PMC Members Newsletter

The Personalized Medicine Coalition, representing a broad spectrum of academic, industrial, patient, provider and payer communities, seeks to advance the understanding and adoption of personalized medicine concepts and products for the benefit of patients.

Spring | 2010

Drug Regulation Must Evolve, FDA Official Says

WASHINGTON, D.C. — The Food and Drug Administration "must serve as a catalyst for innovation" in addition to reviewing and regulating drugs and medical devices, FDA Commissioner Margaret Hamburg, M.D., told members of the Personalized Medicine Coalition at a meeting on February 25.

"In order for the FDA to build on the promise that personalized medicine holds for new and better therapies, in addition to our roles as reviewer and regulator, FDA must also serve as a catalyst for innovation," Dr. Hamburg told more than 150 leaders from industry, government and academe at PMC's Sixth Annual State of Personalized Medicine luncheon. "This involves, among other things, increased outreach and collaboration with industry, academia and our government research colleagues.

Personalized medicine will likely be one of the "most important themes for healthcare in the future, promising not only better and safer treatments for patients, but also potentially lowering overall healthcare costs," Dr. Hamburg said in a speech titled "Bringing Home the Genome: The FDA's Role in Realizing Personalized Medicine."

As part of FDA's commitment to helping personalized medicine advance, the agency will produce draft guidance on companion diagnostics by the end of this year, she said. The companion continued on page 2



Margaret Hamburg, M.D., Food and Drug Administration Commissioner

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FROM THE PRESIDENT



New Guidelines Would Ease Adoption of Personalized Medicine

BY EDWARD ABRAHAMS

"There are many challenges before us," Margaret Hamburg, M.D., Commissioner of the Food and Drug Administration, noted at the Sixth Annual State of Personalized Medicine Address at the National Press Club in Washington, D.C. on February 25th. "But I believe that a future that provides safer and more effective therapies for all of us is well worth the effort." Her statement is in keeping with the message

of the Personalized Medicine Coalition.

Personalized medicine is well worth the effort, she exclaimed, because it opens the door for higher quality outcomes at lower costs, while she acknowledged that FDA must create a new regulatory framework to ensure that that promise is realized. She is the highest ranking official in the Obama Administration to recognize that medical continued on page 10

CMS Lacks Clear Guidance on Reimbursement, Policy Committee Says

Members of the Personalized Medicine Coalition's Public Policy Committee told officials from the Centers for Medicare and Medicaid Services (CMS) at a meeting on February 24 that guidance is lacking on the scientific evidence CMS requires to approve reimbursement of a genetic test. Jim Rowlands, M.D. and Jeffrey Roche, M.D., medical officers in CMS's Office of Clinical Standards and Quality, told the committee they want to "ensure that Medicare beneficiaries have access to any demonstrated improved health outcomes of pharmacogenomic testing." The Public Policy Committee has formed a workgroup comprising a broad variety of PMC members to express its concerns to CMS in an effort to help the agency clarify its regulations.

PMC Committee to Propose Changes to GPMA

Members of PMC's Public Policy Committee in March discussed proposed changes to the Genomics and Personalized Medicine Act. Mark Hoeft, M.D., a legislative fellow for Representative Patrick Kennedy, D-R.I., sought the committee's help at its December 15 meeting. PMC members praised the draft's codification of the Personalized Healthcare Initiative and its funding for workforce training and genomics research. Without business incentives, however, they said it is difficult to overcome the barriers to personalized-medicine adoption that result from existing business models. PMC will continue to advocate for provisions such as a research and development tax credit and patent extension in the Senate bill.

HHS Office to Meet in April on Policy Framework for HIT

The Office of the National Coordinator for Health Information Technology at the Department of Health and Human Services will hold seven workgroup meetings in April to discuss a policy framework for a nationwide infrastructure that permits the electronic exchange of health information. The announcement of the workshops comes as PMC has asked the Brookings Institution to write a new white paper on the intersection between health information technology and personalized medicine. For further information, contact Judy Sparrow at 202-205-4528 or judy.sparrow@hhs.gov.

Regulation of Personalized Medicine Must Evolve

continued from page 1 diagnostics guidance will clarify the agency's expectations for the clinical trials and levels of confidence needed to demonstrate that a test is accurate and can be used for clinical assessments.

Another guidance document will focus on biomarker qualifications, which will inform developers of the criteria FDA will use to vet the usefulness of biomarkers and evaluation of clinical trial data, Dr. Hamburg said. Both pieces of guidance are part of an overall plan to improve FDA's approval process for personalized-medicine products and services, she said.

"It is clear to me that we need to develop a consistent, comprehensive and integrated approach to the evaluation and regulation of medical products which separately, and in combination, comprise the practice of personalized medicine," she said.

Consistent, fair regulation of personalized medicine cannot be accomplished, Dr. Hamburg said, until the agency rethinks the way it regulates such products. Centers within FDA need to improve their communications and work together to help regulatory policy evolve, the FDA leader said, particularly for incorporating companion diagnostics tests into the drug approval process.

"Just as biomedical research has evolved in the past decade, regulatory science—the science and tools we use to assess and evaluate a product's safety, effectiveness, potency, quality and performance—must also evolve," Dr. Hamburg said.

The companion diagnostics guidance is among the most significant of planned pieces of regulation related to personalized medicine. Because drugs and diagnostics have traditionally been regulated by different centers at FDA, companies have found it difficult to coordinate the release of a drug with a companion diagnostic test that would guide the drug's use. Last year, PMC sent the agency a white paper with recommendations for companion diagnostic regulation. Regulation must take account of the different ways in which companion products are developed and brought to market, PMC said, and FDA's

oversight must be open and transparent.

