

## 8. Companion Diagnostics: Evolving FDA Regulation and Issues for Resolution

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### I. Introduction

Companion diagnostics—tests that provide information about a patient’s genetic and genomic characteristics that is then used to make therapeutic treatment decisions—hold great promise for “personalizing” medicine and streamlining drug development. Existing approval authorities for drugs, biologics, medical devices and combination products were not designed with these “pharmacogenomic” and “pharmacogenetic”<sup>1</sup> tests in mind, however. Consequently, the appropriate premarket pathways and labeling requirements for companion diagnostics and their associated therapies are unclear and in need of development.<sup>2</sup>

The United States Food and Drug Administration (FDA or the agency) has undertaken to clarify the regulatory framework for companion diagnostics and their related therapies through a concept paper and other statements. Nevertheless, the agency’s efforts are in the early stages and the regulatory construct for these products remains ambiguous at this time. FDA’s case-by-case regulation provides some glimpse into the agency’s approach and the governing requirements; however, some aspects of this regulation arguably have been inconsistent thus far. Future FDA efforts, including projects commenced through the agency’s Critical Path Initiative (CPI), will target development of the regulatory structure for companion diagnostics and hopefully provide greater clarity on currently confusing issues.

Section II outlines FDA’s publications and statements about its proposed approach to regulating companion diagnostics and to determining the necessity and appropriateness of “cross-referenced” or “mutually conforming” labeling for these diagnostics and their associated therapies. Section III describes FDA’s case-by-case regulation of companion diagnostics and related drugs to date. Section IV discusses the status of FDA’s efforts to resolve issues related to companion diagnostics, including through the CPI.

### II. The Emerging FDA Regulatory Framework

Companion diagnostics present several regulatory issues. *First*, the sponsor (and the agency) must decide whether the therapy and diagnostic are required to be co-developed, approved together, and/or considered a combination product.<sup>3</sup> FDA has released a concept paper

discussing such issues, but has not yet issued a draft or final guidance discussing its regulatory approach on these points. *Second*, the appropriate regulatory pathway for the diagnostic test itself must be ascertained. This involves determining whether clearance of a 510(k) notification, clearance through the *de novo* classification pathway, or approval of a premarket approval application (PMA) is required. FDA has discussed the principles used in these decisions in guidance. *Third*, the appropriateness and necessity of cross-labeling the products or providing mutually conforming labeling for them must be determined. FDA also is developing its approach to these issues.

#### **A. Co-Development/Linked Approval/Combination Product Requirements for Companion Diagnostics**

In 2005, FDA released a concept paper outlining its preliminary views on the appropriate regulatory framework for companion diagnostics.<sup>4</sup> Stakeholders sharply criticized the concept paper as proposing unrealistic and inflexible regulatory requirements. Despite stating for several years that it plans to release draft guidance on these issues, FDA has not yet done so. Nevertheless, statements by key FDA officials and recent developments suggest that the agency has taken the criticism to heart and that the draft guidance could differ significantly from the concept paper.

##### *1. The Concept Paper*

###### *a. Scope*

The concept paper only covers issues related to mandatory use of a diagnostic in drug selection decisions in clinical practice.<sup>5</sup> It encompasses use of pharmacogenomic tests to identify likely therapy responders, non-responders and/or patients most likely to experience adverse events that might require contraindication of the treatment.<sup>6</sup> It does not address use of pharmacogenomic testing in dosing or therapy monitoring, although FDA notes its principles “may be relevant” to development of these tests.<sup>7</sup> The concept paper is also limited to “development of a single test in conjunction with a single drug.”<sup>8</sup>

###### *b. Defining “Co-Development” and Relationship to “Combination Product” Status*

For purposes of the concept paper, “co-development” means “products that raise development issues that affect both the drug therapy and the diagnostic test.”<sup>9</sup> This term encompasses, for example, scientific issues for each product that impact the other’s development.<sup>10</sup> Under the concept paper, “[c]o-developed products ... may or may not be combination products,” in part because FDA expects that many of the therapies and tests will be marketed separately by different companies.<sup>11</sup>

*c. Suggested Co-Development Pathways*

To obtain approval of a drug, a sponsor must demonstrate that it is safe and effective through submission of a New Drug Application (NDA).<sup>12</sup> For diagnostics, the sponsor must show that the product is both analytically validated and clinically validated and has clinical utility to obtain approval.<sup>13</sup> The concept paper calls for sponsors to identify the co-development pathway of the diagnostic “early in development” and recommends parallel development of the drug and companion diagnostic:

Ideally, a new diagnostic intended to inform the use of a new drug will be studied in parallel with early drug development (phase 1 or 2 trials) and diagnostic development will then have led to prespecification of all key analytical and clinical validation aspects for the subsequent (late phase 2 and phase 3) clinical studies. These include the intended population and selection of diagnostic cut-off points for the biomarker intended to delineate test positives, test negatives, and, when appropriate, equivocal zones of decision making.<sup>14</sup>

According to the concept paper, the test should be developed and analytically validated early in the development process “[w]hen possible” so that the diagnostic’s clinical validity and utility can be assessed in later stage clinical trials.<sup>15</sup> Analytical validation of a test with multiple biomarkers “ideally” will occur in clinical trials enrolling patients with the intended indication.<sup>16</sup> Clinical test validation then should be determined by investigating the test’s relationship to clinical outcome “in patient subgroups with and without the analyte of interest.”<sup>17</sup>

A “definitive” drug clinical study will allow for evaluation of the drug’s safety and efficacy and verification of the biomarker’s clinical utility in guiding drug use (including patient selection).<sup>18</sup> The safety or efficacy endpoints for the drug should match those used for clinical utility.<sup>19</sup> The sponsor may wish to use a simple two-arm randomization scheme comparing treatment to control, in which all patients receive the test and then are randomized (especially if the test results are not readily available at the investigation sites).<sup>20</sup> Alternatively, the protocol may call for stratification of the patients by test result before randomization to drug or placebo in a four-arm design, which will ensure balance in biomarker-positive and -negative patients among treatment versus control.<sup>21</sup> Where data support the theory that the test predicts enhancement of safety or efficacy as compared to an untested population, FDA will strongly recommend that the clinical development program be designed to determine the response in both patients with known biomarker status and patients of unknown test status to establish an overall risk/benefit ratio in the general population.<sup>22</sup> The concept paper also recommends this approach in cases where “there is a reasonable likelihood that [the drug’s] use would occur

in a wider population than the test-targeted population,” e.g., where the drug treats cancer.<sup>23</sup> Nevertheless, if the sponsor is reasonably sure that only patients having a specific biomarker status will respond, the sponsor may use biomarker status as a selection criterion. In this case, approval of the drug is integrally linked to availability and use of the diagnostic at the time of its approval.<sup>24</sup>

According to the concept paper paradigm, the device submission (510(k) or PMA) should be sent to FDA at approximately the same time that the sponsor submits the NDA/BLA for the therapy.<sup>25</sup> The concept paper acknowledges that the amount of data needed to support the test will vary depending on the facts of the particular case, but states that “normally data from two or more adequate and well-controlled trials would be collected to ... establish[] the clinical utility of the test.”<sup>26</sup> Generally, FDA prefers submission of prospective data, but “in cases where the analyte is stable and where collection bias ... can be carefully characterized and addressed, prospectively designed retrospective clinical utility studies may be possible.”<sup>27</sup> In these retrospective studies, “every effort should be made to verify the clinical hypothesis being claimed with a study that is independent from the analytical and clinical [studies] on which the diagnostic test was initially developed.”<sup>28</sup> In situations where clinical *validation* is examined post-hoc, an additional prospective study “ordinarily” is needed to confirm clinical validation, but FDA will consider retrospective validation with robust statistical technique.<sup>29</sup> The concept paper offers the following cautions regarding use of different development approaches for the companion diagnostic than the parallel scheme described in the paper:

If the[] performance parameters and other aspects of analytical and clinical test validation are not established at the point where phase 3 clinical utility studies are being commenced, acceptable documentation of clinical utility may not be possible within these studies. Rather, in such cases, the phase 3 clinical trials of the drug should be aimed at exploring clinical performance of the test and identifying appropriate cut-offs. To confirm clinical performance, including clinical utility, additional clinical studies may be called for to avoid post-hoc specification of the diagnostic cut-off points.<sup>30</sup>

FDA also states that, in cases where the diagnostic test is not incorporated into the trial design or primary outcomes, any resulting associations between test results and clinical outcomes will “usually be considered exploratory” and not as “confirming clinical performance or utility.”<sup>31</sup> The association “may be confirmed in another clinical trial,” and “[o]ptimally,” this confirmatory testing would take the form of a prospective clinical trial.<sup>32</sup> Nevertheless,

“alternative retrospective validation methods may be considered,” where “the pathophysiological status of disease is well known, drug and diagnostic mechanisms well elucidated, and all of the effect comes from a defined subset.”<sup>33</sup> If the sponsor banks samples for retrospective analyses of associations between events of interest and test results, “the approach to these associations and analysis should be specified in advance and not after the study is completed.”<sup>34</sup>

*d. FDA Review of Co-Developed Products and Timing of Drug and Diagnostic Approval*  
Under the concept paper, FDA will apply different review and approval procedures depending on the biomarker’s importance to use of the new drug. If all patients “had a reasonable, albeit different, response to treatment,” then review of the diagnostic “can be subsumed in the general review of the therapeutic and may not require independent credentialing of the assay as a diagnostic test for expected clinical use of the drug.”<sup>35</sup> In other words, where the therapy’s risk/benefit ratio is acceptable in the entire target population, the drug can be approved before the diagnostic test is refined and developed.<sup>36</sup> In this case, approval will be based on the overall database for the product.<sup>37</sup>

In contrast, the diagnostic “may prove to be so integral [to] the use of the new drug that testing will be considered a prerequisite to use.”<sup>38</sup> If multi-site testing is expected in practice, FDA will require premarket review of the diagnostic and the drug may be labeled as requiring prior use of the diagnostic before initiating the therapy.<sup>39</sup> Although in many cases sequential approval/clearance of the drug and diagnostic may be permitted, in this situation FDA may require “simultaneous approval” of the two products, with or without considering the products to comprise a “combination product.”<sup>40</sup>

*e. Test Clearance/Approval Process*

Companion diagnostics may face a different path to market than diagnostics developed for general uses not tied to a particular therapy or class of therapies. Companion diagnostics may be more likely to be regulated as medical devices requiring clearance or approval rather than as laboratory-developed tests (LDTs). The 510(k) or *de novo* classification pathways may be available for some companion diagnostics, while others will require PMAs. In the co-development concept paper, FDA indicated that it expects most diagnostics that test biomarkers for drug selection (and especially products “with high risk profiles”) will require PMAs.<sup>41</sup>

