

Cancer Drug Development and the Evolving Regulatory Framework for Companion Diagnostics in the European Union

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Abstract

The European Union (EU) legal framework for medical device regulation is currently under revision. The European Commission has proposed a new framework to ensure that medical devices serve the needs and ensure the safety of European citizens, aiming for a framework that is fit for purpose, more transparent, and better adapted to scientific and technological progress. The proposed new framework is described as an evolution of the current regime keeping the same legal approach. An important proposed change is that companion diagnostics will no longer be considered as low risk and subject to self-certification by the manufacturer. According to the new proposal, companion diagnostics will be classified as high individual risk or moderate public health risk (category C) and require conformity assessment by a notified body. It has also been proposed that evidence of the clinical utility of the device for the intended purpose should be required for companion diagnostics. In this article, we review the EU legal framework relevant for companion diagnostics, describe the proposed changes, and summarize the available scientific guidance from the European Medicines Agency and its regulatory experience with cancer drug development including companion diagnostics.

See all articles in this CCR Focus section, "The Precision Medicine Conundrum: Approaches to Companion Diagnostic Co-development."

Clin Cancer Res; 20(6); 1458–68. ©2014 AACR.

Introduction

European pharmaceutical legislation has been evolving rapidly over the last decades, although since the 1960s, its primary aim has remained unchanged, that is, to safeguard public health and to encourage development of new medicines. Another important objective has been to encourage the development of the pharmaceutical industry and the creation of a single market for pharmaceuticals in the European Union (EU). In 1995, the European Medicines Agency (EMA) came into operation and a centralized procedure was established. This leads to a single EU-wide approval, which is harmonized with regard to identical approved indications and conditions of use in all Member States. Since November 2005, all new anticancer drugs for which marketing authorization is sought in the EU must undergo scientific assessment through the centralized pro-

cedure. A comparison of the oncology drug approval processes in the United States and the EU is provided in this edition of *CCR Focus* (1).

Biomarker-driven patient selection has become increasingly important for new cancer drugs. Indeed, for many years, the EMA has emphasized the importance of predictive biomarkers to be used throughout phases of clinical drug development of oncology drugs. Such markers are considered essential to identify the target population for therapy and typically are mentioned in the therapeutic indication in the labeling of an approved drug. Currently, most of the regulatory experience with biomarkers is based on genomic biomarkers for patient selection and protein expression.

The EMA has produced draft guidance on the co-development of companion diagnostics for genomic biomarkers in the context of cancer drug development (2–7). Some of the principles may apply to nongenomic biomarkers in the context of drug development.

In the EU, the legal framework for regulation of *in vitro* companion diagnostics is distinct from the framework for regulation of drugs. Companion diagnostics are regulated within the medical devices legal framework. The rules on medical devices were harmonized in the EU in the 1990s. In 1993, the first in a series of medical device directives was issued, allowing Conformité Européenne (CE)–marked products to circulate freely in the European Economic

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doi: 10.1158/1078-0432.CCR-13-1571

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Area, and introducing harmonized requirements, device certification, and assessment of quality systems of manufacturers. The European legislation on medical devices including companion diagnostics is currently under review.

In this article, we describe the current EU legal framework for companion diagnostics in the context of cancer drug development; we describe some of the changes recently proposed and summarize available scientific guidance and recent experience with companion diagnostics for genomic biomarkers in the context of cancer drug regulation in the EU.

The Current Regulatory Framework for Companion Diagnostics

On the basis of the current legal framework for medical devices, companion diagnostics for genomic biomarkers for cancer patient selection generally fall into the classification of *in vitro* diagnostic (IVD) medical devices. An IVD is defined in a separate directive ("IVD Directive" 98/79/EC) as any medical device which is a "reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment, or system, whether used alone or in combination, intended by the manufacturer to be used *in vitro* for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information concerning a physiologic or pathologic state, or concerning a congenital abnormality, or to determine the safety and compatibility with potential recipients, or to monitor therapeutic measures" (8).

A manufacturer wishing to place a medical device on the EU market under the IVD Directive must assign the device to the relevant risk category defined in the directive. Currently, companion diagnostics to assay genomic biomarkers in cancer would be classified as general IVDs (low risk) for which clinical efficacy data or establishing clinical utility are not required. For low-risk IVDs, the manufacturer self-certifies conformity provided the device meets the "essential requirements" which aim to ensure that the products do not compromise the health and safety of patients and users and are designed and manufactured to achieve the performance specified by the manufacturer. Once certified, devices bear the CE marking, which allows them to be circulated freely in the EU/EFTA countries (Iceland, Liechtenstein, Norway, and Switzerland) and Turkey.

Manufacturers must maintain systematic procedures to review postproduction experiences and must notify the national competent authorities of any incidents or recalls that result, or could have resulted, in death or serious injury (8). For higher-risk IVDs, additional requirements apply depending on the classification of the devices and the conformity assessment route a manufacturer has chosen and may involve a notified body. A notified body is a third-party certification organization designated and monitored by the national authority (the competent

authority) of a Member State to carry out one or more of the conformity assessment procedures.

IVDs that are not placed on the market but which are put into service must also follow the appropriate conformity assessment procedure. However, devices manufactured and used only within the same health institution and on the premises of their manufacture or used on premises in the immediate vicinity without having been transferred to another legal entity are outside the scope of the IVD Directive ("in-house derogation"; ref. 8).

