Learning from product labels and label changes: how to build pharmacogenomics into drug-development programs

The 2010 US FDA–Drug Industry Association (DIA) Pharmacogenomics (PGx) Workshop follows a series that began in 2002 bringing together multidisciplinary experts spanning regulatory authorities, medical research, healthcare and industry. This report summarizes the 'Building PGx into Labels' sessions from the workshop which discussed the critical elements in developing PGx outcomes leading to product labels that inform efficacy and/or safety. Examples were drawn from US prescribing information, which integrated PGx knowledge into medical decisions (e.g., panitumumab, warfarin and clopidogrel). Attendees indicated the need for broader dialogue and for guidelines on evidentiary considerations for PGx to be included into product labels. Also discussed was the understanding of appropriate PGx placement on labels; how to encourage adoption by medical communities of label recommendations on PGx tests; and, given the global nature of drug development, worldwide considerations including European Summary of Product Characteristics.

KEYWORDS: biomarkers ▪ genetic tests ▪ pharmacogenomics ▪ pharmacogenetics ▪ product label ▪ summary of product characteristics ▪ US prescribing information

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'Generating and Weighing Evidence in Drug Development and Regulatory Decision Making' was the fifth workshop sponsored by the US FDA and Drug Information Association (DIA) on Pharmacogenomics (PGx). This report focuses on Track 1 sessions which discussed how pharmaceutical companies, healthcare providers and regulators are using product or medicine labels to convey PGx information (Box 1). Based on previous output from the 4th FDA–DIA PGx workshop which focussed on determining the best practices for future labeling integrating PGx [1], the 2010 topics included considerations on the different levels of PGx evidence on product labels requested to effectively communicate safety compared with efficacy.

Worldwide attention by regulatory authorities on the contribution of genetic factors to drug response has increased. This is reflected by a developing regulatory framework that facilitates PGx integration into drug development such as Voluntary Exploratory Data Submissions in the USA and PGx Briefing Meetings in Europe and Japan, as well as the more recent, formal biomarker qualification by the regulators. Regulatory authorities in these three major geographic regions are increasingly adding PGx information to label updates of approved drugs, as well as incorporating PGx into their regulatory review of a new product. The purpose of the product label is to provide prescribers with information that is most useful in treating their patients. The FDA, European Medicines Agency (EMA), and the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) require the product label to be balanced, scientifically accurate and not misleading. In addition, clear instruction must be communicated to healthcare practitioners for drug prescription. These basic principles also apply to PGx information on product labels. PGx biomarkers can be divided into two broad categories of efficacy and safety. While there may exist different evidentiary standards used among regulatory authorities to establish relevance for patients on a product label (i.e., which data to include for efficacy or safety), the common objective is to improve the benefit–risk profile of a medicine.

To date, most efficacy-related PGx biomarkers involve oncology therapies, with evidence for the addition of PGx information to the labels primarily based on prospective clinical trials. More recently, efficacy-related PGx biomarkers have been retrospectively identified based on emerging data generated in the postapproval setting. An example is *KRAS*, in which patients with metastatic colorectal cancer whose tumors harbor genetic mutations are unlikely to respond to therapies such as panitumumab [2] or cetuximab [3]. In comparison, many safety-related PGx biomarkers have involved common

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Box 1. Building PGx into label session topics and expert panels.

Steering committee:
- Lawrence Lesko (US FDA, MD, USA), Nadine Cohen (J&J, NJ, USA), Linda Surh (GlaxoSmithKline, Middlesex, UK)

Plenary session 1
- An Objective Analysis of the Regulatory Decisions to Include Genetic Test Information in Drug Product Labels, Lawrence Lesko (FDA)

Plenary session 2
- *KRAS* as a Negative Selection Biomarker: The Path to Clinical Usefulness, Scott Patterson (Amgen, CA, USA)

Breakout session 1
- Safety Pharmacogenomic Models for Updating Drug Product Labels: Susanne Haga (Duke University, NC, USA), Bryan Dechairo (Medco, MD, USA), Myongjin Kim (FDA), Arlene Hughes (GlaxoSmithKline, NC, USA), Marisa Papaluca-Amati (EMA, London, UK) and Issam Zineh (FDA)