*2. Criticism of the Concept Paper and FDA Response*

Following the concept paper’s release, stakeholders criticized various facets of it. First, comments contended that the concept paper was “based on an unrealistic model ... of parallel

timelines of drug and device development.”<sup>42</sup> These comments emphasized that identification of a biomarker before phase II drug testing “is rare” and “[i]t is much more likely that an appropriate biomarker for [diagnostic] development will be identified in Phase 2 or even Phase 3 studies.”<sup>43</sup> Stakeholders contended that the document should allow “other more-probable co-development pathways, which begin during the end of phase 2 or phase 3 of drug development”<sup>44</sup> without delaying approval of the therapy.<sup>45</sup> One manufacturer also suggested that the concept paper’s development timeline should reflect that diagnostics can be developed much more quickly than therapies.<sup>46</sup>

Relatedly, several commentators have suggested creating an accelerated approval scheme for personalized medicine products, similar to the one for drugs for serious and life-threatening conditions, in which evidentiary burdens for approval may be lowered subject to postmarketing study requirements.<sup>47</sup> According to one author, other incentives for personalized medicine development should be created to urge incremental improvement in approved therapies to achieve better “targeting” of patients likely to experience a favorable risk/benefit ratio.<sup>48</sup>

Stakeholders also objected to the concept paper’s suggestion that companion diagnostic approval would require two prospective adequate and well-controlled trials, as is required for approval of a drug.<sup>49</sup> Multiple commenters pointed out that the drug standard does not apply to medical devices and contended that the two trial recommendation was excessive in light of section 513 of the FDCA, which requires the agency to use “the least burdensome appropriate means of evaluating device effectiveness that would have a reasonable likelihood of resulting in approval.”<sup>50</sup> Commenters urged that the concept paper should acknowledge that 1) performance of prospective, confirmatory trials for the biomarker “will be the exception rather than the rule” in co-development; 2) clinical validation could be accomplished through “prospectively defined analysis of drug clinical trial data”; and 3) “diagnostic statistical analysis may be conceived and conducted” after completion of the drug trial and such analysis may “include, under the appropriate circumstances . . . prospective testing of banked specimens.”<sup>51</sup> AdvaMed, a trade association representing manufacturers of medical devices, diagnostic products and medical information systems, commented that FDA should permit clinical utility of a biomarker for which there is no predicate device to be shown through scientific literature references, without the need for confirmation in a prospective clinical study, “consistent with the *de novo* process.”<sup>52</sup> FDA’s suggestion that clinical utility be established for all companion diagnostics drew this comment from one company:

An approved [PMA] is currently required for all medical devices with claims of clinical utility. If establishing clinical utility is necessary for a co-development program, this requirement presents a major burden for the diagnostic partner, who otherwise might be able to develop their [diagnostic] through a less burdensome pathway (510(k), or *de novo* 510(k)). We suggest FDA consider that [sic] the *de novo* 510(k) route as an option for the co-development pathway.<sup>53</sup>

Stakeholders also commented that the scope of the concept paper was unduly narrow. According to comments, the eventual draft guidance should address 1) whether the concept paper encompasses LDTs and analyte specific reagents; 2) whether the concept of clinical utility includes “informational utility” (use and interpretation of the diagnostic test results at the physician’s discretion rather than merely in terms of how clinical practice will be changed by the test results); 3) the scenario in which multiple tests are developed for use with a single therapy; 4) development of markers after drug approval; and 5) labeling implications of co-development, including guidance on cross-labeling, labeling changes, supplements and revisions.<sup>54</sup> AdvaMed also requested that FDA issue updated regulations regarding informed consent and Institutional Review Board issues related to banking samples for subsequent study.<sup>55</sup>

FDA officials have responded to criticism of the concept paper, indicating they are receptive to a more flexible regulatory approach. In a 2006 speech, then-Director of the Office of In Vitro Diagnostic Device Evaluation and Safety Steven Gutman described the concept paper as “a little idealized” and stated “if you do not have a diagnostic at the time of the drug study, that’s OK,” as long as banked samples are stored “in a stable and clearly documented manner.”<sup>56</sup> Gutman also said that the draft guidance will “look a good bit different” than the concept paper and will address diagnostic test development that occurs late in therapy development.<sup>57</sup>

It now appears that FDA is “going back to the drawing board” on the content of the draft guidance.<sup>58</sup> In 2009, Center for Drug Evaluation and Research (CDER) Director Janet Woodcock stated that FDA will issue additional concept papers on co-development topics to identify the most current knowledge on these issues.<sup>59</sup> FDA also has been working with the Personalized Medicine Coalition (PMC), an independent, non-profit group comprising an array of entities with interests in personalized medicine, including therapy and diagnostic companies, clinical laboratories, patient groups, research institutions, providers and federal agencies,<sup>60</sup> to update its thinking on regulation of co-developed and companion diagnostic

products. At FDA's request, PMC released a December 2009 white paper offering updated comments on the 2005 concept paper and proposing a list of topics for a public workshop and/or FDA white paper series on co-development.<sup>61</sup> Thus, FDA appears to be actively working to reconsider the concept paper. Based on an October 2009 speech by Commissioner of Food and Drugs Margaret Hamburg, the eventual goal of these efforts is still "developing a draft guidance that will establish a regulatory pathway for co-development of new drugs and diagnostics."<sup>62</sup> FDA's drug center has indicated that it plans to issue the draft in 2010,<sup>63</sup> and in a February 2010 speech, Dr. Hamburg stated that she expects that the guidance will be completed by the end of 2010.<sup>64</sup>

Based on preliminary indications, FDA's eventual draft guidance on co-development may address some of industry's concerns with the 2005 concept paper. In her October 2009 speech, Dr. Hamburg stated "[r]egulatory agencies are not known for being flexible, but that is exactly what we need to be,"<sup>65</sup> seemingly indicating receptiveness to the industry's comment that the concept paper's approach was too rigid. FDA's request for input from PMC also reflects a willingness to work with industry on the draft guidance. If FDA adopts even some of PMC's recommendations, the draft guidance likely will more closely align with industry's suggestions than the concept paper. The PMC white paper echoes many of the concerns previously expressed by stakeholders in their comments on the concept paper, while emphasizing that the draft guidance should account for developments in personalized medicine since 2005.<sup>66</sup> The white paper urges FDA to tackle three main issues:

- account for the array of development models for diagnostic tests, including both co-development (within a single company or among two companies working together) as well as "independent development" of a companion diagnostic;
- initiate rulemaking addressing how "regulatory oversight and approval requirements" will differ for LDTs and IVDs that serve as companion diagnostics; and
- clarify the levels of validation evidence needed to include in drug labeling (a) a reference to a test, or (b) a requirement for a test's use (and clarify the requirements for updating these aspects of drug labeling).<sup>67</sup>

PMC also asked FDA to identify examples of companion diagnostic approvals, discuss the regulatory approach used in those cases, and explain how those approaches differed from that recommended in the concept paper.<sup>68</sup> Further, the white paper called for FDA to clarify the process for working across different components of the agency when co-developing a diagnostic, including clarifying the Center (or other part) of FDA in charge of appropriate meetings and the role of the CPI in this process.<sup>69</sup>

## **B. Cross-Labeling and Mutually Conforming Labeling**

FDA also is grappling with issues associated with “cross-labeling” and “mutually conforming” labeling for related products, including drugs and their companion diagnostics. “Cross-labeling” refers to the situation where a therapy label refers to use of a diagnostic (and vice-versa).<sup>70</sup> “Mutually conforming labeling” has been defined by FDA to mean “labeling for each product that provides directions for using that product with [another] sponsor’s product.”<sup>71</sup> FDA is considering situations where cross-labeling might be required or appropriate. As with co-development, FDA’s regulation is still at an early, exploratory stage, and many issues must be resolved before the governing regulatory principles will be evident.

In March 2005, FDA held a meeting and sought comment on a number of issues related to cross-labeling and mutually conforming labeling. FDA indicated a particular interest in developing an appropriate regulatory approach for situations where a manufacturer develops its diagnostic for a new use; that new use would require off-label use of the drug; and the drug manufacturer does not agree to seek revision of its label to incorporate the new information.<sup>72</sup> The agency sought comment on whether it could approve the diagnostic in that situation despite that the labeling of the drug would not mention it or contain information about using the products together.<sup>73</sup> FDA identified the following issues as relevant to resolution of this main concern:

- whether cross-labeling or mutually conforming labeling may be required, and if so, under what circumstances;
- the degree to which labeling of drugs and related diagnostics could be required to conform, e.g., with respect to instructions for use, indications, and other aspects of the labeling;
- the impact of changes to the approved product on the necessity for changes to the new product’s labeling and duties to monitor the approved product to become aware for the need for such changes; and
- issues related to improper reliance on proprietary data for the approved product and the impact of exclusivity for it on the ability to obtain cross-referenced or mutually conforming labeling.<sup>74</sup>

FDA recognized that, where companies are willing to work together, cross-labeling issues generally may be easily resolved. Typically, the sponsor of the already-approved product will submit a supplement to its approved application, reflecting the new condition of use and updating other components of the labeling to ensure adequate directions are given for use of the

product with the new product.<sup>75</sup> Companies may refuse to work together for a number of reasons, however, e.g., products liability exposure, divergent business goals, intellectual property concerns, etc.<sup>76</sup> In these situations, there is a significant question as to whether FDA even has legal authority to require cross-labeling.<sup>77</sup> As part of the 2005 public meeting and subsequently, FDA proposed solutions that avoid this thorny legal question. FDA considered incentives for collaboration, such as reduced user fees or enhanced exclusivity for the manufacturer of the approved product for agreement to modify its labeling to reflect the new product.<sup>78</sup>

In comments to the related FDA docket, AdvaMed proposed a regulatory framework in which cross-labeling would be required only when: 1) the labeling of the new product individually specified the proprietary name of the approved product; *and* 2) the labeling of the approved product would not be consistent with the new product's labeling without changes.<sup>79</sup> In this situation, an official collaboration between the companies would be required and both companies would need to modify their labeling to take account of the other product under AdvaMed's proposal.<sup>80</sup> In contrast, according to AdvaMed, if the new product's labeling did not mention the proprietary name of the approved product *or* the approved product's labeling was "generally consistent" with the new product labeling in terms of indications, mode of delivery, and dosing schedule, cross-labeling would be unneeded and the new product labeling could address use of the drug and device together.<sup>81</sup> With respect to exclusivity and intellectual property issues, AdvaMed concluded that FDA may utilize public information as well as "findings" of safety and effectiveness regarding approved products to approve the second product, but noted that existing restrictions on disclosure of proprietary data submitted in an NDA must be respected and should not be changed.<sup>82</sup>