Proposed Revision of the Regulatory Framework: Current Status

The European Commission has published legislative proposals which, once adopted by the European Parliament and by the Council, will replace the existing medical devices legislation. Here, we summarize some of the issues relevant for companion diagnostics following the Commission proposal.

New risk-based (class A, lowest risk; class D, highest risk) conformity assessment requirements are proposed on the basis of the Global Harmonization Task Force for medical devices [a voluntary group of representatives from national medical device regulatory authorities and the regulated industry, now replaced by the International Medical Device Regulators Forum (IMDRF)] system of 2008 (Table 1; ref. 9). Accordingly, companion diagnostics (newly defined as devices specifically intended to select patients with a previously diagnosed condition or predisposition as eligible for a targeted therapy) and devices intended to be used for disease staging or screening or diagnosis of cancer would be classified within class C. Class C devices present a moderate public health risk, or a high individual risk, where an erroneous result would put the patient in an imminent life-threatening situation or would have a major negative impact on outcome.

A notified body will be systematically involved in the conformity assessment procedure of companion diagnostics. This practice represents a departure from the simpler system of self-certification (Fig. 1). The notified body will check the quality management system and the technical documentation of representative samples. Companion diagnostics will have to demonstrate compliance with general safety and performance requirements, including analytic performance and clinical performance, such as diagnostic sensitivity, diagnostic specificity, positive and negative predictive value, likelihood ratio, and expected values in normal or affected populations. The clinical performance shall be demonstrated on the basis of clinical performance studies, literature, or experience gained by routine diagnostic testing. The clinical performance study report will include the method of data analysis, the study conclusion, and the relevant details of the study protocol (the individual data points need only be included for class D devices; ref. 10).

Table 1. General classification system for IVD medical devices based on the Global Harmonization Task Force for medical devices system of 2008

Class	Risk level	Examples
A	Low individual risk and low public health risk	Clinical Chemistry Analyzer, prepared selective culture media
B	Moderate individual risk and/or low public health risk	Vitamin B12, Pregnancy self-testing, antinuclear antibody, urine test strips
C	High individual risk and/or moderate public health risk	Blood glucose self-testing, HLA typing, PSA screening, Rubella, sexually transmitted diseases, cancer markers (screening for selection of patients for selective therapy and management, or for or for disease staging, or in the diagnosis of cancer; e.g., personalized medicine), cardiac markers, genetic tests
D	High individual risk and high public health risk	HIV blood donor screening, HIV blood diagnostic

NOTE: Examples are taken from ref. 9.

The notified body will also have to consult the EMA (or one of the medicinal product national competent authorities) on the basis of the draft summary of safety and performance and the draft instructions for use, although the precise scope of such consultation is currently not detailed. A similar process is envisaged for changes affecting the suitability of the device in relation to the medicinal product concerned. The competent authority consulted shall give its opinion, if any, within 60 days (this period

may be extended once for a further 60 days on scientifically valid grounds; ref. 10).

The clinical evidence and its documentation has to be updated throughout the life cycle of the device concerned with data obtained from the implementation of the manufacturer's postmarket surveillance plan. After initial certification, Notified Bodies will regularly conduct surveillance assessments in the postmarket phase (10).

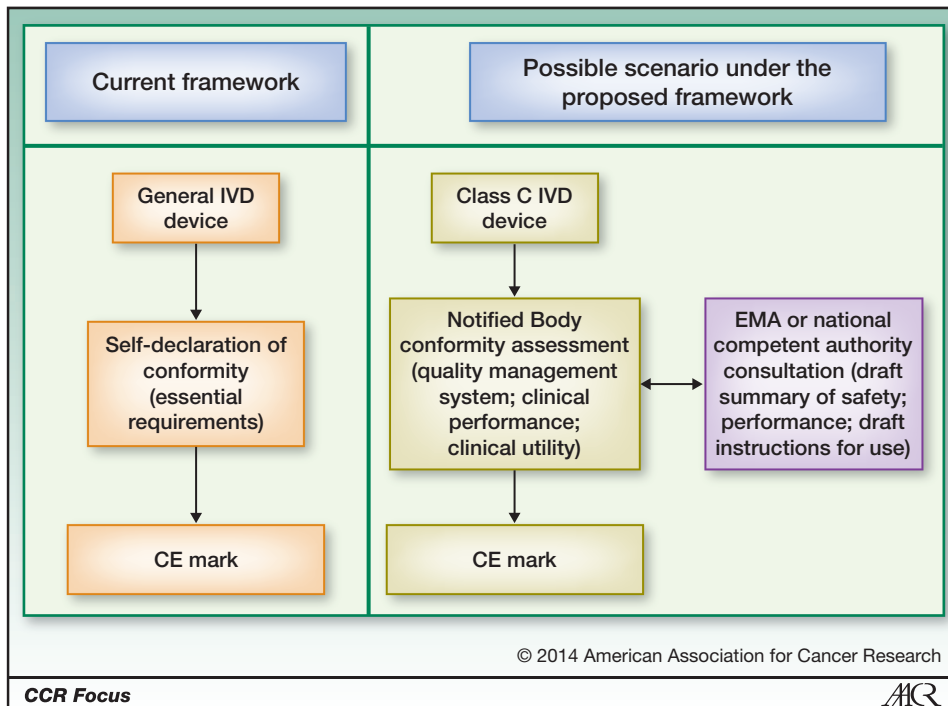


Figure 1. Pathway to CE marking of companion diagnostics under the current legal framework and possible scenario under proposed new legal framework under discussion (10, 11).