Breakout session 2
- Efficacy Pharmacogenomic Models for Labeling New Drug Products: Michael Pacanowski (FDA), Michael Mosteller (GlaxoSmithKline, NC, USA), Sandra Close Kirkwood (Eli Lilly & Company, IN, USA), Stuart Hobbs (GlaxoSmithKline, NC, USA), Scott Gottlieb (American Enterprise Institute, Washington, DC, USA), Graham Gardner (Generation Health, NJ, USA), Marisa Papaluca (EMA), Steve Grant (FDA), Linda Surh (GlaxoSmithKline)

gene variants in the CYP superfamily (such as *CYP2C19*, *CYP2C9* and *CYP2D6*) which have proven to be involved in drug metabolism and more recently, with *HLA* genes associated with serious adverse events. Although the *CYP* variants could also be classified as efficacy-related when low exposures result in reduced effect, the focus has tended to be on safety due to raised exposures associated with drug toxicity which are frequently observed earlier in drug development during pharmacokinetic studies. In comparison, identification of *HLA* variants associated with serious adverse events have predominantly occurred after approval of a medicine, following accumulation of a sufficient number of events in observational studies.

The incorporation of PGx information in product labels raises a number of questions regarding the impact of this information on medical practice:

- The appropriate use of the test (i.e., is a PGx test required or recommended or is the PGx knowledge for information purposes only?);
- Placement of the PGx information in the label (such US prescribing information [USPI] sections as Therapeutic Indications, Clinical Pharmacology, Warnings and Precautions, among others);
- Perhaps most importantly, differences in how professional medical organizations, individual physicians and third-party payers weigh the evidence upon which the product label update is based, as their decisions can potentially alter medical practice through integration of PGx testing.

The current thinking and issues on when and how to include PGx information (or PGx-based tests) in product labels were discussed during the plenary and breakout sessions. To provide background for the discussions, a historic overview of changes to labels was presented during the plenary session, followed by specific case studies on current drugs that have incorporated PGx data, with examples including panitumumab, warfarin and clopidogrel. Although the discussed data involved DNA methodologies and thus, is defined as 'Pharmacogenetics', as per ICH15 a guideline from the (International Conference on Harmonisation endorsed by USA, Europe and Japan) [101] ,we have used the term 'PGx' to be inclusive of biomarkers based on molecular approaches. Attendee participation in the breakout sessions was encouraged for specific questions by individual electronic response devices, so that a multidisciplinary expert panel could then reflect and comment on audience responses (in real time). The following cases and their discussion outlines key questions/answers, current understandings, ongoing gaps and future considerations. These include moving forward from examples of postapproval label updates with PGx to new product labels in which PGx information will have less certainty on its clinical usefulness to guide drug prescription, and will be compared with already established medical practices or professional guidelines.

Plenary sessions

Plenary session 1

An objective analysis of the regulatory decisions to include genetic test information in drug product labels

Lawrence Lesko (Office of Clinical Pharmacology, FDA) reviewed for the audience the purpose of product labels in communicating the benefits and risks of a prescribed medicine in populations. In addition, the label needs to inform healthcare providers about the drug in a relevant, concise and comprehensive way that leaves room for judgment and control when making decisions for individual patients in the context of practicing medicine. Existing regulations, guidelines and policies were highlighted, specific to product labels, in which relevant PGx knowledge is relevant and informative [4,5,102] Precedents from seven recent postapproval product labels, updated with PGx information, were compared and contrasted: warfarin (2010),

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clopidogrel (2009), panitumumab (2009), cetuximab (2009), abacavir (2008), carbamazepine (2008), irinotecan (2006) and 6-mercaptopurine (2004). It was highlighted that past regulatory decisions relating to the addition of PGx in product labels are not necessarily precedents for future decisions, as science and regulatory policies are rapidly evolving. In summary, four key lessons about new product labels were shared:

- The evidence of the clinical usefulness (such as improved benefit–risk and in some cases by more tailored dosing) of an *in vitro* diagnostic is paramount to including PGx information in the label, but will require a consensus on generating evidence (quantity and quality), as well as anticipating the prescriber and patient needs;
- The communication of genetic information on labels is complex, so it is critical to consider the link between the intent of the PGx information, its interpretation and potential impact on medical practice;
- Many of the questions and issues of including PGx on labels can be addressed with clearer regulatory processes, policies and authority within and between FDA centers at a global level, as well as better clinical data on how to use genetics;
- Many of the uncertainties expressed by industry and others involved in drug development could be addressed by regulatory guidance for industry (e.g., early PGx in drug development, clinical trial efficiencies such as adaptive design or enrichment, codevelopment of drug with diagnostic and *in vitro* diagnostic multivariate index assays).