Although FDA reviewed and analyzed the stakeholder feedback it obtained,<sup>83</sup> the agency has not yet released a comprehensive guidance document on cross-labeling and mutually conforming labeling. In 2007, FDA announced its plan to issue a concept paper specifically addressing the situation described above: where the sponsor of a new product wishes to label its product for a novel use of an approved therapy and the sponsor of the approved product will not revise its labeling to make conforming changes.<sup>84</sup> In the meantime, FDA indicated it was working on a "product-specific basis to develop approaches to resolve the difficult and complex" issues associated with determining the need for cross-labeling and mutually conforming labeling for an approved therapy.<sup>85</sup>

FDA released draft guidance that attempted to grapple with these issues as to imaging products in 2008<sup>86</sup> and finalized the guidance in 2009.<sup>87</sup> The final guidance states FDA's belief that imaging drug and device labeling "should be generally consistent," but that, "under appropriate circumstances" information about new contrast indications may be added to drug or

device labeling without necessitating changes to the other's labeling.<sup>88</sup> Specifically, the guidance provides that, in most cases,<sup>89</sup> only a device submission is needed where a new imaging device or device modification “enables an approved imaging drug (i.e., at its approved formulation, dose, dosing regimen, rate, and route of administration) to be used for a new imaging contrast indication in a manner that is consistent with its approved indication.”<sup>90</sup> According to the guidance, FDA may require, “in certain instances,” that the holder of the device submission monitor the approved drug labeling and other changes to the drug and “other postmarket surveillance related to the drug.”<sup>91</sup> The guidance generally calls for only a drug submission and labeling change where an imaging drug change “enables the currently approved/cleared imaging device to be used for a new indication for use without a change to the device.”<sup>92</sup>

The agency expects both sets of product labeling will need to be updated if the device modification “cause[s] the drug and device to interact in a manner that affects the safety or effectiveness of the product(s),” necessitates a change to imaging dosing or the safety or effectiveness information, or results in “labeling inconsistencies.”<sup>93</sup> Specifically, the guidance calls for submissions to change both the drug and device labeling where a new device or device modification: 1) requires changes to the imaging drug formulation; 2) causes changes to the patient population; 3) necessitates changes to the dose, rate or route of administration of the drug or to the safety profile; 4) “is for a new indication not in the approved drug labeling,” such as where the “drug imaging indication category”<sup>94</sup> changes; or 5) results in device labeling changes that could confuse practitioners.<sup>95</sup> Dual submissions also will be required where a change to an imaging drug “necessitates a change in the approved imaging device performance characteristics, specifications, or design for its currently approved/cleared imaging indication or for a new indication for use.”<sup>96</sup> The guidance states that clinical trials involving both the drug and device will be expected irrespective of which label includes the new indication information.<sup>97</sup>

### III. Case-By-Case Regulation

Although FDA has not yet established a framework governing approval of companion diagnostics and their related therapies, FDA has regulated these products on a case-by-case basis. This ad hoc regulation provides some insight into the principles FDA is using to approve drug-diagnostic pairs at this time, although the agency's regulation arguably has been inconsistent in some regards thus far.

FDA publishes on its website the *Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels* (the *Table*), which identifies and summarizes its approvals of therapies with pharmacogenomic information in the labeling.<sup>98</sup> Until recently, the *Table* categorized

diagnostic testing for the biomarker of interest as “required,” “recommended” or “information only” for use of the drug.<sup>99</sup> This column of the *Table* has since been eliminated, but these three categories remain useful for explaining and classifying existing approvals. This section discusses the approvals summarized in FDA’s *Table* and a selected few others.

When the companion diagnostic is required for use with the therapy, FDA has in some cases mandated that it be approved simultaneously with the therapy. The linked approval requirement has been used where only patients with a certain biomarker are likely to respond to the therapy. In other instances, FDA has permitted separate approvals of a drug and a required-use diagnostic, typically where either the kit or drug was already approved or cleared for a general indication. Finally, FDA has in a few cases allowed a required-use diagnostic to remain an LDT even when used in patient selection. FDA has not been clear about when such an arrangement is permissible and has consequently been criticized for inconsistent regulation on this point.

FDA generally “recommends” genetic testing where the diagnostic provides information regarding adverse events associated with the therapy, but is not used in patient selection. In one case, however, testing is recommended to de-select patients. “Information only” labeling generally has been used where the diagnostic guides dosing, provides information about rare or non-serious adverse events, or selects one group of patients likely to benefit (where other groups are known to benefit). In several cases, however, “information only” labeling contains content on patient de-selection.

Overall, FDA’s regulation thus far arguably has been inconsistent in some regards, particularly with respect to: 1) use of a diagnostic to select or de-select patients will render the diagnostic test “required;” and 2) a required-use companion diagnostic may remain an LDT or must be approved/cleared. Future agency guidance or statements may clarify these points.

## **A. Required Use of Diagnostic**

### *1. Simultaneous Approvals*

In three situations, the agency has mandated that therapies be approved at the same time as their companion diagnostics, where the diagnostic was used in patient selection. In these cases, the focus was on the tumor expression of a particular protein for purposes of patient selection. These therapies are Herceptin (trastuzumab), Erbitux (cetuximab) and Vectibix (pantumumab). Herceptin and Erbitux were approved on the same day as their corresponding diagnostics.<sup>100</sup> With respect to Vectibix, FDA approved a PMA supplement for the accompanying diagnostic on the same day.<sup>101</sup> FDA lists the initial Vectibix approval and the

2006 approval of Erbitux for an additional indication on its webpage titled “Other Types of Combinations of FDA Regulated Products,” which describes products that “are used together in a way that does not meet the regulatory definition of a combination product, but that may raise similar development or regulatory issues,” for example, because the products involve “the concomitant use of drugs, devices, and/or biological products that are not ‘individually specified’ in the product labeling” so as to bring them into the combination product definition.<sup>102</sup>

Herceptin is indicated for treating only certain breast cancer tumors—those overexpressing the HER-2 protein. Although Herceptin’s clinical trials utilized an LDT to measure expression of the HER-2 protein, FDA required that a test kit be approved with Herceptin. The Dako HercepTest was approved on the same day as the drug in 1998.<sup>103</sup> Additional diagnostics were approved subsequently for use with Herceptin: the current labeling also references the Pathway HER-2/neu, PathVysion and HER2 FISH pharmDx assays.<sup>104</sup> In 2008, FDA approved another test, the SPOT-Light HER2 CISH Kit, for use with Herceptin, but Herceptin’s labeling does not mention this assay by name.<sup>105</sup> Tykerb (lapatinib), which also treats breast cancer tumors overexpressing HER-2, was approved in 2007 for use after failure of Herceptin.<sup>106</sup> Presumably patients already treated with Herceptin will have had the HER-2 test prior to treatment with Tykerb, but the clinical studies of Tykerb did require use of a HER-2 diagnostic prior to entrance.<sup>107</sup>

Erbitux is indicated for treatment of colorectal tumors expressing the Epidermal Growth Factor Receptor (EGFR) protein. Its companion diagnostic, the DakoCytomation EGFR pharmDx determines whether a given patient’s tumors express this protein.<sup>108</sup> Patients enrolled in the clinical study had been required to evidence EGFR expression based on the Dako test kit.<sup>109</sup> In contrast, pretreatment screening for EGFR expression is not required for use of Erbitux in treating head and neck cancer. Because expression of EGFR has been detected in nearly all squamous cell head and neck cancers, clinical studies for the head/neck cancer indication did not have entry criteria based on EGFR tumor expression.<sup>110</sup>

Vectibix also is indicated for treating EGFR-expressing colorectal tumors. On the same day that FDA approved this drug, it approved a PMA supplement for the Dako EGFR pharmDx kit; enrollment in the clinical study of the drug had been based on evidence of EGFR expression using this Dako test kit, and the drug labeling states that such patients are the only ones studied and for whom drug benefit was shown.<sup>111</sup> As noted, FDA has identified Vectibix and this companion diagnostic as not actually meeting the definition of “combination product” but raising similar types of issues.<sup>112</sup>

## 2. *Separate Approvals*

FDA has permitted a therapy and its required companion diagnostic to be approved at different times, generally where the drugs were proven effective in a general population (as opposed to a pharmacogenomic-guided population) or a test kit already was available. For example, Gleevec was approved before any of its companion diagnostics because it had been shown to be safe and effective for an indication not implicating a companion diagnostic: treatment of patients with chronic myeloid leukemia (CML) in blast crisis; accelerated phase; or in chronic phase after failure of interferon-alpha therapy.<sup>113</sup> This initial indication did not refer to the CML's chromosomal status (Philadelphia chromosome-positive or -negative), nor did the initial labeling include indications for gastrointestinal stromal tumors dependent on the tumors' c-KIT status. These references are now in the Gleevec labeling.<sup>114</sup> FDA listed Gleevec and one of its companion diagnostics for the c-KIT indication, DakoCytomation's c-KIT (9.7) pharmDx,<sup>115</sup> on its list of examples of product tandems that do not meet the definition of "combination product" but present similar issues.<sup>116</sup> In contrast, a previously approved c-KIT test, the Ventana PATHWAY Anti-c-KIT (9.7) Primary Antibody, is approved for use with Gleevec,<sup>117</sup> but is not listed on this webpage. The reason for this is unclear.

The labeling for Elitek (rasburicase) recently was updated to mandate genetic testing for which a test kit was already available. The labeling now includes a black box warning requiring pretreatment screening of patients "at higher risk" of glucose-6-phosphate dehydrogenase (G6PD) deficiency based on their ancestry, because patients with this deficiency could develop severe hemolysis upon treatment with Elitek.<sup>118</sup> Prior to this October 2009 labeling change, G6PD testing was merely recommended.<sup>119</sup> Screening tests for G6PD deficiency received 510(k) clearance prior to the initial approval of Elitek in 2002.<sup>120</sup>

## 3. *Approval of Therapy for Use with an LDT*

In several cases, FDA has allowed a required-use companion diagnostic test to remain an LDT without FDA clearance or approval. FDA did not require simultaneous approval of companion diagnostic test kits for Selzentry, Ontak and Revlimid, even though genetic testing is needed to determine whether treatment with these drugs is appropriate.