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The proposed regulations foresee to strengthen the supervision of the Notified Bodies by the Member States, to ensure that all bodies have the necessary competence to carry out the premarket conformity assessment (10). The ultimate responsibility for designating and monitoring Notified Bodies is left with the individual Member State. The monitoring of Notified Bodies will also receive "joint assessments" with experts from other Member States and the European Commission, thus ensuring an effective control at Union level.

In October 2013, the European Parliament proposed amendments for companion diagnostics, such as to include the requirement for evidence of the clinical utility of the device for the intended purpose (including clinical evidence relating to the impact of a positive or negative test on patient care and health outcomes when used as directed with the stated therapeutic intervention), and, depending on the conformity assessment route for the diagnostic, to involve reference laboratories to verify compliance with common technical specifications (or with other solutions chosen by the manufacturer to ensure a level of safety and performance that is at

least equivalent). It also introduced amendments to require that class C companion diagnostics may only be supplied on a medical prescription (previously, this was proposed to be determined nationally; ref. 11). The discussion between European institutions to agree on a revised legislation is ongoing. Once adopted, the new rules could gradually come into effect from 2015 to 2019 (12).

EMA Guidelines on Biomarkers and Companion Diagnostics in the Context of Cancer Drug Development

The EMA has produced guidance on the importance of identification and validation of genomic biomarkers (2–5). Although development of companion diagnostics has not been the focus of EMA guidance, a number of observations relevant for companion diagnostic have been made. The guidance should be seen in the context of a number of other activities and procedures for biomarker identification and validation purposes promoted by the agency (see Table 2). The guidance is expected to be

Table 2. EMA biomarker and companion diagnostic-related activities and procedures

- **Biomarker qualification**

The EMA qualification process is a new, voluntary, scientific pathway leading to either a scientific opinion or scientific advice on innovative methods or drug development tools. The EMA can issue an opinion on the acceptability of a specific use of a method, such as the use of a novel methodology or an imaging method in the context of research and development. The method can apply to nonclinical or to clinical studies, such as the use of a novel biomarker.

- **Innovation Task Force (ITF)**

The ITF is a multidisciplinary group that includes scientific, regulatory, and legal competences. It was set up to ensure coordination across the EMA and to provide a forum for early dialogue with applicants. The scope of the ITF activities encompasses emerging therapies and technologies and borderline therapeutics for which there is no established EMA scientific, legal, and regulatory experience. Recent areas of ITF engagement have included nanomedicines, pharmacogenomics, synthetic biology, biomaterials, modeling and simulation, and mobile health.

- **Scientific advice**

The EMA offers scientific advice to support the qualification of innovative development methods for a specific intended use in the context of research and development into pharmaceuticals. The advice is designed to facilitate the development and availability of high-quality, effective, and acceptably safe medicines, for the benefit of patients. Companies can request scientific advice from the EMA at any stage of development of a medicine.

- **Combined advanced therapy medicinal products (ATMP) and medical devices**

ATMPs are medicinal products including gene therapy, somatic cell therapy, and tissue-engineered products. ATMPs may incorporate, as an integral part of the product, one or more medical devices, in which case they are referred to as "combined" ATMPs. Those devices must meet the essential requirements laid down in the relevant directive and notified body for medical devices may be involved in the assessment of quality and safety of the device.

- **EMA consultation on ancillary substances in medical devices**

If medical devices contain as an integral part "ancillary substances" that, used separately, may be considered to be a medicinal product, notified bodies must verify the quality, safety, and usefulness of such ancillary substances. To do this, the Notified Body must seek a scientific opinion from one of the competent authorities designated by the Member States or the EMA.

finalized following revision of the EU legal framework for medical devices.

Biomarker discovery and validation

The EMA guidance has focused on prospective advice for parallel development, including separate development and confirmation phases. However, experience has shown that this is an ideal scenario and that it is also important to consider strong signals from exploratory analyses, in particular, if these can be supported with additional knowledge, such as improved knowledge of the role of the biomarker in the pathogenesis of the disease and some confirmatory evidence from other trials. Thus, the guidance also addresses situations in which biomarker discovery occurs during later stages of drug development before or after approval (5).

In general, to validate biomarkers that have been identified in exploratory studies or *post hoc* analyses, an independent replication of findings is required. Prospective randomized clinical trials provide the gold standard for the validation of biomarkers. Tailored trial designs for this purpose have been proposed (8, 13–16), as, for example, enrichment designs (where only biomarker-positive patients are included), stratified designs (where the randomization is stratified by biomarker status), or adaptive enrichment designs (where first-stage biomarker-positive and biomarker-negative patients are included and there is an option to restrict randomization after an interim analysis to biomarker-positive patients only; refs. 17–19). Although enrichment designs are most efficient to confirm a positive benefit–risk balance in the biomarker-positive population, they give no information on biomarker-negative patients. In contrast, designs including biomarker-positive and negative patients allow confirmation that the biomarker indeed predicts treatment response but require larger sample sizes.

In cases where there is insufficient information about the benefit–risk balance in biomarker-negative patients, such studies may be requested after approval. For example, crizotinib is indicated for the treatment of adults with previously treated anaplastic lymphoma kinase (ALK)-positive advanced non–small cell lung cancer (NSCLC). At the time of approval, it was not known whether crizotinib was only effective in patients with ALK-positive status. Thus, the enrolment of ALK-negative NSCLC patient as a new cohort in the ongoing pivotal phase I/II study has been requested as postmarketing commitment (20).