"Dr. Hamburg has the capability and the opportunity to become a transformational FDA Commissioner at a pivotal time in its history," said Ralph Snyderman, M.D., Chancellor Emeritus, Duke University. "Dr. Hamburg's talk demonstrated that she clearly understands the critical role that FDA will play in enabling personalized medicine and she is committed to having this be a major theme for her administration. Her address gives me great confidence in her leadership as well as her understanding of the importance of the role FDA will play in enabling the adoption of appropriate uses of personalized medicine."

Dr. Snyderman introduced Dr. Hamburg at the luncheon, which was sponsored by the Friends of the Personalized Medicine Coalition, a group of leaders in personalized medicine who have committed to personally supporting PMC and its agenda. A complete transcript of Dr. Hamburg's remarks is available at http://PersonalizedMedicineCoalition.org.

POLICY BRIEF



Personalized Medicine, Patients Win Victory

BY AMY MILLER | PUBLIC POLICY DIRECTOR

The passage of the landmark health-care reform legislation marked a major victory for personalized medicine. Not only did the bill recognize the emerging science of personalized medicine, it also ensured its alignment with the conduct and use of comparative effectiveness research. Significantly, it is also the first time that the principles of personalized medicine were signed into law.

Throughout the debate, PMC has supported policy solutions that are rooted in science and advance the interests of patients by incorporating personalized medicine concepts into comparative effectiveness research. The Coalition will continue to advocate for policy rooted in science throughout the implementation process.

With healthcare reform behind us, we can turn our attention to policy barriers to personalized medicine in business, reimbursement, and health information technology, knowing that there will be considerable interest in it because personalized medicine promises to improve patient care while lowering systemic costs.

Reintroduction of the Genomics and Personalized Medicine Act offers one such opportunity. Designed to advance personalized medicine by overcoming barriers to it, the original Obama Bill, first introduced in 2007, provided for research funding, genetics education, and studies of barriers to personalized medicine. PMC supports a bill that will build on that platform and also break down business model barriers by providing a research and development tax credit, a patent extension for

targeted therapeutics, and a streamlined FDA process for personalized medicine products.

From our discussions with congressional leaders we know that policy-makers are deeply interested in clarifying FDA's role in the regulation of personalized medicine test services. It is an open question as to how

PMC supports a bill that will also break down business model barriers by providing a research and development tax credit, a patent extension for targeted therapeutics, and a streamlined FDA process for personalized medicine products.

the Agency will regulate laboratorydeveloped tests, though we expect that both FDA and Congress will focus on the issue in the coming months.

Engagement of Federal agencies has long been a PMC focus. To that end, PMC has organized a workgroup to develop an issues brief regarding problems facing personalized medicine products at the Centers for Medicare and Medicaid Services (CMS). At our February public policy meeting, Jeffrey Roche, M.D., and James Rowlands, M.D., both medical officers at CMS. discussed personalized medicine with PMC members. The Committee raised several issues, including whether personalized medicine products could and should be considered differently than stand alone diagnostics, devices

and therapies. It also discussed relevant standards of evidence for personalized medicine products, a subject of great concern for many PMC members.

PMC's new workgroup, led by Scott Alloco, President of **Biomarkers Strategies** and Steve Phillips, Director, Health Policy, Government Affairs & Policy, **Johnson & Johnson**, will

conceptualize the problem, in an issues brief that will serve as a guide both for the PMC and CMS, leading later to policy considerations and proposed solutions.

PMC is also working with the Brookings Institute to examine the critical intersection between health information technology and personalized medicine with the

goal of offering specific and actionable recommendations on how to move healthcare forward by aligning the two. In a Brookings white paper, Darrell West, Vice President and Director of the Governance Studies Program at the Institute, will outline policies that can facilitate "the seamless and rapid flow of digital information [to develop] a broader view of HIT beyond electronic medical records."

On a personal note, spring brings me to a new status, that of expectant mother. I will be on maternity leave from April 1 until August 1. While I am out, PMC will continue its policy efforts outlined above. I look forward to working with you to move these policies from concept to reality upon my return.

Personalized Medicine May Resurrect Drugs That Didn't Get to Market

As a result of advances in science and technology, the Food and Drug Administration may soon approve three drugs that have been blocked from the market due to concerns about safety or lack of general efficacy, but that are more effective than available medications for some patients.

Novartis has asked FDA to take a second look at osteoarthritis drug lumiracoxib (Prexige), along with a companion test for a biomarker to determine which patients may safely take the drug. In 2007, the FDA stopped Novartis from bringing lumiracoxib to market after the drug was linked to liver damage. Now, Novartis officials say they have found a biomarker that will exclude those patients.

ARCA biopharma is seeking FDA approval for bucindolol hydrochloride, a beta blocker and mild vasodilator, whose phase III clinical trial was halted when two other heart failure trials involving beta-blockers reported positive data, establishing the benefit of beta-blockers for heart failure patients. Analysis of the trial data showed that a polymorphism in the beta-adrenergic receptor appears to alter response to the drug. Last year FDA fast-tracked bucindolol (Gencaro) development in a genotype-defined heart failure population. A study comparing the effectiveness of Gencaro with a diagnostic to another betablocker drug could begin as early as the

end of this year.

Pfizer is conducting new trials of its melanoma therapy tremelimumab, whose Phase III trial was halted in 2008

when the drug was found to offer no benefit over standard chemotherapy. However, evaluation of the trial data revealed a biomarker that predicted patients who were more likely to respond to tremelimumab. The drug company is now preparing for a new Phase III trial with patients who possess the biomarker.