Plenary session 2

KRAS as a negative selection biomarker: the path to clinical usefulness

Scott Patterson (Amgen, CA, USA) reviewed panitumumab as a single agent for the treatment of EGFR-expressing metastatic colorectal carcinoma with disease progression or following specified chemotherapy regimens. Key to the background of this example was that candidate PGx biomarkers based on the biological target, which were prospectively investigated during development, did not predict drug response. However, another already known DNA biomarker, *KRAS*, was able to identify a less responsive patient subgroup. This biomarker was identified post-FDA approval based on retrospective analysis of data from the pivotal clinical trial, for which *KRAS* status was ascertained in 92% of study participants. The details of retrospective PGx analysis with different types of data collection and their potential regulatory implications were discussed in another workshop track, so that the focus in this session was the level of evidence with which to guide appropriate prescriber actions and observed changes in medical practice. New US medical practice guidelines regarding *KRAS* testing preceded PGx label changes by the FDA and followed initial EMA approval, demonstrating that the practice of medicine can rapidly change based on compelling data. In conclusion, the rationale for prospective DNA collection with retrospective PGx analysis, as highlighted in this example, enables timely investigation and generates integration of new scientific knowledge into product labeling and to a proposal for a consistent regulatory approach to this PGx approach (i.e., prospective–retrospective).

Discussion arising from the plenary sessions

Overall interpretation and opinions given on key scientific issues were discussed among the different regulatory authorities such as the FDA, EMA and Pharmaceuticals and Medical Devices Agency (CPMDA). Using the recent regulatory review on panitumumab as an example in which data sets were analyzed retrospectively, different approaches between agencies were described. In the case of panitumumab, the company focused on the benefit (i.e., the exclusion of a subgroup identified as less responsive by a PGx biomarker). In contrast, the FDA considered the PGx data as an example relevant to a safety update (defined as absence of benefit) of the label and thus, the level of evidence using retrospective data was deemed acceptable.

Details of the USA and EU approach to the labeling of a new medicinal product differ with respect to timing, process, updates and interpretation. Specific to PGx, the timing of labeling changes was discussed at length, specifically the level of evidence and access to information aspects. In a separate, expert panel on the final day, Dr Russell Katz (Division of Neurology Products, FDA) speculated that the timing of the generation of data (i.e., pre- vs post-approval) was less important than data quality. In his view, the interpretation of specific PGx findings would be independent regardless of whether or not the review division learned about it prior to or after approval, if based on scientifically sound data. Dr Patricia Keegan

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(Division of Biologic Oncology Products, FDA) was of the opinion that a phase III trial, including a prespecified efficacy analysis plan with appropriate adjustments to preserve Type 1 error rates, that demonstrated efficacy in a PGx-defined subgroup, as determined by an analytically valid assay in the intention-to-treat population, could have supported efficacy claims in the panitumumab example.

Breakout sessions

Two case studies of USPIs, warfarin and clopidogrel, provided recent examples of developing PGx markers in the context of already approved medicines as well as some of the unique challenges being faced. Breakout Session 1 focused on PGx for safety decisions in which label updates of previously approved drugs with addition of a diagnostic test improve the benefit–risk ratio of the drug. These case examples involved the development of a diagnostic test that took place independently of the development and registration of a drug (i.e., postapproval). The test can then be marketed by one or more companies. By contrast, Breakout Session 2 emphasized PGx markers in relation to efficacy whereby a diagnostic test is intended to optimize the benefit–risk ratio of the drug and/or clinically differentiate a competitor. Both breakouts ended with questions to the audience and expert panel with individual electronic responses providing an audience sampling of 99 electronic response devices among approximately 120–150 attendees per breakout (Tables 1 & 2). Attendees participating in the electronic responses were predominantly industry scientists (43%) followed by industry regulatory affairs (18%), regulatory authorities (17%), healthcare providers (2%), other scientists from medical, university or government (8%) and others not specified (8%). Among the regulatory authorities, there were a substantial number from the FDA, EMA and PMDA with representation from FDA drug review divisions (Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research) and *in vitro* diagnostics (Center for Devices and Radiological Health).

Breakout session 1

Safety PGx models for updating drug product labels

A case study on warfarin was presented to illustrate the types of data and changes made to a product label for a safety biomarker. The subsequent discussion focused on how the quality and quantity of evidence triggers a label update, rationale and placement of new label text and/or sections, and in addition, how healthcare professionals respond to and adopt label recommendations into clinical practice and their standards of care. The multiple choice questions posed to the panel and audience, along with attendee responses, are outlined in Table 1.