In settings where prospective randomized trials are not feasible for ethical or practical reasons, replication based on retrospective subgroup analysis of one or more randomized clinical trials has been proposed. Such retrospective validation is only appropriate if the data of these trials were not used for the biomarker identification and the number of candidate biomarkers investigated in the replication studies is accounted for. The study identifying the association between wild-type *KRAS* in metastatic

colorectal cancer and improved progression-free survival after panitumumab provides one such example of retrospective validation. In this instance, a differential effect of panitumumab between carriers of wild-type and mutated *KRAS* suggested by a *post hoc* analysis formed the basis of conditional authorization in the EU, along with a biologic plausibility for the association derived from trials of cetuximab. The authorization stipulated that further data should be generated prospectively (4, 21).

In comparison, the interaction between EGFR FISH or EGFR mutation status with gefitinib was evaluated in several studies (ISEL, INTEREST, and IPASS) in patients with NSCLC in a *post hoc* (retrospective) analysis (only the INTEREST study included EGFR FISH–positive-based difference as the coprimary objective). The differential response rates noted in these studies might have been influenced by differences in patient, disease, and treatment characteristics. The differences in the number of subjects with known marker status may also have played a role. Notwithstanding the differences, the pooled analysis suggested benefit from gefitinib therapy in case of EGFR mutation–positive tumors because of the directional concordance between various comparisons and the replicated interaction between EGFR mutation status and response to gefitinib. Thus, a restricted indication was accepted in the EU. This example highlights two important aspects of retrospective evaluation of biomarkers: the need for replication in different studies and populations, and second, the need for minimizing missing data (4, 22).

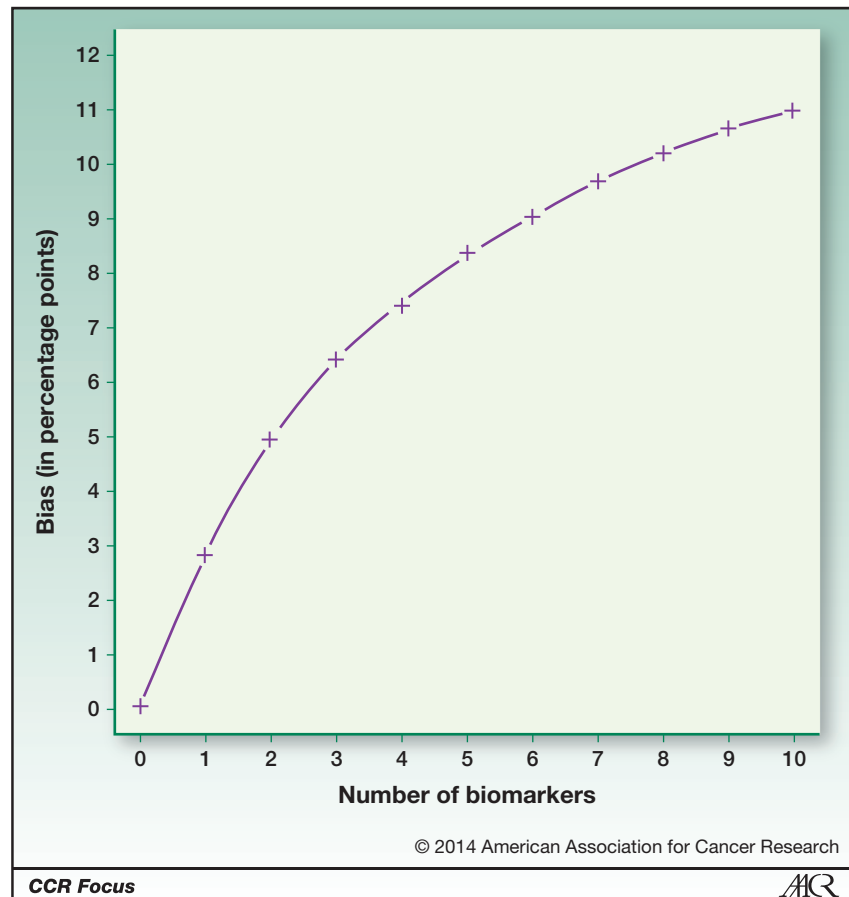
Regardless of the approach, there is a need to plan for a learning phase and a confirmatory phase, aiming to minimize bias and control for multiplicity. If subgroups are selected without appropriate adjustment, the treatment effect estimates will be biased and the false-positive rate will be inflated because of the arising multiplicity problem (Figs. 2 and 3). Furthermore, particular attention should be given to handling of continuous marker variables, handling of missing data, planning and interpreting subgroup analyses, establishing clinical utility, and handling of uncertainty in the regulatory decision (4, 23).

Companion diagnostic development

The co-development of the companion diagnostic should be seen as a continuous process that goes through analytic validity of the assay at an early stage of drug development, clinical validity studies (to ensure that the assay is able to select or otherwise stratify patients), and ultimately clinical utility (to establish that treatment with the drug after patient selection with the companion diagnostic is associated with improved benefit–risk balance compared with the absence of patient selection; ref. 5).