These actions herald the emergence of a longawaited development

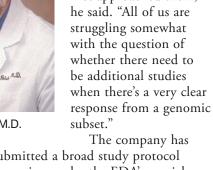
in personalized medicine: using biomarkers to rescue so-called "failed" drugs—therapies that never made it to market—from the scrap heap. Over the years, companies have abandoned hundreds of promising therapies after discovering that they didn't help enough patients or were harmful to some—problems that could be resolved by using biomarkers to target the drugs narrowly for those people for whom they are both safe and effective.

Because targeted therapies are a relatively new idea, their path at FDA has sometimes been slow. For example, ARCA has been working on its bucindolol submission with FDA since

Stephen B. Liggett, M.D., a co-founder of ARCA and a professor at the University of Maryland, gives credit

> to FDA for its efforts to understand and apply the scientific advances that have occurred.

"The FDA has come a long way from when we first approached them," he said. "All of us are struggling somewhat with the question of whether there need to be additional studies when there's a very clear response from a genomic subset."





Michael Bristow, M.D.

submitted a broad study protocol for review under the FDA's special protocol assessment process before the end of this year and hopes to begin the proposed study within a year of receiving FDA's concurrence on the study design. The proposed study would include about 3,200 patients with a particular genotype and would

Three Drugs That Could See New Life As Targeted Therapies						
Company/ <i>Drug</i>	Drug Class	Condition	Diagnostic	Biomarker	FDA Status	
O ARCA biopharma Gencaro (bucindolol)	Beta blocker	Heart failure	Efficacy	Polymorphisms in the targeted beta1-adrenergic receptor that affects cardiac output	Not accepted June 2009, resubmission in progress	
NOVARTIS Prexige (lumiracoxib)	Cox-2 painkiller	Arthritis	Safety	Genes in the major histocompatibility complex (MHC Class II)	Never approved in US, pulled from foreign markets in 2007 due to potential liver toxicity	
Pfizer Tremelimumab	Melanoma	Melanoma	Safety	Genome studies in progress	Pfizer is conducting a second set of drug trials after finding a biomarker that identifies patients who benefit from the drug	

compare bucindolol, with an extendedor controlled-release formulation of metoprolol, another beta-blocker.

"This proposed clinical trial would be the first full-sized cardiovascular trial performed in a genetically defined subpopulation to predict efficacy enhancement by the tested drug," Michael Bristow, M.D., ARCA's chief executive officer, said in a statement. "As such, the proposed trial would be a landmark undertaking in pharmacogenetic drug development."

Pfizer is already moving ahead with a second drug trial for tremelimumab, a fully human anti-CTLA4 mAb. In a paper published in the February 1 issue of *Clinical Cancer Research*, researchers said that in a new Phase II trial, the drug showed a 6.6% objective response rate in patients with advanced refractory or relapsed melanoma, with responses lasting more than six months. Fifteen of 16 responders had lived an additional

20 to 34 months when the authors wrote their paper.

By contrast, the median overall survival rate for the entire cohort was ten months.

"Let's shift the paradigm and say, why do we have to rescue failed drugs at all? Let's do a better job of looking at their benefit/risk profiles in a prospective way and get it right the first time."

- Lawrence Lesko, Ph.D.

"There is an urgent need for new treatment options for patients with stage IV (metastatic) melanoma," wrote the report's lead author, Dr. John M. Kirkwood of the University of Pittsburgh Cancer Institute. "It is now of paramount importance to identify

the patient population that responds to tremelimumab and determine early indicators of later response to therapy."

Lawrence Lesko, Ph.D., Director of FDA's Office of Clinical Pharmacology,

said he's pleased that the use of biomarkers may increase drug benefits or reduce their risk.

However, he said he's sorry to see biomarkers being used after one or more adverse events have already occurred with a therapy.

"Why can't we do a better job, so we don't have

to wait to see the drug fail and then rescue it?" Dr. Lesko asked. "Let's shift the paradigm and say, why do we have to rescue failed drugs at all? Let's do a better job of looking at their benefit/risk profiles in a prospective way and get it right the first time."

Personalized Medicine Coalition 2010 Membership

Organizations new to the coalition are underlined

Agency Participants

Centers for Disease Control and Prevention Centers for Medicare and Medicaid Services National Cancer Institute U.S. Food and Drug Administration

Clinical Laboratory Testing Services

Genelex Corporation Iverson Genetic Diagnostics, Inc. Kimball Genetics, Inc. Laboratory Corporation of America (LabCorp) Laboratory for Personalized Molecular Medicine

Pathway Genomics Corporation **Quest Diagnostics**

Consumer Genetic Testing Services

23andMe DNA Direct, Inc. Intervention Insights Navigenics, Inc.

Diagnostic Companies

Agendia BV Allegro Diagnostics Almac Diagnostics **Aperio** Artemis Health Inc. AssureRx Health, Inc. Axial Biotech, Inc BD (Becton, Dickinson and Company) Biodesix BioMarker Strategies

BioMérieux BioStat Solutions, Inc. Brain Resource Company Limited CancerGuide Diagnostics CardioDx, Inc. Caris Life Sciences Celera Crescendo Bioscience, Inc. Curidium Medica

Cylex Inc. Dako Denmark A/S deCODE Genetics, Inc. DNAVision s.a.

Expression Analysis, Inc. Expression Pathology

Gen-Probe Incorporated GeneDx

Genomic Health, Inc. Genoptix Medical Laboratory

Gentris Corporation HistoRx

Interleukin Genetics, Inc. LineaGen, Inc.