In August 2007, FDA approved Selzentry (maraviroc), an antiretroviral drug for use in adults infected with only CCR5-tropic HIV-1, while allowing the companion diagnostic to remain an LDT.<sup>121</sup> In this case, the focus of the laboratory test was on the profile of the virus. Selzentry prevents the HIV virus from entering cells by blocking the CCR5 co-receptor,<sup>122</sup> and will not work in patients with other types of HIV. During clinical trials, the Trofile assay was used to identify patients having the CCR5 tropic form of HIV.<sup>123</sup> The initial approved labeling stated

“Tropism and treatment history should guide the use of SELZENTRY” and subsequent labeling enhanced this statement to read “Tropism testing is required for the appropriate use of SELZENTRY.”<sup>124</sup> Nevertheless, FDA did not require approval of the Trofile assay, the only available tropism test.<sup>125</sup> At the time of Selzentry’s approval, Trofile was not FDA-cleared and instead was available as a test service out of a Clinical Laboratory Improvement Amendment (CLIA)-certified laboratory.<sup>126</sup> Trofile apparently remains an LDT.<sup>127</sup>

FDA approved Ontak (denileukin diftitox) for “treatment of patients with persistent or recurrent cutaneous T-cell lymphoma whose malignant cells express the CD25 component of the IL-2 receptor.”<sup>128</sup> Even though the labeling directs the practitioner to “[c]onfirm that the patient’s malignant cells express CD25 prior to administration of Ontak,” it refers the prescriber to a testing service rather than a diagnostic kit.<sup>129</sup>

Revlimid (lenalidomide) is indicated for the treatment of patients with “transfusion-dependent anemia due to Low- or Intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.”<sup>130</sup> Revlimid was not approved with a companion diagnostic for testing for the deletion 5q abnormality.<sup>131</sup> Although the cytology testing involved is well-established and performed by commercial labs, the approval of Revlimid has been described as “inconsistent” with those situations in which FDA has required approval of a companion diagnostic.<sup>132</sup>

These therapeutic drug approvals show that FDA’s criteria for mandating clearance or approval of a required-use companion diagnostic are unclear.

## **B. Recommended Use of Diagnostic**

FDA has approved drug labeling that “recommends” a genetic test where the diagnostic provides information regarding adverse events associated with the therapy. Testing also is recommended for certain mutations that can cause non-response to Vectibix and Erbitux.

The labeling of the anti-epileptic drug carbamazepine (marketed as Tegretol, Carbatrol, Equetro and generics) was updated in 2007 to contain a black box warning regarding the potential for serious and sometimes fatal skin reactions associated with having HLA-B\*1502, an allelic variant of the HLA-B gene that is found almost exclusively in patients of Asian ancestry.<sup>133</sup> This labeling change occurred after postmarketing adverse event data showed a much higher rate of these adverse events in Asian countries.<sup>134</sup> The black box labeling now recommends genetic testing for “patients with ancestry in genetically at-risk populations.”<sup>135</sup> At the time of this labeling change, FDA had already cleared a number of tests for general HLA

typing, but recognized that, in most cases, only specialized CLIA-certified labs would be able to conduct the type of high complexity assay necessary to test for the HLA-B\*1502 allele.<sup>136</sup> FDA received confirmation from several national laboratories that they could conduct such testing at that time.<sup>137</sup>

Similarly, after FDA reviewed data from two new studies showing a link between patients with the HLA-B\*5701 allele and hypersensitivity reactions upon treatment with the HIV treatment abacavir (marketed as Ziagen), the drug manufacturer was required to update its labeling to add this information to the black box.<sup>138</sup> The revised boxed warning reads: “[p]rior to initiating therapy with abacavir, screening for the HLA-B\*5701 allele is recommended; this approach has been found to decrease the risk of hypersensitivity reaction.”<sup>139</sup> At the time of the labeling change, testing for this allele already was available through several commercial labs.<sup>140</sup>

The labeling of Camptosar (irinotecan) deems testing “recommended” for detecting whether the individual has a UGT1A1\*28 polymorphism (which can cause the adverse event of neutropenia upon treatment with the drug) advising that “a reduction in the starting dose by at least one level ... should be considered for patients known to be homozygous for the UGT1A1\*28 allele.”<sup>141</sup> FDA approved Camptosar in 1996, and later cleared the Invader UGT1A1 Molecular Assay for performing the relevant genetic testing.<sup>142</sup>

The Imuran (azathioprine) labeling recommends testing to determine whether patients have low or absent thiopurine 5-methyltransferase (TPMT) activity, which poses an enhanced risk for development of severe myelotoxicity with standard Imuran doses.<sup>143</sup> According to the labeling, doctors may wish to consider different treatments for patients having low or absent TPMT activity, and reduced doses are recommended if therapy is initiated in patients with diminished TPMT activity.<sup>144</sup> TPMT testing is commercially available through laboratory services.<sup>145</sup>

Prior to administration of valproic acid, testing for urea cycle enzyme disorder (UCD) is recommended.<sup>146</sup> UCD is a deficiency in any one of several enzymes in the urea cycle, which removes ammonia from the blood.<sup>147</sup> Upon treatment with valproic acid, patients having UCD have developed hyperammonemic encephalopathy that has in some cases been fatal.<sup>148</sup> The labeling recommends that patients with a family history of UCD or signs or symptoms of UCD be evaluated for UCD prior to initiation of valproic acid therapy.<sup>149</sup> Lab testing services are available to do genetic testing,<sup>150</sup> which plays a role in UCD diagnosis.<sup>151</sup>

FDA followed a somewhat controversial path in implementing genetic information into the labeling of Vectibix and Erbitux regarding de-selection of patients having tumors with mutations of the K-RAS oncogene.<sup>152</sup> Retrospective analysis of data from the phase III trial supporting Vectibix approval showed an association between K-RAS mutation status and the ineffectiveness of the therapy.<sup>153</sup> At first, FDA found these data insufficient to support labeling claims regarding K-RAS testing, because no prospective data existed on this point.<sup>154</sup> European regulators then narrowed both drugs' indications to exclude patients with tumors having K-RAS mutations, and U.S. professional societies, including the American Society of Clinical Oncology, recommended K-RAS testing prior to treatment with these drugs.<sup>155</sup> In July 2009, more than a year after European regulators' action and several months after the recommendation of U.S. professional societies, FDA issued a class labeling determination applying to Vectibix and Erbitux.<sup>156</sup> FDA "was criticized for lagging behind advancing regulatory science" in this instance.<sup>157</sup>

The class labeling determination requires that the manufacturers of Vectibix and Erbitux update their labeling to include, in the indications statement, language noting that retrospective subset data "have not shown a treatment benefit" for the drug "in patients whose tumors had *K-RAS* mutations in codon 12 or 13" and therefore that use of the drug "is not recommended for the treatment of colorectal cancer with these mutations."<sup>158</sup> The labeling does not recommend use of a specific diagnostic test by trade name.<sup>159</sup> DxS' K-RAS testing kit currently has the CE Mark in Europe and the company is seeking PMA approval of it in the United States.<sup>160</sup> Several laboratories offer CLIA-regulated laboratory testing for the K-RAS mutation.<sup>161</sup>

### **C. Information-Only Drug Labeling Content on Diagnostic Tests**

Drug labeling has included content on genomic testing in an informational manner where the test 1) guides dosing; 2) aids in avoiding rare or non-serious adverse events; and 3) identifies one group (among other known groups) of likely responders. Additionally, in a few instances, informational labeling content has been included regarding tests used to de-select likely non-responders.

Many of the drugs having pharmacogenomic dosing information in their labeling are metabolized through cytochrome P450 (CYP) enzymes, which are associated with polymorphisms affecting drug metabolism.<sup>162</sup> FDA has cleared the Roche AmpliChip to identify patients' CYP2C19 and CYP2D6 genotypes, as these two enzyme pathways commonly are involved in drug metabolism.<sup>163</sup> Other factors may influence drug metabolism, however. According to one article, for example, "[m]etabolism by CYP2D6 does not ensure that pharmacogenomic

information will be directly applicable to patient care.”<sup>164</sup> According to this article, further study is needed with many drugs before FDA can decide whether recommending specific pharmacogenomic testing is appropriate.<sup>165</sup>

Several “information-only” labels provide background regarding rare side effects. As one example, Xeloda (capecitabine) is contraindicated for patients who are known to lack the enzyme dihydropyrimidine dehydrogenase (DPD), which converts the 5-FU metabolite of capecitabine to a much less toxic substance.<sup>166</sup> The related diagnostic test is offered as an LDT.<sup>167</sup> As another example, information regarding the potential for moderate-to-severe hemolytic reactions in patients with G6PD deficiency is noted in the primaquine labeling; a G6PD deficiency testing kit was cleared in the 1990s as described above.<sup>168</sup> The labeling for Rifater (rifampin, isoniazid and pyrazinamide) indicates that the rate of acetylation of the drug’s isoniazid component is “genetically determined.”<sup>169</sup> About 50 percent of Caucasians and African Americans are “slow inactivators,” which may result in higher drug blood levels and a consequent increase in toxic reactions.<sup>170</sup> The Tasigna (nilotinib) labeling contains information regarding polymorphisms of UGT1A1 and their potential association with hyperbilirubinemia in patients receiving Tasigna.<sup>171</sup> As noted above, there is a cleared test for UGT1A1 variants.

There are several examples of drug labeling containing “information-only” pharmacogenomic content regarding patients not likely to benefit from the drug. The labeling of Myleran (busulfan) advises that the drug is “is clearly less effective in patients ... who lack the Philadelphia (Ph<sup>1</sup>) chromosome.”<sup>172</sup> Nevertheless, the labeling does not recommend or require testing prior to initiation of busulfan therapy, perhaps because the drug was initially approved in the 1950s.<sup>173</sup> Vesanoind (tretinoin) is indicated for inducing remission in a subtype of acute promyelocytic leukemia (APL) “characterized by the presence of the t(15;17) translocation and/or the presence of the PML-RAR $\alpha$  gene.”<sup>174</sup> According to the Vesanoind labeling, genetic testing should be done to confirm the diagnosis of this type of APL by detecting the t(15;17) marker and/or fusion of the promyelocytic leukemia gene and the retinoic acid receptor alpha gene.<sup>175</sup> According to the labeling, the efficacy of Vesanoind therapy in other subtypes of APL has not been shown, so physicians should consider other drugs for patients without the relevant markers.<sup>176</sup> Nevertheless, in prior versions of the *Table*, FDA classified the genetic information in the Vesanoind labeling as “information only.”<sup>177</sup> The rationale may be that genetic testing is confirmatory of the diagnosis rather than the sole basis. Laboratory testing services are available for the genetic testing.<sup>178</sup>

Genetic testing may be used in conjunction with prescribing Sprycel (dasatinib), but is not necessary to identify a patient as within a target population for the therapy. Sprycel is indicated for certain types of chronic myeloid leukemia (CML) where the patients are resistant or intolerant to Gleevec.<sup>179</sup> Gleevec resistance may be assessed through genetic testing for certain mutations of the BCR-ABL gene; several companies offer such tests through their laboratories.<sup>180</sup> However, factors other than genetic testing may indicate that the patient is Gleevec resistant or intolerant as defined in the Sprycel labeling; for example, a clinical study for Sprycel defined “imatinib resistance” as failure to attain certain types of disease responses after a certain period of time on Gleevec.<sup>181</sup> Thus, genetic testing is not necessarily needed for doctors to identify patients appropriate for Sprycel treatment. Similarly, Tasigna is indicated for treatment of Philadelphia chromosome positive CML in Gleevec-resistant and -intolerant patients, and its labeling also does not require or recommend pre-treatment genetic testing for the same reasons.<sup>182</sup>

#### **IV. Looking Forward: Current and Future Agency Efforts Relating to Companion Diagnostics**

Recent FDA actions suggest an enhanced emphasis on personalized medicine at the agency level (including through the CPI), which could result in greater clarity in the regulation of companion diagnostics. Subsection A describes FDA’s work to establish a regulatory infrastructure for personalized medicine in recent months and the agency’s agenda items for the near future. Subsection B discusses the CPI and its present and future involvement in FDA efforts to devise a coherent regulatory system for companion diagnostics.