During the co-development of the drug and of the companion diagnostic, the use of a central laboratory facility is the preferred option to ensure consistency in the results

Figure 2. Bias by number of biomarkers. Estimation bias in percentage points of a parallel group clinical trial with subgroup analysis based on different numbers of biomarkers comparing response rates between a treatment and a control group ($n = 200$). For each setting, treatment groups are compared within the subsets of the biomarker-positive populations as well as the overall population. The subgroup with the highest treatment effect estimate is selected. For the calculation, we assumed that the treatment has no effect in any of the biomarker-positive subgroups and the response rate in all treatment and subgroups is 50%. The biomarkers are assumed to be independent with a prevalence of 50%.



observed. Quality assurance networks of clinical laboratories are encouraged to obtain evidence of reproducibility in the validation steps of the assay (5). This helps to validate the suitability of the marker although eventually it should also be shown that the test could be run on multiple sites with different operators.

It is important for the development of the companion diagnostic to be initiated early in the drug development process to be able to bridge data obtained later during clinical qualification. A prototype assay might be acceptable for *in vitro* and nonclinical drug development studies, but should have the essential characteristics permitting its evaluation: acceptable and comparable methods/assays, tissue, and disease specifications (5).

At the confirmatory stage of clinical development (phase III), full documentation of all aspects of analytic performance of the companion diagnostic should be available to prepare for and facilitate the transition of the testing methodology in the postapproval clinical use. Demonstration of performance versus existing reference tests may need to be provided (e.g., retrospective evaluation of original specimens in completed studies with known outcome; ref. 5).

After approval of the drug to be used with a companion diagnostic, the postmarket surveillance activities may

include a requirement to show consistency of results obtained with the assay used in pivotal clinical trials (e.g., research grade) and with the assay implemented after approval, be it a commercial kit or a test performed in accredited clinical laboratories (5).

Medicinal product labeling of companion diagnostics

Currently, a variety of information on companion diagnostics has been included in the labeling of drugs (Summary of Product Characteristics) approved in the EU; from no information to detailed information specifying the trademark, the manufacturer, and the CE-marked number.

Examples of anticancer medicinal products with pharmacogenomics biomarkers for patient selection in the licensed indication approved via the EMA are provided in Table 3. For these products, the Summary of Product Characteristics generally mandates the need for a validated test. Of note, none of the products contained a reference to a specific companion diagnostic product in the therapeutic indication. However, where applicable, reference to a specific companion diagnostic has been included in the description of the clinical studies. For example, "(...) patients ranged in age from 18 to 83

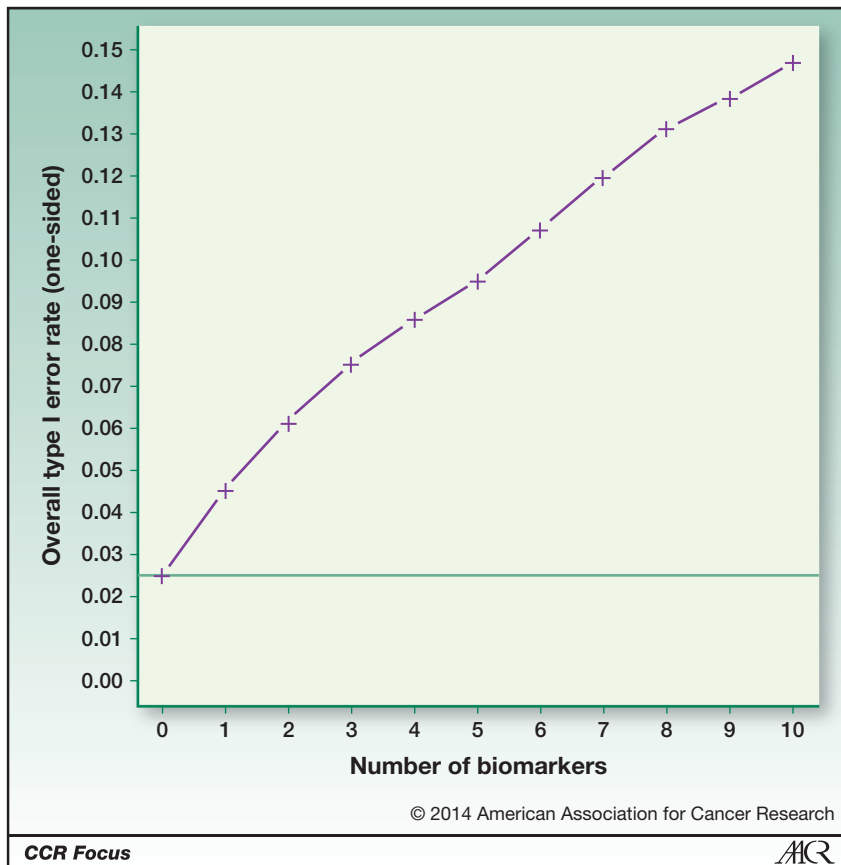


Figure 3. False-positive rate by number of biomarkers. Overall false-positive rate for unadjusted one-sided hypothesis tests at 2.5% if the test is performed in the biomarker-positive subgroups as well as the overall population.

years old and had a pathologic diagnosis of Kit-positive malignant gastrointestinal stromal tumors (GIST) that was unresectable and/or metastatic. Immunohistochemistry was routinely performed with Kit antibody (A-4502, rabbit polyclonal antiserum, 1:100; Dako Corporation) according to analysis by an avidin–biotin–peroxidase complex method after antigen retrieval" (24). Also, when the companion diagnostic used in the clinical trial is replaced with a new or different test, concordance between the clinical trial companion diagnostic and the new or different test is expected.