As exemplified by warfarin, updating a product label is an iterative process that relies on subsequent clinically relevant confirmation of emerging data. Several product labels have been updated to include safety-related PGx data, such as carbamazepine and abacavir. At the time of theworkshop the product label for warfarin was the only one to have been updated twice, in August 2007 and again in January 2010. Warfarin is also unique in that the label includes information on two polymorphic genes, *CYP2C9* and *VKORC1*; the first being involved in warfarin metabolism and the latter being its target. Several studies, both retrospective and prospective, have examined the factors (including genetic factors) contributing to the variability in warfarin doses [6], as well as the risk of overanticoagulation and increased risk of bleeding [7,8].

A substantial number of these studies were published after the first label update in 2007, necessitating a re-evaluation of the data and a possible second update. Of particular interest, several prospective studies provided data regarding the initial dose of warfarin, accounting for genetic variability in *CYP2C9* and *VKORC1*. In particular, the International Warfarin Pharmacogenetics Consortium published their findings estimating the initial warfarin dose with both clinical and DNA data in 2009. Thus, in January 2010, a second label update was released, summarized in a table on the range of expected therapeutic doses based on *CYP2C9* and *VKORC1* genotypes, as well as other label sections including Genetic Testing and Clinical Pharmacology – Metabolism.

The final part of the case briefly compared warfarin with PGx-based changes in the product labels of abacavir and carbamazepine, and their impact on medical practice. Like warfarin, carbamazepine was approved several decades ago (for epilepsy). Four months after the initial warfarin, label update with PGx in 2007, the carbamazepine USPI was updated with a boxed warning based on retrospective PGx data. This box described the increased risk for serious cutaneous adverse events in those with an ancestry across broad areas of Asia (including Chinese and South Asians) in association with the *HLA-B*1502* variant. It was subsequently described that PGx testing should be performed in the

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Table 1. Breakout 1: safety PGx models for updating drug product labels.

Question	Answers	%
Question 1.1 (n =79)		
Are data from retrospective or observational studies appropriate to support a PGx safety label update (e.g., as in this case of warfarin and retrospective data)?	a) Yes	32
	b) No	6
	c) Under certain circumstances	62
	d) Not sure	0
Question 1.2 (n = 65)		
For new drugs, preapproval with safety signals associated equivocally with genomic biomarkers, when would postmarketing studies be most valuable to improve the risk–benefit of the drug?	a) For serious AEs where a test would identify a subset of patients who should not get the drug	82
	b) For serious AEs where a test would stratify dosing in the total population of patients	17
	c) For serious AEs where a test is only applicable to a given racial/ethnic subgroup	0
	d) Not required	2
Question 1.3 (n = 68)		
What is the best way to communicate effectively with physicians and healthcare providers regarding label changes involving a PGx test and its appropriate medical use, particularly for existing drugs?	a) US FDA 'Dear Doctor' letter	34
	b) FDA website alerts	7
	c) Drug company representative	6
	d) Hospital or Pharmacy Benefit Manager	3
	e) Laboratory offering PGx test	3
	f) Medical groups (e.g., American College of Cardiologists)	44
	g) Expert government panels (e.g., USPSTF)	0
	h) Press conference and/or press release	3
	i) Other	0
Question 1.4 (n = 60)		
What is the best way to express genomic data in product labels to achieve these objectives?	a) Genotypes (e.g., *CYP2C9*2/*2*)	3
	b) Protein function (e.g., 2C9 intermediate metabolizer)	0
	c) Phenotypes (e.g. increased bleeding risk for patients carrying either the *CYP2C9*2* or *CYP2C9*3* alleles	33
	d) All three types	33
	e) Does not matter if linked clearly to a decision	30
	f) No idea	0
Question 1.5 (n = 63)		
Why has the uptake of warfarin genetic testing been apparently slow?	a) Physicians are not aware of it	8
	b) Physicians are aware but are not convinced by the evidence of clinical utility	49
	c) Professional guidelines have not supported testing	30
	d) Warfarin is off-patent and sponsors do not care or promote test	3
	e) Insurance companies do not reimburse test costs	10

AE: Adverse events; PGx: Pharmacogenomics; USPSTF: US Preventive Services Task Force.

at-risk population prior to administration. The second comparison was abacavir, a drug used for the treatment of HIV infection, first approved in 1998. A specific *HLA* variant, *HLA-B*5701*, predicts an increased risk for abacavir hypersensitivity, a potentially life-threatening adverse event. Based on a combination of retrospective data and a prospective randomized controlled clinical trial [9], product labels for abacavir-containing products were updated in the USA and Europe to, respectively, recommend or necessitate *HLA-B*5701* screening prior to abacavir (initiation).