##### **A. New FDA Infrastructure and Agenda**

Recently, FDA has taken steps to improve its organizational capabilities for pharmacogenomics. In early 2009, the FDA Office of the Chief Scientist added a “senior genomics advisor” position and the Center for Devices and Radiological Health (CDRH) has created a diagnostics and personalized medicine matrix network to facilitate cross-Center interaction on pharmacogenomics topics.<sup>183</sup> The agency also established the new “Personalized Medicine Staff,” which will prioritize personalized medicine goals and identify particular topics that require new policy and guidance.<sup>184</sup> FDA also is planning to release a guidance document governing interaction between CDRH and CDER, potentially for release in 2010.<sup>185</sup>

Moreover, as discussed above, current FDA leadership appears committed to improving personalized medicine regulation, and in particular, to establishing a workable framework for regulation of personalized medicine products. In her speeches, Dr. Hamburg has

acknowledged that FDA's existing regulatory scheme will not work well for personalized medicine and indicated that guidance on pharmacogenomics topics will be a priority for the agency during her tenure.<sup>186</sup> She has also pointed to specific planned agency efforts to clarify the regulation of companion diagnostics. As described above, Dr. Hamburg indicated that FDA expects to have the co-development guidance completed in 2010. According to the trade press, FDA also plans to issue guidance on adaptive clinical trial designs, pharmacogenomics in early drug development, clinical trial enrichment, and biomarkers sometime in 2010.<sup>187</sup>

On the topic of cross-labeling, Office of Combination Products Director Thinkh Nguyen stated in 2009 that FDA is grappling with the challenges of resolving cross-labeling issues where therapy manufacturers will not cooperate.<sup>188</sup> He indicated that the agency is "weighing whether all product labels should be required to change concurrently" and that resolving this issue will be a priority for 2010.<sup>189</sup>

## **B. The Critical Path Initiative**

FDA has considered refinement of the regulatory processes for approval of companion diagnostics as part of the CPI, a Commissioner-level FDA program launched in 2004,<sup>190</sup> and future efforts on these issues may involve the CPI.

FDA created the CPI because innovative product development began to slow in 2000 despite "exponential" advances in the basic biomedical sciences.<sup>191</sup> The CPI aims to encourage, facilitate and, in some cases, carry out efforts to bridge the gap between advances in basic science and improvements in product development. Recognizing the importance of these efforts, Congress provided direct funding for the CPI in 2008.<sup>192</sup>

In its initial CPI report, FDA called for research to develop biomarkers, assays, and related standards and clinical trial endpoints as key to achieving the CPI's goals.<sup>193</sup> In its 2004 and 2006 CPI reports, FDA recognized the great promise that biomarkers hold for numerous purposes, including targeting and stratifying therapy; predicting responders; individualizing dosing; monitoring therapy; measuring efficacy (including as surrogate endpoints); and predicting drug safety.<sup>194</sup> Also relevant to regulation of companion diagnostics is FDA's acknowledged role in the CPI: to "modernize FDA policies and standards," elucidate the appropriate regulatory pathways for complex products (including combination products), accelerate guidance document development, and improve the "consistency of FDA policies and procedures both within and across divisions."<sup>195</sup>

FDA's 2006 *Critical Path Opportunities List*, which identified 76 "specific opportunities that, if implemented, can help speed the development and approval of medical products," emphasized the importance of clarifying the regulatory pathway for co-developed products.<sup>196</sup> The List noted that "a framework for co-development of a drug and its partner diagnostic could promote biomarker development and facilitate integration of personalized medicine into clinical practice."<sup>197</sup> FDA identified goals of establishing consensus on use of biomarkers for various purposes (including to determine drug toxicity prior to human testing, select doses for dose-ranging trials, evaluate dose response in subsequent trials, and guide patient selection in clinical trials) as well as creating standards for the "types and levels of evidence ... needed to accept a biomarker as a surrogate endpoint for product efficacy."<sup>198</sup>

FDA has cited its efforts on the co-development draft guidance as an important CPI effort. A 2006 CPI report listed drafting of this draft guidance as a CPI activity that FDA had undertaken, stating that the agency "received numerous useful comments [on the concept paper] ... and is developing a draft guidance using this input."<sup>199</sup> Thus, future efforts to produce this guidance may involve the CPI, with CPI officials potentially playing a role in the guidance development process and the principles of the CPI guiding those efforts.

Several other CPI activities could impact developments in the regulation of personalized medicine products.<sup>200</sup> The first CPI effort of interest could play an important role in determining regulatory standards and procedures for obtaining clearance/approval of a companion diagnostic test. After recognizing enthusiasm for the concept of "an independent organization to offer voluntary certification of the performance of diagnostic tests,"<sup>201</sup> the Critical Path Institute (C-Path), a nonprofit organization created by the University of Arizona and FDA to support CPI efforts,<sup>202</sup> launched plans for an affiliated nonprofit organization, United States Diagnostics Standards (USDS), to fill this role.<sup>203</sup> C-Path's vision is that the USDS would evaluate tests before the corresponding device submissions are sent to FDA and also offer testing services for LDTs.<sup>204</sup> In some cases, USDS could test companies' assays against standard samples, after which the company would own the generated data.<sup>205</sup> USDS also could test clinical utility where data are available.<sup>206</sup> User fees would fund USDS review functions, but USDS would have no enforcement powers.<sup>207</sup>

CPI collaborations targeting development of the scientific foundation for different forms of co-development also could influence FDA's thinking on the relevant issues. FDA has partnered with Medco Health Solutions, Inc. on a project aimed at "[e]valuat[ing] the usefulness of pharmacogenetic testing in making therapies safer and more effective for individual

patients” and assessing the ability of a “prescription-driven feedback program” to expedite use of such testing “in clinical practice.”<sup>208</sup> When Medco receives a prescription for which a related pharmacogenetic test is available, it will notify patients and prescribers of the test’s availability, facilitate testing and provide relevant feedback on the results.<sup>209</sup> The pilot stage involves the drug warfarin, while the expanded study will include a number of drug-test pairs. Safety or efficacy in tested patients will then be compared to a cohort receiving standard treatment. Results will be published in peer-reviewed literature. FDA has indicated that the data from this study could be used to re-label the drugs in question.<sup>210</sup> In sum, the CPI could play an important role in FDA’s efforts to flesh out and modernize its regulatory approach to companion diagnostics.

## V. Conclusion

FDA has recognized the potential of companion diagnostics, but has not yet refined and formalized its regulatory framework and standards for approval of these products. Clarification may be forthcoming, as the agency has indicated plans to focus on personalized medicine efforts in the next few years. Anticipated FDA guidance regarding the appropriate approval pathway for co-developed products could go a long way toward providing such clarification. In particular, the agency will need to resolve issues regarding the appropriate criteria for determining when a diagnostic is required for use of a drug and when the diagnostic must be approved or cleared as opposed to remaining an LDT. These activities might also be affected by parallel efforts relating to how LDTs should be regulated. FDA also will need to assemble a workable framework for cross-labeling and mutually conforming labeling. Whether these goals are achieved through the CPI or other agency efforts, the agency should make these objectives a priority to ensure that innovation is not stifled.

## Endnotes

- \* The views expressed here are solely those of the author and do not necessarily reflect the views of her employer or any of its clients.
- 1. “Pharmacogenomics” is defined as “[t]he study of variations of DNA and RNA characteristics as related to drug response.” FDA, *Guidance for Industry: E15 Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories* 3 (Apr. 2008). “Pharmacogenetics” is defined as “a subset of pharmacogenomics” that encompasses “[t]he study of variations in DNA sequence as related to drug response.” *Id.*
- 2. E.g. Barbara J. Evans, *What Will It Take to Reap the Clinical Benefits of Pharmacogenomics?*, 61 *FOOD & DRUG L.J.* 753, 755 (2006) (“pharmacogenomics strains the existing regulatory paradigm for development, validation, approval, clinical introduction, and use of new medical technologies”).

3. “Combination product” is defined to include the following:
  - (1) A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity;
  - (2) Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products;
  - (3) 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; or
  - (4) Any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.

21 C.F.R. § 3.2(e).

4. FDA, *Drug-Diagnostic Co-Development Concept Paper* (Draft—Not for Implementation) (Apr. 2005).
5. *Id.* at 2.
6. *Id.* FDA acknowledges that these tests also might have valuable optional uses in understanding disease mechanisms or in enrichment or patient selection during clinical trials. *Id.* With respect to enrichment, however, FDA provides some cautionary words. Where predictive values have been derived from enriched trials, these values “may not be representative of values likely to be found in unselected patient populations in clinical practice ... [and] consideration should be given in drug-test co-development programs to how to generalize the results from enrichment studies to the target population for the drug and test.” *Id.* at 14.
7. *Id.* at 2.
8. *Id.*
9. *Id.* at 4.
10. *Id.*
11. *Id.*
12. FDCA § 505.