Biomarker information may also be included in the labeling in case of negative selection (i.e., if the biomarker is used to select a population unlikely to respond) or in case of uncertainty about the value of the biomarker but where a negative selection is suspected. One such example is vandetanib, which is indicated for the treatment of aggressive and symptomatic medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease. For vandetanib, the therapeutic indication mentions that in patients in whom Rearranged during Transfection (*RET*) mutation is not known or is negative, a possible lower benefit should be taken into account before individual treatment decision. The applicant company committed to conduct an open label trial comparing *RET*-negative and *RET*-positive patients

with sporadic medullary thyroid cancer treated with vandetanib (25).

Discussion

The EMA has recommended using predictive biomarkers throughout the phases of clinical drug development of oncology drugs. A number of approved products currently contain relevant pharmacogenomics information for patient selection. Nevertheless, biomarker identification and validation remain challenging. The EMA has adopted a flexible approach advocating rigorous biomarker validation methods whenever possible while also considering results from exploratory analyses, in particular, if these can be supported with corroborative evidence, such as improved knowledge of the role of the biomarker in the natural history of the disease and evidence from other trials (4).

Although serum biomarkers or other sources of biologic samples are being studied extensively, currently, there is not yet an adequate body of evidence indicating that they can be used to guide drug development and treatment decisions in terms of selection of patients. Therefore, tumor samples are still expected to constitute an integral part of the biomarker identification, even in the metastatic setting, due to genetic changes over time.

Table 3. Examples of indications including pharmacogenomic biomarker implications for oncology drugs between (EMA experience 2000–2013)

EU Name (Manufacturer)	INN	Year of approval	Type of approval (obligations at time of approval)	Marker in indication	Indication (short)
Herceptin (Roche)	Trastuzumab	2000	Standard	HER2	Breast cancer Gastric cancer
Gleevec (Novartis)	Imatinib	2001	Exceptional circumstances	<i>BCR-ABL</i>	Chronic myeloid leukemia; acute lymphoblastic leukemia
				PDGFR rearrangement	Myelodysplastic/myeloproliferative diseases
				FIP1L1–PDGFR rearrangement Kit	Hyper eosinophilic syndrome; chronic eosinophilic leukemia
Trisenox (Teva)	Arsenic trioxide	2002	Exceptional circumstances	t(15;17) translocation/RAR α	Acute promyelocytic leukemia
Eribut (Merck)	Cetuximab	2004	Standard	EGFR, <i>Ras</i> wild-type	Colorectal cancer
Tarceva (Roche)	Erlotinib	2005	Standard	EGFR	Lung cancer
Sprycel (Bristol-Myers Squibb)	Dasatinib	2006	Standard	<i>BCR-ABL</i>	Chronic myeloid leukemia; acute lymphoblastic leukaemia
Tasigna (Novartis)	Nilotinib	2007	Standard	<i>BCR-ABL</i>	Chronic myeloid leukemia
Vectibix (Amgen)	Panitumumab	2007	Conditional (RCT in first and second line)	<i>Ras</i> wild-type	Colorectal cancer
Tyverb (GlaxoSmithKline)	Lapatinib	2008	Conditional (RCT to assess incidence of brain metastases; updated overall survival analysis)	HER2	Breast cancer
Iressa (AstraZeneca)	Gefitinib	2009	Standard	EGFR activating mutation	Lung cancer
Adcetris (Takeda)	Brentuximab vedotin	2012	Conditional (updated overall survival analysis; postauthorization safety study; single-arm study in indication)	CD30	Hodgkin lymphoma
Caprelsa (AstraZeneca)	Vandetanib	2012	Conditional (single-arm study in approved indication)	<i>RET</i> mutation	Medullary thyroid cancer
Xalkori (Pfizer)	Crizotinib	2012	Conditional (RCT in first and second line)	ALK	Lung cancer
Zelboraf (Roche)	Vemurafenib	2012	Standard	<i>BRAF</i> V600 mutation	Melanoma
Bosulfif (Pfizer)	Bosutinib	2013	Conditional (single-arm study in approved indication)	<i>BCR-ABL</i>	Chronic myeloid leukemia
Giotrif (Boehringer Ingelheim)	Afatinib	2013	Standard	EGFR-activating mutation	Lung cancer
Iclusig (Ariad)	Ponatinib	2013	Standard	<i>BCR-ABL</i> ; T315I mutation <i>BCR-ABL</i>	Chronic myeloid leukemia Acute lymphoblastic leukemia
Kadcyla (Roche)	Trastuzumab emtansine	2013	Standard	HER2	Breast cancer
Perjeta (Roche)	Pertuzumab	2013	Standard	HER2	Breast cancer
Tafinlar (GlaxoSmithKline)	Dabrafenib	2013	Standard	<i>BRAF</i> V600 mutation	Melanoma

Abbreviations: INN, International non-proprietary name or common name; PDGFR, platelet-derived growth factor receptor; RCT, randomized controlled trial.

Furthermore, single biopsies may not be representative due to tumor heterogeneity (26). Normal tissues samples may also be used in early clinical studies, if nonclinical studies indicate that there is a correlation between the changes observed in normal tissues and the features of the tumor (7). A commonly voiced concern is that investigators and patients are unwilling to engage in studies where taking deep-tissue biopsy is considered mandatory. However, the attitude has changed and at least for exploratory studies it is considered essential to enroll investigators and study sites where tumor biopsies are part of the clinical routine (2, 27).