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Session 1 concluded with a brief overview on physician education and guidelines. During the question and answer session, attendees expressed a range of views on the apparently slow healthcare uptake of warfarin PGx testing (Question 1.5, TABLE 1). Although product labels may serve to educate physicians on new advances that can improve the use of the drug, the low awareness among the audience on the content of product labels suggested that additional resources, including medical guidelines, could be used to inform the use of new medical applications of PGx. While several professional medical organizations have developed position statements on the use of PGx testing for warfarin use, consensus is still lacking. In addition, a recent ruling by the Centers for Medicaid and Medicare Services, a US federal agency that governs health insurance coverage for the elderly and/or on low income, ruled that current evidence does not demonstrate that routine DNA testing improves health outcomes for warfarin.

■ Breakout session 2

Efficacy PGx models for labeling new drug products

Whereas most of recently updated product labels now include PGx information related to serious adverse events, as described in the first breakout session, numerous product labels now include PGx information related to efficacy or a lack thereof. Representative examples include erlotonib, imatinib, maraviroc, clopidogrel, cetuximab and panitumumab. Information regarding PGx predictors of efficacy has generally been included prior to the drug's approval, when clinical trials enroll populations defined by the molecular biomarker. However, in some cases, retrospectively analyzed data has been used to support the inclusion of PGx into product labeling. To characterize evidentiary considerations, as well as the breadth and depth of efficacy-related PGx information included in labels, this session focused on the following key issues:

- Types of PGx tests referenced in product labels;
- Quantity of PGx information in product labels;
- Intended prescriber actions related PGx information;
- Relevant sections of a label;
- Leveraging existing knowledge;
- Levels of evidence leading to medical practice recommendations.

Specific questions posed to the panel and audience may be found in TABLE 2.

This breakout session focused on the most recent label update of clopidogrel, which included PGx information related to lack of intended pharmacology. Clopidogrel is an antiplatelet drug that is commonly prescribed for patients with cardiovascular disease to prevent thrombotic events. As a prodrug, clopidogrel requires activation by multiple CYP enzymes. Since 2006, substantial evidence has accrued, demonstrating that the *CYP2C19* gene variants linked to reduced metabolic activity decrease an individual's ability to convert the prodrug to the active moiety. As a consequence, patients carrying one or more of these gene variants and reduced *CYP2C19* metabolism have diminished antiplatelet responses, reducing the clinical benefit from clopidogrel in terms of preventing major adverse cardiovascular events [10]. The clopidogrel USPI was initially updated in May 2009 to include this retrospectively derived PGx information. The Dosage and Administration, Warnings, Special Populations and Clinical Pharmacology sections were revised to include information related to drug metabolism and the impact of the *CYP2C19* gene variants on pharmacokinetics, pharmacodynamics and clinical outcomes due to the active metabolite of clopidogrel. Highlighting the way that regulatory authorities work in an iterative process as relevant data emerges, there was an additional label update after the workshop in the form of a boxed warning informing healthcare professionals on the availability of tests to identify genetic differences in *CYP2C19*.

Summary of breakout discussions

■ Types of PGx tests referenced in product labels

Developing new medicinal products which include genetic covariates predicting drug response relies on the availability of an analytically valid *in vitro* device or test. Different types of tests may be used in medical practice, ranging from laboratory-developed tests in Clinical Laboratory Improvement Amendments-certified laboratories to tests cleared/approved by the CDRH, FDA. Warfarin and clopidogrel represent examples of labels updated with PGx information in the postapproval setting. Tests for *CYP2C9*, *VKORC1* and *CYP2C19*

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Table 2. Breakout 2: efficacy PGx models for labeling new drug products