13. See FDA, *Drug-Diagnostic Co-Development Concept Paper*, at 3. The concept paper defines “[a]nalytical validation” as “[t]he in-vitro ability to accurately and reliably measure the analyte of interest.” *Id.* at 25. For purposes of the concept paper, “[c]linical validation” is “[t]he process of determining the ability of a test to detect or predict the associated disorder (phenotype); this includes assessment of clinical sensitivity, clinical specificity, and/or other attributes of testing biological samples.” *Id.* Finally, “clinical utility” is defined to mean “[t]he elements that need to be considered when evaluating the risks and benefits in diagnosing or predicting risk for an event (drug response, presence or risk of a health condition).” *Id.*
14. *Id.* at 5, 10; see also FDA, *Guidance for Industry: Pharmacogenomic Data Submissions* 6, 15 (March 2005). Although FDA’s *Pharmacogenomic Data Submissions* guidance generally describes requirements for submitting pharmacogenomic data to NDA, biologics license application (BLA), and investigational new drug application (IND) files, it also briefly discusses situations where “a pharmacogenomic test shows promise for enhancing the dose selection, safety, or effectiveness of a drug” and the sponsor therefore wishes “to fully integrate pharmacogenomic data into the drug development program.” FDA, *Guidance for Industry: Pharmacogenomic Data Submissions*, at 6. According to the guidance, this integration could take two forms. First the sponsor could seek to include the pharmacogenomic information in the therapy labeling “in an informational manner,” e.g. to discuss possible dose adjustments based on genotype or possible side effects that are more common or severe in patients with particular genetic characteristics. In this case, FDA advises sponsors to consult the appropriate FDA review division for advice on the appropriate pathway in a particular case, given that “an FDA-approved pharmacogenomic test may not be available or required to be available, or a commercial pharmacogenomic test may not be widely available.” *Id.* Second, the sponsor may seek to include the pharmacogenomic information in the therapy labeling for use in choosing a dose and dose schedule, excluding patients at risk from the treatment, or identifying responders. See *id.* In these situations, “FDA recommends co-development of the drug and the pharmacogenomic tests, if they are not currently available, and submission of complete information on the test/drug combination to the Agency.” *Id.*
15. FDA, *Drug-Diagnostic Co-Development Concept Paper*, at 6.
16. *Id.* at 9.
17. *Id.* at 13.
18. *Id.* at 15.
19. *Id.* at 13.
20. *Id.* at 16.

21. *Id.* at 17.
22. *Id.* at 18.
23. *Id.*
24. *Id.* at 21.
25. *See id.* at 5.
26. *Id.* at 18.
27. *Id.* at 18-19.
28. *Id.* at 20.
29. *Id.*
30. *Id.* at 15.
31. *Id.* at 19.
32. *Id.*
33. *Id.*
34. *Id.*
35. *Id.* at 21.
36. *See FDA, Guidance for Industry: Pharmacogenomic Data Submissions*, at 15-16.
37. *Id.* at 16.
38. FDA, *Drug-Diagnostic Co-Development Concept Paper*, at 21.
39. *Id.*
40. *Id.* at 6; *see also FDA, Guidance for Industry: Pharmacogenomic Data Submissions*, at 15 (noting that, in situations where pharmacogenomic data on dosing or potential adverse events is available, “FDA’s usual approach in such cases has been to request that information be added to the drug labeling” but where the sponsor decides “to develop the drug solely in populations from which certain patients were excluded based on pharmacogenomic testing,” the agency recommends “co-development of the [test and therapy] because FDA would be unable to approve a drug for which the risk or benefit was predicated on a pharmacogenomic test that was unavailable”).
41. FDA, *Drug-Diagnostic Co-Development Concept Paper*, at 6.
42. Comments of Roche, Docket No. 2004N-0279 (July 8, 2005), at 1; *see also* Comments of AdvaMed, Docket No. 2004N-0279 (July 15, 2005), at 2 (“It appears that much of the document is based on ... an idealized classic model of twentieth century drug development”).
43. Comments of Roche, *supra* note 42, at 1.
44. Comments of AdvaMed, *supra* note 42, at 3; *see also* Evans, *supra* note 2, at 755.
45. Comments of AdvaMed, *supra* note 42, at 2; *see also* Comments of Roche, *supra* note 42, at 1.
46. Comments of Roche, *supra* note 42, at 1.

47. Evans, *supra* note 2, at 759; *Personalized Medicine Group Plans Talks With FDA on Approval Path*, FDA WEEK (May 2, 2008) (discussing proposal of Personalized Medicine Coalition).
48. Evans, *supra* note 2, at 792.
49. See, e.g., *Industry Seeks Changes in FDA Drug/Diagnostic Co-Development Model*, THE GRAY SHEET (Aug. 8, 2005), at 13.
50. FDCA § 513(a)(3)(D)(ii); Comments of Roche, *supra* note 42, at 2; Comments of AdvaMed, *supra* note 42, at 2-3.
51. Comments of AdvaMed, *supra* note 42, at 6, 7.
52. *Id.* at 2.
53. Comments of Roche, *supra* note 42, at 2.
54. *Id.* at 2, 3; Comments of AdvaMed, *supra* note 42, at 2, 3.
55. Comments of AdvaMed, *supra* note 42, at 3.
56. *FDA Adjusts Thinking on Drug/Diagnostic Co-Development Draft Guidance*, THE GRAY SHEET (July 31, 2006), at 9.
57. *Id.* (internal quotation marks omitted).
58. *PMC Asks FDA to Issue New Guidance Reflecting Rapidly Evolving Rx/Dx Co-development Landscape*, GENOME WEB (Dec. 16, 2009).
59. *See FDA Top Officials Discuss Ongoing Efforts to Bring Agency Into Genomics Era*, GENOME WEB (Nov. 11, 2009).
60. PMC, *About PMC*, [http://www.personalizedmedicinecoalition.org/about/pmc\\_members.php](http://www.personalizedmedicinecoalition.org/about/pmc_members.php) (last visited Feb. 10, 2010).
61. PMC, *COMMENTS ON DEVELOPMENT OF COMPANION DIAGNOSTICS AND THE APRIL 2005 FDA DRUG-DIAGNOSTIC CO-DEVELOPMENT CONCEPT PAPER 1*, 13 (Dec. 9, 2009), [www.personalizedmedicinecoalition.org/sciencepolicy/Comments-to-FDA-Development-of-Companion-Diagnostics.pdf](http://www.personalizedmedicinecoalition.org/sciencepolicy/Comments-to-FDA-Development-of-Companion-Diagnostics.pdf) (PMC White Paper).
62. Margaret Hamburg, M.D., Commissioner of Food and Drugs, FDA, *Remarks at AAAS-The Future of Personalized Medicine* (Oct. 26, 2009), *available at* <http://www.fda.gov/NewsEvents/Speeches/ucm191356.htm>.
63. FDA, *Guidance Agenda: New Draft Guidances CDER is Planning to Publish During Calendar Year 2010*, at 2, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079647.pdf> (last visited Feb. 8, 2010).
64. *FDA Chief Commits to Completing Rx/Dx Codevelopment Guidance This Year, Improving Regulatory Science*, GENOME WEB (Mar. 3, 2010).
65. Margaret Hamburg, M.D., Commissioner of Food and Drugs, FDA, *Remarks at AAAS-The Future of Personalized Medicine* *supra* note 62.

66. PMC White Paper, *supra* note 61, at 2. PMC contended FDA should expand the scope of the concept paper to address approval and labeling requirements in a greater multitude of situations, for example: where the companion diagnostic to an investigational therapeutic product is already approved for a different indication; where one component of an already-approved tandem is approved for a new indication; where a new or modified diagnostic is developed for use with a particular approved drug; and where the final version of the diagnostic is not available during drug clinical trials. *See id.* at 8, 12. The PMC White Paper also exhorted FDA to clarify the situations where co-development should be pursued instead of “the traditional two-track process.” *Id.* at 7, 8.
67. *Id.* at 4, 5.
68. *Id.* at 13.
69. *Id.* at 8, 13.
70. *See* 70 Fed. Reg. 15,633, 15,634 (Mar. 28, 2005); Evans, *supra* note 2, at 785.
71. 70 Fed. Reg. at 15,633. According to the agency, mutually conforming labeling results in a “combination product” under 21 C.F.R. § 3.2(e)(3). *Id.*; *see also supra* note 3.
72. 70 Fed. Reg. at 15,633.
73. *Id.*
74. *Id.* at 15,634; *FDA Mulls Off-Label, Medical Imaging Issues in Cross-Labeling*, FDA WEEK (Sept. 25, 2009).
75. 70 Fed. Reg. at 15,633.
76. Comments of AdvaMed, Docket No. 2005N-0098 (July 8, 2005), at 15.
77. *Id.* (citing *Ass’n of Physicians & Surgeons, Inc. v. FDA*, 226 F. Supp. 2d 204 (D.D.C. 2002)).
78. *See* Nancy Stade, Associate Chief Counsel for Devices, FDA, *Legal Considerations in Cross-Labeling Policy* (presentation at FDA/DIA Combination Products & Mutually Conforming Labeling Workshop) (May 10, 2005).
79. Comments of AdvaMed, *supra* note 76, at 33-34. The Association for Molecular Pathology argued in a 2009 letter to FDA that the agency should discourage use of a particular brand name in drug labeling because this amounts to “a tacit endorsement of one company’s tests” over other tests. Letter from Jan Nowak, M.D., Ph.D., President, Ass’n for Molecular Pathology, to Janet Woodcock, M.D., Director, CDER (Aug. 27, 2009).
80. Comments of AdvaMed, *supra* note 76 at 20, 34.
81. *Id.* “General consistency” as defined by AdvaMed does not mean identity in labeling but instead requires that the company with the new product show that safety or effectiveness issues can be addressed in the new product labeling and/or a risk management plan. *Id.* at 34.

82. *Id.* at 16-17 (noting that “AdvaMed members believe that any cross-labeling solution must protect data to which Company B by law does not have a right to reference” and that “existing restrictions [on the disclosure of data in NDAs] are adequate”); *id.* at 17 (“combination policies acknowledge that prior approvals may be relied on as findings to reduce safety and efficacy data demands for combined drug/device products. These principles permitting Company B’s appropriate reliance on public domain information, have stood the test of time, have fostered innovation, and should remain fully protected and preserved”).
83. FDA, FY 2005 PERFORMANCE REPORT TO CONGRESS FOR THE OFFICE OF COMBINATION PRODUCTS, 12 (2006).
84. *Office of Combination Products Keeps Up Work to Clarify Regulatory Process*, THE GRAY SHEET (Aug. 6, 2007), at 15.
85. FDA, FY 2007 PERFORMANCE REPORT TO CONGRESS FOR THE OFFICE OF COMBINATION PRODUCTS, 11.
86. FDA, *Draft Guidance: New Contrast Imaging Indication Considerations for Devices and Approved Drug and Biological Products* (Sept. 2008).
87. FDA, *Guidance for Industry: New Contrast Imaging Indication Considerations for Devices and Approved Drug and Biological Products* (Dec. 2009).
88. *Id.* at 6-7.
89. The guidance indicates that “individual imaging contrast indications may present unique or complex issues of safety or effectiveness that necessitate a review approach” distinct from that set out in the guidance. *Id.* at 7.
90. *Id.* at 7.
91. *Id.* at 20.
92. *Id.* at 7.
93. *Id.* at 8.
94. FDA guidance categorizes imaging drug indications for one of the following:
  - 1) “[s]tructural delineation;” 2) “[d]isease or pathology detection or assessment;”
  - 3) “[f]unctional, physiological or biochemical assessment; or 4) “[d]iagnostic or patient management.” *Id.* at 11-12 (citing FDA, *Guidance for Industry, Developing Medical Imaging Drug and Biological Products: Part 2, Clinical Indications* (June 2004), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071603.pdf>).
95. *Id.* at 8, 12.
96. *Id.* at 7.
97. *Id.*