Luminex Corporation MolecularMD

Monogram Biosciences Nanosphere, Inc.

Nodality

OncoMethylome Sciences

On-Q-ity ParagonDx

PGx Health (A Division of Clinical Data, Inc.)

Prognomix Inc.

Proventys QIAGEN, Inc.

RedPath Integrated Pathology, Inc.

Rosetta Genomics Saladax Biomedical, Inc.

Sequenom Center for Molecular Medicine

Siemens Medical Solutions SomaLogic, Inc.

TcLand Expression Tethys Bioscience

Transgenomic, Inc. VitaPath Genetics, Inc. XDx Inc.

Emerging Biotech/ Pharmaceutical Companies

Alper Biotech, LLC ARCA biopharma **BIOCRATES Life Sciences AG** Cabernet Pharmaceuticals, Inc. KineMed, Inc. Merrimack Pharmaceuticals

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CVS/Caremark Generation Health, Inc. Humana Inc.

Medco Health Solutions, Inc.

Industry & Trade Associations

AdvaMed (Advanced Medical Technology Association)

American Clinical Laboratory Association

Association of Medical Diagnostics Manufacturers (AMDM) BIO (Biotechnology Industry

Organization)

PhRMA

IT/Informatics Companies

5AM Solutions, Inc. HP Health and Life Sciences IBM Healthcare and Life Sciences Lead Horse Technologies, Inc. McKesson Oracle Health Sciences SAIC Health Solutions **UNIConnect** XIFIN, Inc.

Large Biotech/Pharmaceutical Companies

Abbott Amgen, Inc. Bristol-Myers Squibb Company Eli Lilly and Company **Endo Pharmaceuticals** Genzyme Corporation

GlaxoSmithKline

Johnson & Johnson Pharmaceutical Research & Development, L.L.C. Millennium: The Takeda Oncology

Company Novartis

Pfizer Inc

sanofi-aventis US Inc.

Patient Advocacy Groups

Alliance for Aging Research Hypertrophic Cardiomyopathy Association-HCMA National Alliance for Hispanic Health

National Brain Tumor Society **Research & Educational**

Institutions American Institute for Medical & Biological Engineering (AIMBE) American Medical Association

American Society of Human Genetics (ASHG)

Association for Molecular Pathology (AMP)

Baylor College of Medicine **Brown University**

Children's Hospital Oakland Research Institute

Children's Mercy Hospitals and Clinics

Cleveland Clinic Genomic Medicine Institute

College of American Pathologists Coriell Institute for Medical Research The Critical Path Institute (C-Path) **Duke University**

El Camino Hospital

FasterCures

Fox Chase Cancer Center Genome British Columbia

The George Washington University Medical Center

Georgetown University School of Nursing & Health Studies

H. Lee Moffitt Cancer Center & Research Institute, Inc.

Ignite Institute Institute of Genomic Medicine,

UMDNJ-New Jersey Medical School The Jackson Laboratory

The Dr. John T. Macdonald Foundation, Department of Human Genetics, University of Miami

Marshfield Clinic Mayo Clinic

National Coalition for Health Professional Education in Genetics (NCHPEG)

National Foundation for Cancer Research

The National Jewish Medical and Research Center

National Pharmaceutical Council The Ohio State University Medical Center

Partners HealthCare Center for Personalized Genetic Medicine The Personalized Medicine Group of Connecticut

Poliambulatorio Euganea Medica Scripps Research Institute United States Diagnostic Standards (USDS)

University of Rochester University of Utah Vanderbilt University Medical Center VCU Health System

Research Tool Companies

Affymetrix, Inc. Biosearch Technologies, Inc. Helicos BioSciences Illumina, Inc. Life Technologies Corporation

Strategic Partners

Arrowhead Publishers and Conferences Boston Healthcare Cambridge Healthtech Institute Corbett Accel Healthcare Group

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Genomic Healthcare Strategies Growing Company Solutions, Inc. HealthFutures, LLC

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Technic Solutions LLC Townsend and Townsend and Crew

Valerie August & Associates, LLC -Biotechnology Recruiter

William Blair & Company Wilson Sonsini Goodrich & Rosati

Venture Capital

Kleiner Perkins Caufield & Byers Lemhi Ventures MDV-Mohr Davidow Ventures Pappas Ventures Third Rock Ventures, LLC

Wall Street Shows Growing Interest in Personalized Medicine

Wall Street will invest significantly in personalized medicine within the next three to five years, according to analysts at Chicago investment bank William Blair & Company, which has created a personalized-medicine coverage area that includes diagnostic services companies, pharmacy benefit managers and companies that sell FDA-approved assays to labs.

Among the companies Blair healthcare analysts Amanda Murphy and Brian Weinstein cover are Bio-Reference Laboratories, Catalyst Health Solutions, Cepheid, Express Scripts, **Genomic**

Health, Genoptix, Gen-Probe, LabCorp, Luminex, Masimo, Medco Health Solutions, Meridian Bioscience, Myriad Genetics, Natus Medical, Quest Diagnostics, Quidel and SSC Health Solutions.

Of these companies, only
Genomic Health and Myriad
are personalized medicine
companies per se, according to
William Blair. "As one of the
few examples of a company
that has been successful in
commercializing a personalized
medicine-based gene expression
assay that has become standard
of care, Genomic Health represents
one of the only ways for investors to
participate in a pure-play personalized
medicine company," Ms. Murphy wrote
in a report on genomic health in April.

It's too early to use personalized medicine as a standalone strategy for investment, but "there are many opportunities for investors to participate in the trend while taking a diversified approach, including through the diagnostic product manufacturers, pharmacy benefit managers, and clinical laboratories on our coverage list," Ms. Murphy said.