Question	Answers	%
Question 2.1 (n = 64)		
Situation: different types of *in vitro* tests may be used in medical practice (e.g., laboratory-developed tests in CLIA-certified laboratories, cleared/approved tests by CDRH-US FDA). Question: for a new drug, to restrict the population, do you think PGx tests in a product label should be cleared/approved by CDRH-FDA concurrent with drug approval by CDER-FDA?	a) Yes, all PGx tests in product labels should be FDA cleared/approved	42
	b) No, if PGx test results will not change a medical action for drug	25
	c) No, PGx tests are like any other laboratory test referenced in labels (e.g., liver function tests)	31
	d) No opinion	2
Question 2.2 (n = 72)		
Situation: the label for clopidogrel states in the Clinical Pharmacology - Pharmacogenetics section "Pharmacogenetic testing can identify genotypes associated with variability in *CYP2C19* activity". Question: to help prescribers, should a product label contain more information about the PGx biomarker, such as assay details (e.g., DNA variants) and how the results are interpreted?	a) Yes, this information is helpful to prescribers	54
	b) No, test performance and knowledge on a biomarker could change	25
	c) No, other tests on the label do not have this much detail	19
	d) No opinion	1
Question 2.3 (n = 62)		
Situation: the product label is intended to help prescribers make decisions for their patients. PGx information included in labels may range from 'information only' (no action), to 'testing recommended' (choice), to 'testing required' action (no choice) based on the increasing certainty for a medical consequence and consequences of not testing Question: would it be useful to prescribers to specify 'requirements' or 'recommendations' in the label for efficacy PGx markers?	a) Yes	84
	b) No	15
	c) No opinion	2
Question 2.4 (n = 64)		
Situation: two Phase III clinical trials show that a PGx covariate helps to explain variability for efficacy Question: where in the label should the results be placed for maximum effect for prescribers?	a) Clinical studies	23
	b) Laboratory tests	3
	c) Clinical pharmacology	13
	d) Indication	33
	e) Specific populations	13
	f) Dosage and administration	16
	g) Another section	0
Question 2.5 (n = 63)		
Situation: a new drug is being approved. A PGx marker is included in the labeling of a marketed drug in the same class and for a similar indication. Question: should the label for the new drug contain information on the clinical performance of the PGx test?	a) Yes	52
	b) No	46
	c) No opinion	2
Question 2.6 (n = 60)		
Situation: Levels of evidence for establishing drug efficacy (i.e., regulated drug development) may differ from the level of evidence for medical practice. For example, a prescriber must weigh the value of population-based PGx data to predict different drug effects for an individual patient. Question: 'If I was a prescriber I would order a PGx test if the difference in drug response between 'marker$^+$' patients and 'marker$^-$' patients was:	a) Tenfold higher	3
	b) Fivefold higher	15
	c) Twofold higher	18
	d) It depends	62
	e) No idea	2
Question 2.7 (n = 63)		
What information is the most important when considering inclusion of PGx information in the product label?	a) Marker effect size and/or clinical performance characteristics	35
	b) Biological plausibility	0
	c) Replication in multiple, independent sample collections	8
	d) All of the above	56
	e) None of the above	2

CDRH: Center for Devices and Radiological Health; CLIA: Clinical Laboratory Improvement Amendments; CDER: Center for Drug Evaluation and Research; PGx: Pharmacogenomics.

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were commercially available, albeit not with CDRH-approval to make dosing decisions or select appropriate antiplatelet therapies (Postworkshop note: A *CYP2C19* test now has CDRH approval). Ideally in the USA, a FDA-cleared or -approved test should be available for drugs that have PGx information included in the product label, which result in medical action (such as dose modification or exclusion of certain patients). The attendees suggested that greater clarity is required from the FDA on the use of PGx tests conducted within CLIA-certified laboratories which may not be cleared or approved by the CDRH. This is because of the rapid advances in PGx knowledge where the intended medical use of a PGx test on a product label may differ from what may be outlined in the version with CDRH clearance or approval (Question 2.1, TABLE 2).

The device framework in Europe significantly differs from that of the USA, as diagnostic tests are assay-approved outside of the EMA via the Conformité Européenne mark. In general, when tests are performed with technology that is ubiquitous, the EMA may be willing to make a recommendation that tests be performed in reliable centers. The EU is investing efforts to encourage quality assurance/quality control networks and standards for qualifying laboratories.

For newly developed drugs with PGx information on the product label, the expectations may differ. Codevelopment of PGx tests with new drug products before their approvals is potentially attractive, but to date has been challenging from a regulatory standpoint (Question 2.3, TABLE 2). Prescribers must have some flexibility in order to make the ultimate decisions regarding the use of a medicine and relevant testing, taking in to account the overall medical situation and individual patient. From a drug development perspective, codeveloping a companion diagnostic and generating adequate data for registration of the test itself can present a significant resource burden, particularly if the biomarker is novel, because the majority of drugs in development fail to reach the market. Finally, if a drug is developed in such a way that its proper use is predicated on the results of a novel test, a FDA-approved test that has demonstrated analytical and clinical validity should be commercially available at the time of drug product approval.