The evidentiary standards for showing clinical utility of a companion diagnostic and subsequent diagnostics developed to detect the same biomarker or set of biomarkers remain controversial (28). Also, the clinical utility of diagnostics represents an additional challenge to the assessment of relative efficacy and effectiveness for health technology assessment bodies and payers. These and other issues are addressed in this edition of *CCR Focus* (29, 30). The EMA has been working closely with Health Technology Assessment (HTA) bodies since 2008 and offers prospective scientific advice in parallel with HTA bodies to help optimize drug development plans.

The European legislation on medical devices including companion diagnostics is under review. What will happen in practice for companion diagnostics in cancer medicine in the EU? The European Commission has proposed new legislation to ensure that these medical devices serve the needs and ensure the safety of European citizens, aiming for a framework that is fit for purpose, more transparent, and better adapted to scientific and technologic progress. The proposed new framework is described as an evolution of the current regime keeping the same legal approach. The discussions on the review of medical device legislation are ongoing and the timing or outcome of dialogues between the European institutions is not yet known. The target for adoption is 2014, and the new rules would then gradually come into effect from 2015 to 2019.

An important proposed change is that companion diagnostics will no longer be considered as low risk and subject to self-certification by the manufacturer. According to the new proposal, companion diagnostics will be classified as high individual risk or moderate public health risk (category C) and will require conformity assessment by a notified body. It has also been proposed that evidence of the clinical utility of the device for the intended purpose should be required for companion diagnostics. After a transitional period, the same stringent requirements are expected to apply to existing devices. The more stringent requirements may have a negative impact on time and cost of CE marking of devices but may also benefits in terms of patient safety and quality of the tests (31).

Currently, specific reference to a diagnostic is not included in the product labeling of new cancer products assessed and approved in the EU, and vice versa, deviating from the pattern of "one drug, one test" that is sometimes followed in

coapproval situations in the United States, as discussed by Mansfield in this *CCR Focus* section (32). In the EU, for approved products, the product information generally mandates the need for a validated test and might describe the specific diagnostic kit or other method used in the clinical studies. However, there has been no requirement that only patients tested with a specific companion diagnostic be treated with the respective targeted drug. The current proposals do not suggest modifying this approach. However, in view of the major clinical implications for the treatment that can be offered to patients, it is generally recommended for such tests to be carried out in experienced laboratories so as to ensure that in the execution of the test also preanalytic and postanalytic steps and data handling are properly controlled as those may be a source of critical errors (2).

The possibility of regulating companion diagnostics within the framework of the legislation on medicinal products was initially considered as a possible option. During the public consultation, however, there were concerns with this option, as it might lead to problems for devices that have several intended uses and would need to follow different regulatory regimes. In addition, it was argued that a regulation under the medicinal products legislation would imply higher regulatory burdens and make the diagnostics more dependent on the manufacturer of the medicinal product. Thus, transfer of the responsibility for the assessment of conformity to medicinal product regulatory authorities was rejected (33).

Similarly, regulation of companion diagnostics within a separate centralized or decentralized framework such as exists for pharmaceuticals, was explored. However, a decentralized marketing authorization system based on mutual recognition was considered to have a significant negative impact on the internal market for medical devices compared with the automatic access associated with CE marking. A central marketing authorization (at the EU level) would require building a new EU public body with sufficiently skilled staff to assess devices, similar to the U.S. Food and Drug Administration. This would have enormous impact on the EU budget, on manufacturers in terms of costs and administrative burden and on innovation in terms of costs for regulatory compliance and time to market (33).

Although the final framework is not yet defined, clearly, there is a need to improve the basis of evidence for companion diagnostics to better serve the interests of patients. Healthcare professionals, academics, and patients have supported the EMA's participation in the evaluation of high-risk medical devices (34). Over the years, the EMA has extended its expertise in the field of companion diagnostics in the context of its many activities in support of innovative technologies and biomarker development. Adequate involvement of the EMA with its network of experts will be essential to ensure that the right expertise is available to assess that companion diagnostics for new cancer drugs lead to clinical decisions that improve outcome.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Acknowledgments

The authors thank Alexandra Graf from Medical University of Vienna for preparing the graphs on estimation bias and false-positive rates, and Sue Spencer from BSI for critical discussion.

Received November 27, 2013; revised January 8, 2014; accepted January 10, 2014; published online March 14, 2014.