In the immediate future, Ms. Murphy and Mr. Weinstein see the greatest opportunity in companion diagnostics, citing an analysis by **L.E.K. Consulting** that growth is expected to be about 30 percent through at least 2011.

"Given that companion diagnostic tests grew at a compound annual rate

of 43 percent from 2004 to 2008, with nearly 150 tests now on the market, we are not surprised that this has been such a strong growth area within molecular diagnostics" said Brian Weinstein, who covers diagnostics.

With the exception of Myriad's BRCA-1 and BRCA-2 analysis for hereditary breast and ovarian cancer, predisposition tests are a smaller piece of the diagnostics market, and growth is expected to be only 10 percent over the next few years, they said.

William Blair is not alone. Other investment firms are also tracking



personalized medicine. Charles Duncan, Ph.D., managing director and senior biotechnology analyst for JMP Securities in San Francisco, has been watching the space since 1997. While JMP is developing coverage for personalized-medicine tools, Dr. Duncan doubts investors will rush into the field anytime soon. "You won't see a ton of interest in this space" until investors see more successes like Genomic Health, Myriad Genetics and **Celera**, he said.

That could be bad news for personalized-medicine companies that have recently filed for an initial public offering (IPO) of common stock with the Securities and Exchange Commission: Rules-Based Medicine, a multiplex molecular diagnostics firm based in Austin, Texas; BG Medicine, a biomarker development firm in Waltham, Mass.; and British molecular diagnostics firm Osmetech, which

has filed under the name of its newly proposed parent, GenMark Diagnostics.

But "there's no pall over this space if those deals don't get done," Dr. Duncan said, because the three filings are for types of products investors don't expect in the space. Investors' interest in personalized medicine will grow as a result of last year's relabeling of colon cancer drugs by the Food and Drug Administration, he said, because it demonstrated that companies with products that preselect those patients who will benefit from a therapy will reap profits. "If you look at Erbitux and

Vectibix, identifying patients [who respond to a therapy] could clearly be a competitive advantage," Dr. Duncan said.

Dr. Duncan said that he looks for two things in personalized-medicine investments: whether the company has identified a high-value question doctors are asking, and whether a company that answers the question can provide substantive clinical data. Private companies that have achieved these goals are **XDx**, **CardioDx**, and **Tethys Bioscience**, among others, he

said. "They have a value proposition with their products that is valuable to three key constituencies: payers, physicians, and patients," he said.

Biotech analysts at **Ernst & Young** say investor interest in personalized diagnostics may grow rapidly once Britain's model of not paying for treatments that don't work spreads to other nations. That will negatively affect drug profits unless companies can develop a companion biomarker that predicts whether a population responds to a therapy, said Ernst & Young global biotechnology leader Glenn Giovannetti.

"Wall Street doesn't necessarily think of personalized medicine as the panacea, but I think it understands that a highly differentiated product is likely to capture the margins that investors are used to seeing," said Ernst & Young senior manager Gautam Jaggi. "We think that's the future of the drug business."

FDA Regulations Lag Development of Diagnostics

BY JONATHAN S. KAHAN, J.D., SUSAN D. TIEDY-STEVENSON, M.S. AND RANDY J. PREBULA, HOGAN & HARTSON LLP

Personalized-medicine diagnostics, along with predictive and prognostic software modeling, are proliferating more quickly than the Food and Drug Administration (FDA)'s ability to oversee them.

FDA considers personalized diagnostics central to improving drug safety and efficacy, but it has not spelled out what it will accept to support the efficacy of personalized medicine biomarkers. For example, it's unclear how the data required for companion-diagnostic biomarkers differs from that needed for disease-risk or recurrence biomarkers; when published scientific literature is adequate to support the clinical utility of personalized diagnostics; and whether the approval process will impose drug regulatory requirements on personalized medicine diagnostics as it develops.

We hope that the final guidance FDA promises on companion diagnostics for this year will provide greater certainty. To realize patient benefits through personalized medicine, industry and FDA must jointly develop clear, balanced and efficient processes for premarket review of personalized diagnostics.

Meanwhile, as the agency's position continues to evolve, the regulatory landscape for personalized diagnostics will likely continue to be unsettled. Following is a brief guide to the FDA's different regulatory approaches.

Personalized-medicine diagnostics include a range of genetic assays that guide selection of patients for a specific drug, predict patient survival, or identify patient-specific genotypes for drug metabolism, hypersensitivity, and toxicity. Personalized diagnostics also include software-based statistical modeling of patient characteristics to assess risks of specific clinical events in the context of therapeutic regimens.

FDA bases diagnostic regulation on a test's intended use and, in part, on whether it was co-developed with a therapeutic. Low-to-moderate-risk devices are regulated under Section 510(k) of the Federal Food, Drug and Cosmetic Act. FDA clears them for market after it determines that a device is substantially equivalent to one previously cleared under the section. FDA also may sometimes use "de novo" classification to clear a low-risk device under 510(k) even though it isn't substantially similar to existing devices.

High-risk devices—defined in the law as those designed to prevent impairment to human health and those presenting a potentially unreasonable risk of illness or injury—must get premarket approval from FDA after the product's safety, effectiveness and clinical utility are validated through clinical trials. Finally, for diagnostic laboratory-developed tests, FDA has relied with few exceptions on regulation under the Clinical Laboratory Improvement Amendments Act (CLIA).