Informational content related to PGx in product labels

Product labels are intended to provide information to physicians enabling informed prescription decisions. Some may argue that information provided by the FDA through product labels, particularly for innovative data such as PGx, is not the most efficient and effective way for recommendations to become embedded into medical practice. Nonetheless, the label serves as a consolidated information resource, forming the basic framework for many downstream communications such as advertising, 'Dear doctor' letters and so on (Question 1.3, TABLE 1). As with any new medical advance, PGx information can still often appear complex and nuanced, rendering it difficult to communicate to physicians, particularly those in general practice. The session expert panels generally agreed with the audience that granular information, including test performance characteristics (e.g., predictive values), racial distributions of genetic markers, specific scenarios for testing and study results are generally appropriate and useful to include in the product label (Question 1.4, 2.2, 2.5, 2.6 and 2.7 TABLES 1 & 2). The FDA tends towards higher level, or summarized, information in the product label because of this challenge, while still providing sufficient context for prescribers to make informed decisions. Both the FDA and EMA panelists agreed that product labels should be easier to read. The challenge is the process by which information is kept up to date, since PGx information is constantly evolving (as highlighted by label updates with PGx to warfarin and clopidogrel following the workshop). During the breakout exchanges, it became evident that, with the example of the USA, *in vitro* device labels are not as publicly accessible as USPIs. In addition, identifying the most up to date product label can be time consuming, even with internet access and requisite search skills.

Relevant sections of the label for PGx (using USPI as an example)

To date, product labels have included PGx information in a variety of sections, ranging from Warnings to Indications to Clinical Pharmacology. In general, the audience's understanding varied on how placement of information in the product label is intended to inform healthcare providers (Question 2.4, TABLE 2). For instance, if the drug is developed as a targeted therapeutic that is efficacious for a specific, biomarker-defined patient population, then that information is generally reflected in the Indications section. However, when the PGx information is relevant to the drug's disposition or mechanism of action, and intended only to be supportive, then the information may be integrated into the Clinical Pharmacology section. PGx information associated with safety

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may be incorporated into different sections of drug labeling; for example, tolerability information may be included in multiple sections (such as Pharmacokinetics, Adverse Events, Drug Interactions and Laboratory Testing), while information about biomarkers predictive of serious adverse events often will be included in the Boxed Warnings section (Question 1.2, TABLE 1). The approach to labeling remains context dependent and is largely a function of the quantity and quality of evidence for the PGx biomarker, testing strategy in a specific medical scenario, and the scope of the intended prescriber's action arising from the test result.

Leveraging existing knowledge gained for one drug to other drugs

In the current climate of benefit–risk assessments and comparative effectiveness, it is increasingly important to understand the predictive potential of PGx biomarkers for other medicines within a drug class or therapeutic area. When a PGx biomarker resides in a target that is common to multiple drugs in a class, labeling all drug products with information on the biomarker may be considered appropriate and relevant to the use of those drugs. In situations whereby the PGx biomarker differentiates one product from another in the same class (i.e., where drug-metabolism pathways may differ between drugs in the same class), the approach to labeling is somewhat more complex as reflected by the audience views (Question 2.5 TABLE 2). However, much like any other type of biomarker in product labels, PGx is handled on a case-by-case basis, ultimately depending on robust and compelling evidence to support proposed claims.

Evidentiary considerations for product label

The evidence required for PGx on product labels involves parameters such as type of trial design, sample size, replication, reproducibility, consistency, effect size and other predictor variables. The level of evidence required to establish a biomarker's efficacy in order to guide drug use in the setting of regulated drug development (i.e., clinical trial setting) may differ from that of medical practice, in that a prescriber must translate the value of population-based genetic data in order to predict certain drug responses to an individual patient. Thus, integrated health systems, which also consider health economic aspects, may need to generate their own PGx efficacy data to determine the clinical utility of adding genetic factors to decision-making in medical practice. The level of evidence required for the PGx safety biomarkers that have been included in the product labels may be different upon comparison to efficacy (Question 1.1, TABLE 1). While some of the safety-related biomarkers, such as *CYP2C19*, *CYP2C9* and *CYP2D6*, were identified through pharmacokinetic studies during clinical drug development, the majority of other safety-related biomarkers were identified through drug-related adverse events during broader healthcare use, and thus mostly by retrospective approaches.

