyman, Phelps & McNamara, to author (Feb. 25, 2009) (on file with author).

²⁵² *Id.*

²⁵³ See 57 Fed. Reg. 62,076, 62,081 (Dec. 29, 1992).

²⁵⁴ See *supra* text accompanying note 211.

²⁵⁵ A *sui generis* system could also use a tiered approach, providing varied benefits depending on the category the PGx-based drug falls into. For example, providing a greater benefit to sponsors of Category 1 PGx drugs than to sponsors of Category 2 or 2a drugs.

²⁵⁶ See FDA, CUMULATIVE LIST OF DESIGNATED APPROVED ORPHAN PRODUCTS, *supra* note 249; SACGHS PHARMACOGENOMICS REPORT, *supra* note 3, at 30; Milne, Christopher-Paul & Tait, Joyce, *Evolution along the Government-Governance Continuum: FDA's Orphan Products and Fast Track Programs as Exemplars of "What Works" for Innovation and Regulation*, 64 FOOD & DRUG L.J. 733, 740 (2009). Prior to the passage of the ODA, only thirty-four orphan drugs were on the market. See Maeder, Thomas, *The Orphan Drug Backlash*, SCI. AM., (May 2003), at 87.

an orphan product, pioneers might be willing to sacrifice sales to the general patient population if they could obtain the benefits of the Act. For unpatented drugs, the value of the seven years of marketing exclusivity granted by the Act would likely provide a sufficient economic incentive to seek approval with a PGx-based label.²⁵⁷ Similarly, for patented drugs, the ability to enter the market one to two years earlier due to FDA assistance and expedited review may provide a sufficient economic incentive, even for drugs that expect only moderate sales. Alternatively, a *sui generis* system could grant the sponsor an extension in its period of exclusive sales, either in the form of a marketing exclusivity extension or a patent term extension.²⁵⁸ Regardless of the precise form, any system that extends the sponsor's exclusive sales period will incentivize sponsors to develop PGx-based drugs.²⁵⁹

Using the Orphan Drug Act to cover PGx-based drugs that can only be used in small patient populations is probably the easiest way to get pharmaceutical companies to develop personalized medicine.²⁶⁰ This solution would avoid modifying FDA regulations relating to clinical trials and premarket approval and also avoid the need for controversial *post hoc* data analysis and conditional drug approvals.²⁶¹

CONCLUSION

Pharmacogenomics has the potential to revolutionize both the process of drug development and the practice of medicine by providing personalized therapies.²⁶² By coupling genetic tests with drugs, it is possible to limit the patients who take a drug to those most likely to benefit and to prevent administration to those likely to suffer adverse reactions.²⁶³

²⁵⁷ Note that sponsors generally already get several years of marketing exclusivity. The Hatch-Waxman Act grants sponsors four to five years of data exclusivity following approval of the sponsor's NDA, during which time FDA will not accept abbreviated new drug applications (ANDAs) from generic challengers. See HUTT ET AL., *supra* note 12, at 762. After the data exclusivity period expires, generic challengers may submit ANDAs seeking permission to market generic versions of the sponsor's brand-name drug. *Id.* Sponsors of unpatented drugs usually get around seven years of effective market exclusivity (five years of data exclusivity plus approximately two years for ANDA approval). *Id.*; Avery, Matthew, Note, *Continuing Abuse of the Hatch-Waxman Act by Pharmaceutical Patent Holders and the Failure of the 2003 Amendments*, 60 HASTINGS L.J. 171, 188 (2008). Sponsors of patented drugs usually get 7.5 years of effective market exclusivity. 21 U.S.C. § 355(j)(5)(F)(ii). However, actions by FDA or a federal district court can shorten these periods. Avery, *supra*, at 177. Consequently, the seven years of marketing exclusivity granted by the Orphan Drug Act generally would not provide any benefit over what is already given by the Hatch-Waxman Act. But the guaranteed marketing exclusivity provided by the Orphan Drug Act is arguably more valuable to sponsors than the variable *de facto* marketing exclusivity created by Hatch-Waxman's data exclusivity and ANDA review scheme.

²⁵⁸ This is similar to the incentive given to sponsors for conducting pediatric studies. See 21 U.S.C. § 355A(b)-(c) (granting a six-month marketing exclusivity extension); see also I. Cohen, Glenn, *Therapeutic Orphans, Pediatric Victims? The Best Pharmaceuticals for Children Act and Existing Pediatric Human Subject Protection*, 58 FOOD & DRUG L.J. 661, 663-664 (2003). It is beyond the scope of this article to analyze the appropriate length of time of the increase in exclusive sales.

²⁵⁹ See Kushner, Leslie, Note, *Incentivizing Postmarketing Pharmaceutical Product Safety Testing with Extension of Exclusivity Periods*, 19 FORDHAM INTELL. PROP. MEDIA & ENT. L.J. 519, 546-547 (2009).

²⁶⁰ But see Loughnot, *supra* note 247, at 365 (arguing that it would be an abuse of the ODA to apply it to PGx-based drugs).

²⁶¹ A similar argument could be made for modifying the Humanitarian Device Exemption of the Safe Medical Devices Act of 1990, which is similar to the Orphan Drug Act, except it only applies to drug therapies for patient populations under 4,000 persons. However, the 1990 Act imposes strict price controls that would likely deter any for-profit pharmaceutical company from taking advantage of its provisions. See SACGHS PHARMACOGENOMICS REPORT, *supra* note 3, at 31.

²⁶² See Woodcock, *supra* note 5, at 93.

²⁶³ See *id.*

While pharmacogenomics holds great promise, only a few PGx-based drugs have been approved in the past decade. Several factors deter pharmaceutical companies from investing in PGx research and development. There is little economic incentive to use pharmacogenomics given its potential to increase the cost of clinical trials and reduce the market size for an approved drug. Also, uncertainty about the evolving regulation of PGx drugs further deters pharmaceutical companies from generating PGx data during clinical trials.²⁶⁴

In order to make the promise of personalized medicine a reality, the economic and regulatory disincentives to developing PGx-based drugs must be removed. FDA needs to provide further guidance on requirements regarding clinical trial design, data submission, marketing clearance, drug-diagnostic co-development, and post-market surveillance. Also, current regulations must be redesigned to encourage sponsors to use PGx data to rescue drugs that would otherwise fail clinical trials. This can be done by conditionally approving PGx drugs with unvalidated biomarkers and requiring sponsors to perform confirmatory Phase IV trials. Alternatively, the economic incentives provided by the Orphan Drug Act, or a *sui generis* system based on it, could be used to spur PGx research.

The hope is that using pharmacogenomic data to develop drugs will become the rule rather than the exception. “Personalized medicine will become a reality when medicine no longer needs to be called personalized medicine to indicate that prescriptions are routinely written for patients based on the unique genetic patterns of polymorphisms in their genome—it will simply be called medicine.”²⁶⁵

²⁶⁴ SACGHS PHARMACOGENOMICS REPORT, *supra* note 3, at 95.

²⁶⁵ Lesko, *supra* note 23, at 815.