Clearly, how FDA defines a device as low-risk or high-risk is an issue for developers. In many cases, personalized diagnostics

have followed the premarket review pathways for other *in vitro* diagnostic tests: the level of oversight depends on whether the test is intended to guide patient selection for a given treatment regimen.

In general, FDA regulates diagnostics that are not used for selecting or dosing decisions under 510(k), and those used to select patients for treatment with a drug (e.g., responders versus non-responders) through premarket approval applications (PMAs). Its position on the latter is that safe and effective use of the drug depends on the diagnostic test, and the drug's label must include the subgroup of patients identified by the diagnostic.

Examples of 510(k)-cleared diagnostics include tests for drug metabolism genotype markers, such as CYP2C9 and VKORC1 gene variants for warfarin therapy and UGT1A1 gene variants for irinotecan therapy. FDA views these biomarkers as unrelated to patient selection, and thus includes genotype information and test recommendations on the drug labels rather than making the tests a requirement. The fact that FDA relied on existing published literature to support the clinical utility of both the CYP2D6 variant drug metabolizer and the CYP2C9 and VKORC1 warfarin biomarkers shows the agency's willingness to be flexible in credentialing such low-risk diagnostics.

Companion diagnostic genetic tests that require PMA approval as high-risk devices, because they are linked to a specific genotype and therefore required for use of the drug, include Herceptin (trastuzumab) for patients with HER2 protein over-expression in tumors, and Selzentry (maraviroc) for HIV patients with detectable CCR5-tropic HIV-1 infection.

Interestingly, the diagnostics and the drugs were approved through separate FDA pathways even though in certain cases the diagnostics were developed concurrently with the therapeutic. However, FDA's 2005 white paper treats companion diagnostics as combination products, where the product's primary mode of action is based on the drug. To be consistent with existing FDA rules, this approach would require developers to submit a New Drug Application (NDA) or Biologic License Application (BLA), with diagnostic test information included in the drug application.

Whether FDA continues to follow separate pathways in the future or chooses to require a single submission for drug/diagnostic combinations remains to be seen. Moreover, laboratory-developed tests (LDT) for personalized diagnostics likely will become more problematic as FDA moves closer to refining the thresholds for which the agency will seek LDT regulatory oversight and issues final guidance on *in vitro* diagnostic multivariate index assays (IVDMIAs). We eagerly await FDA's forthcoming guidance on these subjects.

The views expressed in this article are those of the authors and do not necessarily represent the opinions of the Personalized Medicine Coalition.

FDA Develops New Rules for New Era of Medicine

With new leaders installed in key positions in the Obama administration, the government is moving to update not only its rules, but its entire regulatory process so that it can exercise better and faster oversight over new medical developments like targeted therapies.

The Food and Drug Administration is leading the process.

In recent months, the agency, led by Margarent Hamburg, M.D., has announced

a new partnership with the National Institutes of Health that is designed to more quickly get scientific and medical breakthroughs in personalized medicine, among other fields, into clinical practice. She pledged to have guidance on drug/diagnostic combination therapies completed by the end of the year.

FDA is also seeking \$25 million in new funding from Congress for 2011 so that its regulatory methods can catch up with new fields of science including molecular and genomic medicine, said Vicki Seyfert-Margolis, Ph.D., senior advisor for science innovation and policy in FDA's Office of the Chief Scientist.

"All of personalized medicine is going to be served by having a much more scientifically astute agency, an agency that's involved during the whole product development pipeline and providing some of the wealth of knowledge and expertise that it has to help move forward discoveries into actual products," she said.

But the agency isn't waiting to expedite scientific and medical breakthroughs. FDA has added a warning label to Plavix, the anti-blood clotting medication, which cautions that some patients may be poor metabolizers and thus are at risk of heart attacks. In addition, it has revised the label for warfarin, an anticoagulant that is one of the most widely-used drugs in the world, with new dosing recommendations.

The warfarin label change "makes it easier for physicians to apply the

knowledge of the genetic test to inform them on which dose is likely to be best for patients," said Lawrence Lesko, Ph.D., Director of the FDA's Office of Clinical Pharmacology.

Other developments include a new office for personalized medicine headed

by Elizabeth Mansfield, Ph.D., within the Office of In Vitro Diagnostic Evaluation (OIVD) in FDA's Center for Devices and Radiological Health (CDRH). Dr.

Mansfield's office, created in June 2009, is responsible for improving CDRH's knowledge of genomic devices, pharmacogenomics, and proteomics, as well as introducing new ways to validate complex devices. She is hiring 15 new reviewers.

"We're looking for people who have skills that match what we think will be coming through," she said. "That includes the kind of diagnostics that we don't expect to see until they've reached a certain level of maturity."

Dr. Mansfield's Office of Personalized

Medicine is overseeing the effort to better align FDA's drug and diagnostic divisions by holding meetings regularly among the three agency centers responsible for personalized medicine products and services: CDRH, the Center for Drug Evaluation and Research, and the Center for Biologics Evaluation and Research.

Among the topics under discussion is the companion diagnostics guidance, Dr. Mansfield said.

Once the guidance is finished, Dr. Mansfield said she expects joint drug/diagnostic approvals to occur within the same timeframe as a drug or diagnostic might take on its own. "There are additional issues we'll have to address, and I don't expect that we'll be able to do it much faster," she said.

Even before the guidance is completed, the number of co-development projects appears to be increasing, Dr. Mansfield said. In addition, FDA has already become more proactive about letting companies know when a drug that has been submitted for approval may need a diagnostic.

FDA Initiatives Related to Personalized Medicine

Companion Diagnostics. Currently, drugs and diagnostics are regulated by different centers at FDA, making it difficult to coordinate the release of a drug with a companion diagnostic test to guide the drug's use. The guidance, due out this year, will clarify the agency's expectations for clinical trials and confidence levels needed to demonstrate that a test can be used for clinical assessments.