Future perspective

The primary goal of the 'Building PGx into Labels' sessions was to raise awareness of the already well-established drug development processes and regulatory guidelines involved in product labeling, and demonstrate how this knowledge can be applied to PGx. Communication with prescribers of PGx for new medicines and/or label updates of already marketed medicines will need to employ multiple methods. Unfamiliarity with genetic testing and terminology, as well as ambiguous prescriber actions regarding testing (i.e., for information with no action, recommended action, required or mandated action) and the application of test results to treatment decisions will present serious challenges in the integration of PGx testing in medical practice. This could be improved upon in part by raising general awareness of PGx testing; employing educational resources, such as those developed by the American Medical Association on PGx testing in warfarin [103] and, more specifically for a medicine, through clear description and placement of PGx information in the label with the type of prescriber action suggested.

In the future, PGx will not only be able to add to the conceptual framework being developed globally on benefit–risk assessments but for country-specific initiatives, such as comparative effectiveness in the USA. In return, proactively considering benefit–risk ratios for PGx will help to guide its relevant integration with other covariates that predict drug response. Different levels of evidence in drug development will help guide product label considerations, such as:

- Development Phase: interim development decision versus new label versus label update;
- Drug Response: safety (tolerability vs serious adverse event) versus Efficacy;
- Prescriber actions: none (for information), versus recommended action (choice) versus required action (no choice).

Author Proof

Retrospective data as a source for updating labels has frequently been used for safety, especially associated with severe adverse events. However, the level of PGx evidence for incorporating new knowledge for efficacy on a label is still an area of discussion, as illustrated by the case studies of recent label updates, such as *KRAS* testing for anti-EGFR therapy. The use of retrospective efficacy-related PGx from clinical trials to inform product labeling and patient care is supported by regulators. However, a higher threshold may be perceived than for prospective data collection and prespecified analyses, possibly due to several concerns including types of biases. Key issues related to retrospective data include some of the following:

- When were data collected?
- What information was known before the decision to collect data?
- Was potential bias introduced when less than a completely randomized population was included for analysis of a specified end point?
- Does the proportion of patients retrospectively tested for a biomarker adequately represent the broader patient population?

Many of the PGx markers that have been referenced in product labels have had large effect sizes equivalent to those resulting from a single gene. Thus, there has been the ability to discriminate treatment response, typically toxicity, with relatively modest sample sizes (50–100 study participants) and shorter trial duration. However, it is possible that the majority of drug responses will be multifactorial with multiple, small genetic effects among other types of covariates, reflecting the already well-known complexity in drug development of confirmatory clinical trials, diagnostic codevelopment and informative product labeling. Nevertheless, appropriate confirmatory trials integrating PGx approaches may increasingly be conducted in real-time on the pipeline rather than relying on pre-existing long-term epidemiological datasets built over decades, with hundreds of thousand patient years (e.g., consider cholesterol levels as used in the development and/or approval of cardiovascular medicines).

The carrying out of compelling changes in medical practice often begins at the frontline with patients. Good science drives innovation for healthcare providers, as well as for the pharmaceutical industry and regulatory authorities. There are aspects specific to PGx that may help to proactively guide retrospective data analysis in the regulated environment of developing new medicines. Currently, PGx testing based on DNA methodologies tends to be positioned in advance of giving a drug administration. However, DNA-based drug response is time-independent, so a PGx test may be relevant at any time during the day, chronological age, disease stage, drug administration, clinical trial course and so on. Integrating these and other DNA-specific characteristics into drug development would contribute to the agreement of minimum levels of PGx evidence between industry and regulatory authorities. Just as importantly, different ways to place a new PGx diagnostic test during the course of treatment may be revealed during drug development and/or postapproval administration, so as to better anticipate benefit–risk ratios which are relevant to healthcare providers and their patients.

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Executive summary

- There are well-established drug development processes and regulatory guidelines involved in product labeling that can aid the informative integration of PGx (pharmacogenomics) into the product labels of new medicines.
- However, broader dialogue and additional regulatory guidances were requested by the Workshop attendees to begin the agreement of minimal thresholds in levels of PGx evidence for specific drug development contexts (interim development step vs new label vs label update), type of drug response (safety vs efficacy) and intended prescriber actions (for information vs recommended action vs required action)
- Efficacy-related PGx in clinical trials was discussed, including prospective DNA collection with retrospective PGx analysis (i.e., prospective–retrospective PGx). A case example demonstrated timely investigation and integration of new science knowledge, with medical relevance into product labeling and a proposal for a consistent regulatory approach on this 'prospective–retrospective' approach to clinical trials integrating PGx.

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Financial & competing interests disclosure

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