98. FDA, *Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels*; <http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm> (last visited Feb. 8, 2010). Recently issued FDA draft guidance recommends that drug labeling with significant pharmacogenomic information contain a separate “Pharmacogenomics” subsection within the clinical pharmacology section and also include pharmacogenomic information in other sections of the labeling, e.g. indications and/or warnings, to the extent it is needed for safe and effective use of the drug. FDA, *Draft Guidance for Industry: Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products—Content and Format* 10 (Feb. 2009). Many drug labels have not yet been revised to follow this form however, so pharmacogenomics information may be located in other aspects of their labeling at this time.
99. *See Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels* (May 2007) (on file with author).
100. Press Release, FDA, FDA Approves Erbitux for Colorectal Cancer, P04-20 (Feb. 12, 2004); Press Release, Dep’t. of Health & Human Services (HHS), New Monoclonal Antibody Approved for Advanced Breast Cancer, P98-27 (Sept. 25, 1998).
101. Press Release, FDA, FDA Approves a New Drug for Colorectal Cancer, Vectibix, P06-148 (Sept. 27, 2006); FDA, PMA Database, Entry for Dako EGFR PHARMDX KIT (P030044/S002).
102. FDA, *Other Types of Combinations of FDA Regulated Products*, <http://www.fda.gov/CombinationProducts/AboutCombinationProducts/ucm101464.htm> (last visited Feb. 9, 2010).
103. Press Release, HHS, New Monoclonal Antibody Approved for Advanced Breast Cancer, *supra* note 100; Center for Biologics Evaluation & Research, FDA, Clinical Review Briefing Document: sBLA STN: 103792/5008/0, Trastuzumab, at 4 (Nov. 5, 2001); *see also* Herceptin Prescribing Information, Clinical Studies section (Immunohistochemical Detection) 1 (Sept. 1998).
104. Herceptin Prescribing Information, § 5.5 (Mar. 2009).
105. *Id.*; Approval Letter for P050040 from Maria M. Chau, Ph.D., Center for Devices and Radiological Health (CDRH), FDA, to Kelli L. Tanzella, Ph.D., Invitrogen Corp. (July 1, 2008).
106. Approval Letter from Richard Padzur, M.D., CDER, FDA, to SmithKline Beecham Corp. (Mar. 13, 2007).
107. Tykerb Prescribing Information, § 14 (Mar. 2007). Tykerb now also is indicated for use in combination with “letrozole for the treatment of postmenopausal women with hormone receptor positive metastatic breast cancer that overexpresses the HER2

- receptor for whom hormonal therapy is indicated.” Tykerb Prescribing Information, § 1 (Jan. 2010). The trial for this indication enrolled patients with hormone receptor positive (estrogen receptor positive and/or progesterone receptor positive) metastatic breast cancer but varying HER2 status. *Id.* § 14.2. The labeling does not disclose the test used for receptor status, but a variety of tests for estrogen and progesterone receptor status have been cleared through the 510(k) process. *See, e.g.*, FDA, 510(k) Substantial Equivalence Determination Decision Summary for K042884, DakoCytomation ER/PR pharmDx™ Kit, section H (Feb. 2005), [http://www.accessdata.fda.gov/cdrh\\_docs/reviews/K042884.pdf](http://www.accessdata.fda.gov/cdrh_docs/reviews/K042884.pdf).
108. Erbitux Prescribing Information, § 1.2 (July 2009); Approval letter for P030044 from Steven I. Gutman, M.D., M.B.A., CDRH, FDA, to Ronald F. Lagerquist, DakoCytomation California, Inc. (Feb. 12, 2004).
  109. Erbitux Prescribing Information, Clinical Studies, EGFR Expression and Response section (Feb. 2004).
  110. Erbitux Prescribing Information, § 5.7 (July 2009).
  111. Approval Letter from Richard Padzur, M.D., CDER, FDA, to Alessandra Cesano, M.D., Amgen, Inc. (Sept. 27, 2006). FDA, PMA Database, Entry for Dako EGFR PHARMDX KIT (P030044/S002); Vectibix Prescribing Information, Clinical Studies, EGFR Expression and Response section (Sept. 2006).
  112. FDA, *Other Types of Combinations of FDA Regulated Products*, *supra* note 102.
  113. Approval Letter from Robert Temple, M.D., CDER, FDA, to Robert A. Miranda, Novartis Pharmaceuticals Corp. (May 10, 2001); Gleevec Prescribing Information, Indications and Usage section (revised May 9, 2001).
  114. *See* Gleevec Prescribing Information, Indications and Usage (May 2009).
  115. Approval Letter for P040011 from Robert L. Becker, Jr., M.D., Ph.D., CDRH, FDA, to Tiffany D. Almeroth, R.A.C., DakoCytomation California, Inc. (June 27, 2005).
  116. FDA, *Other Types of Combinations of FDA Regulated Products*, *supra* note 102.
  117. Approval Letter for P020055 from Robert L. Becker, Jr., M.D., Ph.D. CDRH, FDA, to Richard A. Isenberg, M.D., Ventana Med. Systems, Inc. (Aug. 11, 2004).
  118. Elitek Prescribing Information, Highlights, Black Box Warning (Oct. 2009).
  119. Elitek Prescribing Information Black Box Warning (June 2008).
  120. *E.g.* FDA, 510(k) Database, Entry for Glucose-6-Phosphate Dehydrogenase Deficiency Screening Test Kit No. 202-A (K933934) (cleared June 29, 1995). Interestingly, as described below, information regarding G6PD deficiency has not been updated in the primaquine labeling, which still falls into the “information only” category of genomic content, despite that patients with G6PD deficiency taking this drug may experience moderate-to-severe hemolytic reactions. Similarly, the dapsone tablets

- labeling content regarding G6PD deficiency has not been updated to require testing, even though hemolysis may be exaggerated in these patients and can be dose-related. Dapsone Prescribing Information, Precautions section (Apr. 2008). The reason for these differences from the Elitek labeling is unclear. Aczone, a topical dapsone gel, also includes “information-only” content, likely because G6PD deficiency only causes “mild” hemolysis in users of this product. Aczone Prescribing Information, Highlights, Warnings and Precautions section (Apr. 2008).
121. Press Release, FDA, FDA Approves Novel Antiretroviral Drug (Aug. 6, 2007).
  122. *Id.*
  123. *As Pfizer’s HIV Drug Selzentry Gains FDA Approval, Monogram Preps for Trofile Launch*, GENOME WEB (Aug. 8, 2007).
  124. Selzentry Prescribing Information, Highlights, Indications and Usage section (June 2009); Selzentry Prescribing Information, Highlights, Indications and Usage section (Aug. 2007); *see also* Selzentry Prescribing Information, Highlights, Indications and Usage (Nov. 2009) (“Tropism testing with a highly sensitive tropism assay is required for appropriate use of Selzentry”).
  125. *As Pfizer’s HIV Drug Selzentry Gains FDA Approval, Monogram Preps for Trofile Launch*, GENOME WEB (Aug. 8, 2007); Debra Birnkrant, M.D., FDA, Decisional Review for NDA 22-128 (June 20, 2007), at 1-2 (noting that the Trofile assay was unapproved at the time of Selzentry’s review, that “plans are underway for the Center for Biologic Evaluation and Research to encourage” submission of an application for the test, and that “[c]urrently, regulatory policies are evolving for this type of test”); *Pfizer’s Pending HIV Drug Maraviroc May Require Patients to Confirm CCR5-Tropism Status*, GENOME WEB (Nov. 30, 2006).
  126. *Monogram Launches Companion Diagnostic to Pfizer’s New HIV Drug*, THE GRAY SHEET (Aug. 13, 2007), at 5.
  127. *See* Monogram Biosciences, Inc., *How to Order Trofile™ in United States*, [http://www.trofileassay.com/how\\_to\\_order\\_us.html](http://www.trofileassay.com/how_to_order_us.html) (last visited Feb. 10, 2010); *Market for Monogram’s Trofile Assay Poised for Growth as Pfizer Extends Co-Marketing Deal*, GENOME WEB (May 20, 2009) (“Monogram performs the Trofile test at its CLIA-lab facility”).
  128. Ontak Prescribing Information, § 1 (Oct. 2008).
  129. *Id.* § 5.4.
  130. Revlimid Prescribing Information, Indications and Usage section (Feb. 2009).
  131. *FDA’s Rx/Dx Co-Development Approach Overlooks Incentives—Novartis Exec*, THE PINK SHEET (June 26, 2006), at 21.
  132. *Id.*

133. *E.g.*, Tegretol Prescribing Information, Black Box (Dec. 2007).
134. FDA, *Information for Healthcare Professionals: Dangerous or Even Fatal Skin Reactions - Carbamazepine (marketed as Carbatrol, Equetro, Tegretol, and generics)* (Dec. 12, 2007), <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124718.htm>; *see also* FDA, *Phenytoin (marketed as Dilantin, Phenytek and generics) and Fosphenytoin Sodium (marketed as Cerebyx and generics): Healthcare Professional Sheet text version* (Nov. 24, 2008), <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124788.htm> (noting that FDA is investigating preliminary data suggesting that patients with the HLA-B\*1502 allele also may experience serious skin reactions when treated with phenytoin and the pro-drug fosphenytoin, but there is not yet enough information to recommend genetic testing).
135. *E.g.*, Tegretol Prescribing Information, Black Box (Feb. 2009).
136. *FDA Updates Carbamazepine Label to Urge Genetic Testing for Rare Skin Reactions*, GENOME WEB (Dec. 19, 2007).
137. *Id.*
138. FDA, *Information for Healthcare Professionals: Abacavir (marketed as Ziagen) and Abacavir-Containing Medications* (July 24, 2008), <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm123927.htm>.
139. Ziagen Prescribing Information, Black Box (Dec. 2008).
140. FDA, *Information for Healthcare Professionals: Abacavir (marketed as Ziagen) and Abacavir-Containing Medications*, *supra* note 138; *FDA Urges Gene Test before HIV Treatment*, THE GRAY SHEET (July 28, 2008), at In Brief.
141. Felix W. Frueh et al., *Pharmacogenomic Biomarker Information in Drug Labels Approved by the United States Food and Drug Administration: Prevalence of Related Drug Use*, 28 PHARMACOTHERAPY 992, 997 (2008); *Camptosar Prescribing Information, Dosage and Administration & Warnings sections* (July 2008). Subsequent to adding this genetic information to the labeling, a study found that administering irinotecan in low doses over two weeks (instead of monthly) eliminates the need for the genetic test in children. *Lower Drug Dose Spells Trouble for Pharmacogenetic Test*, THE GRAY SHEET (June 25, 2007), at 10. The labeling has not been changed based on this study, however.
142. Talk Paper, FDA, *FDA Approves Drug for Advanced Colorectal Cancer*, T96-42 (June 17, 1996); 510(k) Summary for Invader UGT1A1 Molecular Assay 11 (Aug. 18, 2005).
143. Imuran Prescribing Information, Clinical Pharmacology section (May 2008).