Validation and use of Genomic Biomarkers in Clinical Trials. Also due this year, this guidance will inform developers of the criteria FDA will use to vet the usefulness of biomarkers and evaluation of clinical trial data.

FDA/NIH partnership. The two agencies will coordinate translational science, under which basic scientific discoveries are developed into treatments, and regulatory science, which needs new tools, standards and approaches to more efficiently evaluate the safety, quality and efficacy of new treatments.

In vitro multivariate index assays. CDRH will take a broader look at regulations for laboratory-developed tests for these assays based on the recommendations by the HHS Secretary's Advisory Committee for Genetics, Health, and Society, as well as a petition submitted by Genentech in 2008.

Warfarin/Plavix labeling. In January, FDA updated the label for warfarin to incorporate dosing information based on genotype. The label now recommends that doctors refer to a table of stable maintenance doses observed in patients having different combinations of CYP2C9 and VKORC1 variants, as a guide for selecting the starting dose of warfarin. In March, it added a warning label to Plavix, cautioning that some patients may be poor metabolizers.

Safer, More Effective Therapies Are 'Well Worth the Effort'

continued from page 1 innovation can lead to better patient care and lower systemic costs.

Of course, as she said, it is not going to be easy.

Moreover, since the mapping of the human genome was completed in 2003, progress in bringing new therapies to patients has been slower than many hoped, in large part because the map reaffirmed just how complex human biology actually is. But, as Dr. Hamburg acknowledged, progress is also hampered because we have been slow to redesign the drug development and approval processes to take advantage of our new understanding of genetics and other biomarkers that can assist the development and adoption of personalized medicine. And even where progress has occurred, as in the re-labeling of warfarin, Abacavir, Erbitux, and Vectibix, to name but four drugs for which FDA requires or recommends a molecular diagnostic test, provider and patient education remain hurdles limiting clinical adoption.

Dr. Hamburg also said that government must send the right signals to, among others, the manufacturers of drug-diagnostic combinations.

In December, following a request from FDA and months of hard work integrating the views of pharmaceutical companies, diagnostic kit manufacturers, and laboratories, PMC called on FDA to clarify its requirements for approving drug-diagnostic products. These products are the hallmark of personalized medicine, but are regulated by two separate centers within FDA, namely the Center for Drug Evaluation and Research and the Center for Devices and Radiological Health. Consequently, there is no clear pathway for approving them in the United States. When PMC

published its white paper outlining a series of recommendations to improve and expedite the process, the Coalition pointed out that drug and diagnostic companies "have been left in limbo on how the government will treat new products, even as the science to develop more innovative diagnostic tests and targeted drug therapies has sped forward."

We were gratified that in her speech to the PMC, Dr. Hamburg committed FDA to developing "a consistent, comprehensive and integrated approach to the evaluation and regulation of

"The process of shifting paradigms and creating new models is not easy." - Margaret Hamburg, M.D.

medical products which separately, and in combination, comprise the practice of personalized medicine." She said that the guidance, including defining the standards of evidence necessary to meet FDA requirements, would be completed by the end of the year.

Dr. Hamburg pointed out that the United States' investment of billions of dollars in biomedical research would not lead to medical progress by itself. It must also be linked to investments in what she calls advances in regulatory science. Dr. Hamburg's emphasis on listening to the science and putting in place new regulatory pathways that reflect its new discoveries is emerging as the leitmotif of her administration. It has also made her a champion of personalized medicine.

The day before Dr. Hamburg's address, she and Francis Collins, M.D., Ph.D., Director of the National Institutes of Health, announced that FDA and NIH had established a Joint Leadership

Council to enable their respective agencies to issue grants for research that can lead to improved regulation.

When Ralph Snyderman, M.D., Chancellor Emeritus of the **Duke University**, introduced Dr. Hamburg at the National Press Club on behalf of the Friends of the Personalized Medicine Coalition, which sponsored the address, he noted that we are on the precipice of a second transformation of medicine. That transformation, he said, is focused less on the specific pathogenesis of disease than on its complex origins, in which chronic diseases can develop

sub-clinically. Where the first transformation, a little over one hundred years ago, unintentionally led physicians into a reactive "find it and fix it" mentality,

today's transformation, based on the new insights provided by genomics, proteomics, metabolomics, and systems biology, he said, recognizes that chronic disease, the source of two-thirds of all healthcare expenditures in the United States, may be better addressed by predictive, preventive and personalized diagnosis and treatments.

This is something Dr. Hamburg understands. While she acknowledged that she does not know specifically how to answer the question "how do we accelerate our path to the future and its potential," she did say that the ability to adapt to new challenges and opportunities defines not only evolution but also intelligent government.

"The process of shifting paradigms and creating new models," she concluded, "is not easy." But, she repeated in case the audience missed it the first time, the promise of "safer and more effective therapies for all of us is well worth the effort."

PMC Announces New Board Members

The Personalized Medicine Coalition has elected D. Stafford O'Kelly, President of Abbott Molecular, and Lori M. Reilly, Vice-President for Policy & Research at the Pharmaceutical Research and Manufacturers of America (**PhRMA**), to its Board of Directors.

"Lori Reilly has been a major force in driving the cause of personalized medicine in Washington through her work at PhRMA, while Stafford O'Kelly brings a very high-level of expertise in the molecular diagnostics area to the board from Abbott," said Wayne Rosenkrans, PMC's chairman. "Their combined experience will greatly enhance our efforts to encourage the forward progress of personalized medicine as we move into the new post-reform vote era."