144. *Id.*, Dosage and Administration section.
145. *See id.*, Precautions section; *see also* Prometheus Diagnostics, PROMETHEUS THIOPURINE MANAGEMENT, [http://prometheuslabs2007.egofactory.com/Resources/PTM/DX06045\\_Patient\\_Brochure\\_PTM\\_PRC\\_Approved.pdf](http://prometheuslabs2007.egofactory.com/Resources/PTM/DX06045_Patient_Brochure_PTM_PRC_Approved.pdf) (describing Prometheus TPMT Genetics test). TPMT testing is also recommended for the related drugs mercaptopurine (Purinethol and generics) and Tabloid (thioguanine). Frueh et al., *supra* note 141, at 997.
146. Frueh et al., *supra* note 141, at 997.
147. Nat'l Urea Cycle Disorders Foundation, *What is a Urea Cycle Disorder?* (2005), <http://www.nucdf.org/ucd.htm>.
148. Depakene Prescribing Information, Warnings section (Nov. 2009).
149. *Id.*
150. Marshall L. Summar, M.D., *Urea Cycle Disorders Overview*, Table 1 (2005), <http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=ucd-overview>.
151. *See id.*
152. *See Proof Is In the Pudding*, BIOCENTURY (Mar. 31, 2008), at A2.
153. *Id.* at A3.
154. *Id.*
155. *See id.*; *FDA Update to Erbitux, Vectibix Labels Encourages Rx/Dx Co-development, Industry Expert Says*, GENOME WEB (July 22, 2009).
156. *FDA Update to Erbitux, Vectibix Labels Encourages Rx/Dx Co-development, Industry Expert Says*, Genome Web (July 22, 2009).
157. *FDA Top Officials Discuss Ongoing Efforts to Bring Agency Into Genomics Era*, GENOME WEB (Nov. 11, 2009).
158. FDA, *Class Labeling Changes to anti-EGFR monoclonal antibodies, cetuximab (Erbitux) and panitumumab (Vectibix): K-RAS Mutations*, <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm172905.htm> (last visited Feb. 10, 2010).
159. *See generally* Erbitux Prescribing Information (July 2009); Vectibix Prescribing Information (July 2009); *see also Labs Discourage Referring to 'Companion Diagnostics' by Brand Name*, FDA WEEK (Oct. 9, 2009).
160. *Proof Is In the Pudding*, BIOCENTURY (Mar. 31, 2008), at A3; *Transgenomic Launches Surveyor K-RAS Mutation Test Kit; Touts Advantages Over Rival Platform*, GENOME WEB (Dec. 9, 2009); *Qiagen Buys DxS, Boasts "Deepest" Personalized Medicine Testing Pipeline*, THE GRAY SHEET (Sept. 28, 2009), at 11.
161. *Qiagen Buys DxS, Boasts "Deepest" Personalized Medicine Testing Pipeline*, THE GRAY SHEET (Sept. 28, 2009), at 11-12; *Proof Is In the Pudding*, BIOCENTURY (Mar. 31, 2008), at A5.

162. Frueh et al., *supra* note 141, at 995.
163. *Id.* at 997.
164. *Id.* at 998.
165. *Id.*
166. Xeloda Prescribing Information, Contraindications, Precautions, & Clinical Pharmacology sections (Nov. 2009); *see also* Carac (fluorouracil cream) Prescribing Information, Contraindications and Warnings sections (Nov. 2006) (noting this drug also should not be given to patients with DPD deficiency due to risk of serious toxicity).
167. *See* Myriad Genetics, TheraGuide 5-FU™ Analysis Result, <http://www.myriadtests.com/provider/doc/Sample-Results-TheraGuide-5FU-Indeterminate.pdf> (last visited Feb. 11, 2010).
168. Primaquine Prescribing Information, Warnings section (Nov. 2007); *see also supra* note 120.
169. Rifater Prescribing Information, Clinical Pharmacology section (Apr. 2008).
170. *Id.*
171. Tasigna Prescribing Information, § 12.5 (Aug. 2009). According to PMC, this labeling content was based on an analysis of archival samples from testing conducted prior to drug approval. PMC White Paper, *supra* note 61, at 7.
172. Myleran Prescribing Information, Clinical Pharmacology section, Clinical Studies (Jan. 2004).
173. The insert for Tarceva (erlotinib) previously contained information-only content about EGFR expression status and this information is still reflected in the *Table*, but it has since been removed from the labeling. *See Table, supra* note 98; Tarceva Prescribing Information (Apr. 2009).
174. Vesanoïd Prescribing Information, Indications and Usage section (July 2008).
175. *Id.*, Clinical Pharmacology section, Clinical Studies (July 2008); *see also* Medicine.Net, Inc., Definition of Acute promyelocytic leukemia, <http://www.medterms.com/script/main/art.asp?articlekey=19758> (last visited Feb. 10, 2010).
176. Vesanoïd Prescribing Information, Clinical Pharmacology section, Clinical Studies (July 2008).
177. *See Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels* (Jan. 2008), available at [http://web.archive.org/web/20080223232434/www.fda.gov/cder/genomics/genomic\\_biomarkers\\_table.htm](http://web.archive.org/web/20080223232434/www.fda.gov/cder/genomics/genomic_biomarkers_table.htm); *Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels* (May 2007) (on file with author).
178. *E.g.* Arup Labs., PML/RAR $\alpha$  t(15;17) Translocation by RT-PCR (Feb. 2006), [http://www.arup-lab.com/Testing-Information/resources/TechnicalBulletins/PML-RAR%20t\(15%17\)%20Translocation%20by%20RT-PCR%20Feb%202006.pdf](http://www.arup-lab.com/Testing-Information/resources/TechnicalBulletins/PML-RAR%20t(15%17)%20Translocation%20by%20RT-PCR%20Feb%202006.pdf). Another drug,

- Trisenox, is indicated for patients whose APL is characterized by the presence of the t(15;17) translocation or PML/RAR-alpha gene expression, but it is only indicated for patients who are refractory to, or have relapsed from, retinoid therapy, and therefore presumably would have already had the confirmatory genetic testing. Trisenox Prescribing Information, Indications section (Nov. 2008).
179. Sprycel Prescribing Information, Indications and Usage section (June 2009).
  180. *Gleevec Replacements Sprycel and Tasigna Show Promising Results; Will New Dx Emerge?* GENOME WEB (June 21, 2006).
  181. *See* Sprycel Prescribing Information, § 14 (May 2009); *see also* FDA, Acting Deputy Director/Medical Team Leader's Summary Review for NDAs 21-986 and 22-072 (June 28, 2006), at 8 ("Imatinib resistance was defined as: 1) progression of CP-CML on imatinib  $\geq$  400 mg/day, or 2) progression of AP-CML on imatinib  $\geq$  600 mg/day, or 3) MBP- or LBP-CML after at least 4 weeks of treatment with imatinib  $\geq$  600 mg/day"); FDA, Clinical Review for NDA 21-986 (June 22, 2006), at 38 (same).
  182. Tasigna Prescribing Information, § 1 (Aug. 2009).
  183. *FDA Diagnostics Office Seeks Bigger Role in Personalized Medicine*, THE GRAY SHEET (Apr. 27, 2009), at 6.
  184. *FDA Sets Up Coordination Office for Personalized Medicine*, FDA WEEK (Oct. 30, 2009).
  185. *Industry-Sought FDA Device/Drug Center Coordinating Guide in the Works*, FDA WEEK (Mar. 4, 2010).
  186. *FDA, NIH Chiefs Signal New Focus on Personalized Medicine*, FDA WEEK (Oct. 30, 2009); *Personalized Medicine Does Not Fit In FDA's Current Scheme, Experts Say*, THE GRAY SHEET (Oct. 12, 2009), at 15; *see also* FDA, Guidance Agenda: New Draft Guidances CDER is Planning to Publish During Calendar Year 2010; <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079647.pdf> (last visited Feb. 11, 2010).
  187. *FDA to Release Multiple Guidances on Personalized Medicine This Year*, FDA WEEK (Feb. 11, 2010); *Industry-Sought FDA Device/Drug Center Coordinating Guide in the Works*, FDA WEEK (Mar. 4, 2010); *see also* FDA, Guidance Agenda: New Draft Guidances CDER is Planning to Publish During Calendar Year 2010, *supra* note 186.
  188. *FDA Mulls Off-Label, Medical Imaging Issues in Cross-Labeling*, FDA WEEK (Sept. 25 2009).
  189. *Id.*
  190. FDA, INNOVATION/STAGNATION: CRITICAL PATH OPPORTUNITIES REPORT R-8 (March 2006) (2006 CPI Report).

191. FDA, INNOVATION/STAGNATION: CHALLENGE AND OPPORTUNITY ON THE CRITICAL PATH TO NEW MEDICAL PRODUCTS 3 (March 2004) (2004 CPI Report).
192. FDA, THE CRITICAL PATH INITIATIVE PROJECTS RECEIVING CRITICAL PATH SUPPORT FISCAL YEAR 2008 2 (Apr. 2009) (2008 CPI Report).
193. 2004 CPI Report, *supra* note 191, at 8.
194. 2006 CPI Report, *supra* note 190, at R-10-R-11.
195. *Id.* at iii, R-21.
196. FDA, INNOVATION/STAGNATION: CRITICAL PATH OPPORTUNITIES LIST INTRODUCTION (Mar. 2006).
197. *Id.* at L-1.
198. *Id.*
199. FDA, CRITICAL PATH OPPORTUNITIES INITIATED DURING 2006, at 2-3.
200. *See generally id.*; 2008 CPI Report, *supra* note 192; FDA, KEY FDA CRITICAL PATH ACTIVITIES UNDER WAY IN 2007 (June 2008).
201. Critical Path Institute, IMPROVING THE PATH FOR INNOVATIVE THERAPIES: 2008 ANNUAL REPORT 2 (2009); *see also New C-Path Group Would Smooth FDA-Industry Interaction Over Dx*, GENOME WEB (Jan. 7, 2009).
202. C-Path, *About Us*, <http://www.c-path.org/about.cfm> (last accessed Feb. 11, 2010).
203. Critical Path Institute, *supra* note 201.
204. *New C-Path Group Would Smooth FDA-Industry Interaction Over Dx*, GENOME WEB (Jan. 7, 2009).
205. *Id.*
206. *Id.*
207. *Id.*
208. 2008 CPI Report, *supra* note 192, at 29.
209. *Id.* at 29-30.
210. *Genomic Updates to Drug Labeling Could Boost Gene Testing*, THE GRAY SHEET (Sept. 1, 2008), at 17.