Mr. O'Kelly, who is also Vice President of Abbott Laboratories, was appointed to lead Abbott's molecular division in April 2007. "I look forward to working with the Personalized Medicine Coalition at a time when molecular diagnostics are playing an increasing role in medicine," Mr. O'Kelly said.

Ms. Reilly oversees PhRMA's development of legislative and policy analysis and research studies on healthcare issues including pharmaceutical economics and utilization, healthcare quality, direct-to-consumer (DTC) advertising/ marketing and promotion, import safety, comparative effectiveness and intellectual property.

"I am excited to be joining the PMC Board at this pivotal time in the future of the healthcare system," Ms. O'Reilly said. "The intersection of science and health policy in the coming years will continue to grow and I look forward to working with the diverse membership of the PMC to ensure that public policy with regards to personalized medicine evolves for the benefit of patients."





D. Stafford O'Kelly; Lori M. Reilly

Mr. O'Kelly joined Abbott in 1984 and has served in various management positions. These include Division Vice President finance, Abbott International, Divisional Vice President and Controller, Ross Products Division (now Abbott Nutrition), and Vice President of Finance, TAP Pharmaceuticals, Inc.

He has a bachelor's degree in engineering and MBA from Trinity College in Dublin, Ireland.

Prior to joining PhRMA, Ms. Reilly was counsel at the U.S. House of Representatives Committee on Commerce. Before taking that position, she served as Chief of Staff to Rep. Jon Christensen, R-Neb.

Ms. Reilly received a B.A. in Political Science from the University of Nebraska-Lincoln, where she graduated with Honors, and a J.D. from the University of Nebraska College of Law. She is a member of the Virginia Bar.



PMC IN THE PRESS

Personalized medicine became a part of the national healthcare agenda as President Barack Obama signed the historic healthcare reform bill into law, **Pharmacogenomics Reporter** wrote in March. "For personalized medicine, this vote is historic," said Amy Miller, public policy director at the Personalized Medicine Coalition. "It represents the first time that the principles of personalized medicine have been passed by both houses of Congress."

A coalition of federal, academic and industry stakeholders has launched a new clinical trial design concept that could drastically reduce costs, while increasing the effectiveness

and success rate of trials by assessing biomarkers to determine the impact of experimental drugs, **FDA Week** reported in March. PMC Public Policy Director Amy Miller said, "This illustrates how far the (pharmaceutical) sector has come in embracing the science of personalized medicine, and how important collaboration is—both among private sector companies and between the public and private sectors—in advancing this science."

FDA Commissioner Dr. Margaret Hamburg said at a PMC meeting in February that diagnostic tests based on biomarkers will make it possible for drug companies to salvage data from unsuccessful clinical trials by

resubmitting drugs for approval for smaller subsets of patients, **Bloomberg Business Week** wrote in March. **FDA Week** and the **Pink Sheet** also covered Dr. Hamburg's speech.

Last fall the FDA created a post for a genomics advisor who will coordinate the agency's efforts to address the subject of genetic data and prescription drugs, wrote MIT's **Technology Review** in February. Amy Miller, PMC's public policy director, said the agency has signaled that it's "now ready to give the industry some guidance on how personalized-medicine products will be regulated in the future."

Drugs only work in about half the people who take them, **Bloomberg Business Week** wrote in January, a fact it attributed to the Personalized Medicine Coalition. Nonetheless, personalized medicine has been slow to take off. But that could change now that some pharmacy benefit managers are testing patients for genetic variations, PMC President Edward Abrahams told the magazine. "We are talking about better care for millions of people and keeping costs down for employers, whose insurance costs are exploding. It could be the tipping point."

Medco and CVS Caremark are at the forefront of efforts to make personalized medicine a routine part of drug care, the Boston Globe wrote in January. The two pharmacy benefit managers have begun offering genetic tests to patients to help them determine which drugs will be more effective for them. "This is the most exciting thing in personalized medicine today, because Medco and CVS are big players with enormous impact in the field," PMC President Edward Abrahams said. "The point of personalized medicine is to develop better efficacy, better outcomes, fewer adverse events and lower systemic costs. The pharmacy benefits manager is interested in all of those things."



By the end of the year, FDA will establish a device-centric personalized medicine infrastructure to address *in vitro* diagnostics and other gene-based therapeutics, **FDA Week** wrote in January. PMC Public Policy Director Amy Miller told the publication she would like to see the agency reach out to industry. "I think that industry has had a lot of experience with the different groups at FDA and looks forward to helping the agency hone their processes," she said.

Last year could be remembered as the year in which personalized medicine went mainstream, thanks to direct-to-consumer genomics firms,

pharmacogenomics programs by pharmacy benefit managers, a high-profile anti-gene patenting case, and the healthcare reform debate, **Pharmacogenomic Reporter** wrote in January. The publication cited the report on comparative effectiveness research PMC commissioned from the Lewin Group as an example of how personalized medicine played into the healthcare debate.

Personalized medicine, which now has many real-world applications, promises to make therapy more preventive, more effective, safer, and less expensive, PMC President Edward Abrahams and Mike Silver, founder of Synaptix Communications, wrote in the **California Biomedical Industry 2010 Report** released earlier this year.

Growth in the use of molecular diagnostics and in the co-development of drugs and diagnostics are expected as a result of congressional discussions on comparative effectiveness research, industry experts told **Pharmawire** in December. PMC Public Policy Director Amy Miller said she foresees growth in molecular diagnostics, particularly in cancer, cardiovascular disease and diabetes.