References

1. Senderowicz AM, Pfaff O. Similarities and differences in the oncology drug approval process between FDA and European Union with emphasis on *in vitro* companion diagnostics. *Clin Cancer Res* 2014; 20:1445–52.
2. European Medicines Agency, Committee for Human Medicinal Products. Reflection paper on pharmacogenomic samples, testing and data handling. London (UK): The Agency; 2007 Nov. Report No.: EMEA/CHMP/PGxWP/201914/2006.
3. European Medicines Agency, Committee for Human Medicinal Products. Reflection paper on pharmacogenomics in oncology (draft). London (UK): The Agency; 2008 Apr. Report No.: EMEA/CHMP/PGxWP/128435/2006.
4. European Medicines Agency, Committee for Human Medicinal Products. Reflection paper on methodological issues with pharmacogenomic biomarkers in relation to clinical development and patient selection (draft). London (UK): The Agency; 2011 Jun. Report No.: EMA/446337/2011.
5. European Medicines Agency, Committee for Human Medicinal Products. Reflection paper on co-development of pharmacogenomic biomarkers and assays in the context of drug development (draft). London (UK): The Agency; 2010 Jun. Report No.: EMA/CHMP/641298/2008.
6. European Medicines Agency, Committee for Human Medicinal Products. CHMP assessment report: Pixuvri (pixantrone). London, (UK): The Agency; 2012 Feb. Report No.: EMA/309145/2012.
7. European Medicines Agency, Oncology Working Party. Guideline on the evaluation of anticancer medicinal products in man. London (UK): The Agency; 2012 Dec. Report No.: EMA/CHMP/205/95/Rev.4.
8. Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on *in vitro* diagnostic medical devices. OJ L331, p. 1–37 (December 7, 1998).
9. Global Harmonization Task Force, Study Group 1 of the Global Harmonization Task Force. Principles for *in vitro* diagnostic (IVD) medical devices classification. 2008 Jul. Report No.: GHTF/SG1/N045.
10. European Commission. Proposal for a Regulation of the European Parliament and of the Council on *in vitro* diagnostic medical devices. Brussels (Belgium): The Commission; 2012 Sep. Legislative proposal No.: COM(2012) 541 final. Procedure file No.: 2012/0267 (COD).
11. Amendments adopted by the European Parliament on 22 October 2013 on the proposal for a regulation of the European Parliament and of the Council on *in vitro* diagnostic medical devices (COM(2012)0541–C7-0317/2012–2012/0267(COD)). 2013.
12. European Commission. Citizens' summary: EU proposals on medical devices [Internet]. Brussels, Belgium: The Commission; 2012. Available from: http://ec.europa.eu/health/medical-devices/files/revision_docs/citizen_summary_20120926_en.pdf.
13. Ziegler A, Koch A, Krockenberger K, Grosshennig A. Personalized medicine using DNA biomarkers: a review. *Hum Genet* 2012;131: 1627–38.
14. Beckman RA, Clark J, Chen C. Integrating predictive biomarkers and classifiers into oncology clinical development programmes. *Nat Rev Drug Discov* 2011;10:735–48.
15. Freidlin B, Korn EL. Biomarker enrichment strategies: matching trial design to biomarker credentials. *Nat Rev Clin Oncol* 2013;11:81–90. Epub 2013 Nov 26. doi: 10.1038/nrclinonc.2013.218.
16. Freidlin B, Simon R. Adaptive signature design: an adaptive clinical trial design for generating and prospectively testing a gene expression signature for sensitive patients. *Clin Cancer Res* 2005;11: 7872–8.
17. Brannath W, Zuber E, Branson M, Bretz F, Gallo P, Posch M, et al. Confirmatory adaptive designs with Bayesian decision tools for a targeted therapy in oncology. *Stat Med* 2009;28:1445–63.
18. Wang SJ, O'Neill RT, Hung HM. Approaches to evaluation of treatment effect in randomized clinical trials with genomic subset. *Pharm Stat* 2007;6:227–44.
19. Graf A, König F, Posch M. Enrichment designs for the development of personalized medicines 2014.
20. European Medicines Agency. CHMP assessment report: Xalkori (crizotinib). London (UK): The Agency; 2012 Jul. Report No.: EMA/CHMP/497137/2012.
21. European Medicines Agency. CHMP assessment report: Vectibix (panitumumab). London (UK): The Agency; 2007 Dec. Report No.: EMA/CHMP/394299/2007
22. European Medicines Agency. CHMP assessment report: Iressa (gefitinib). London (UK): The Agency; 2009 Jul. EMEA/CHMP/563746/2008.
23. Wang SJ. Biomarker as a classifier in pharmacogenomics clinical trials: a tribute to 30th anniversary of PSI. *Pharm Stat* 2007;6: 283–96.
24. European Medicines Agency. Product information: Glivec (imatinib). London (UK): The Agency; 2013 Oct. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000406/human_med_000808.jsp&mid=WC0b01ac058001d124.
25. European Medicines Agency. CHMP assessment report: Caprelsa (vandetanib). London, UK: The Agency; 2011 Nov. Report No.: EMA/128076/2012.
26. Gerlinger M, Rowan AJ, Horswell S, Larkin J, Endesfelder D, Gronroos E, et al. Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. *N Engl J Med* 2012;366:883–92.
27. Jonsson B, Bergh J. Hurdles in anticancer drug development from a regulatory perspective. *Nat Rev Clin Oncol* 2012;9:236–43.
28. Woodcock J. Assessing the clinical utility of diagnostics used in drug therapy. *Clin Pharmacol Ther* 2010;88:765–73.
29. Parkinson DR, McCormack RT, Keating SM, Gutman SI, Hamilton SR, Mansfield EA, et al. Evidence of clinical utility: an unmet need in molecular diagnostics for patients with cancer. *Clin Cancer Res* 2014;20:1428–44.
30. Byron SK, Crabb N, George E, Marlow M, Newland A. The health technology assessment of companion diagnostics: experience of NICE. *Clin Cancer Res* 2014;20:1469–76.

31. Le Gledic S, Malek S. The proposed EU IVD Regulation and its impact on diagnostic development. *Scrip Regulatory Affairs*. (21 Jun 2013).
32. Mansfield EA. FDA perspective on companion diagnostics: an evolving paradigm. *Clin Cancer Res* 2014;20:1453-7.
33. European Commission. Impact assessment on the revision of the regulatory framework for medical devices. Brussels (Belgium): The Commission; 2012 Sept. Report No.: SWD (2012) 273 final.
34. European Commission, Enterprise and Industry Directorate-General. Recast of the Medical Devices Directives: summary of responses to the public consultation. Brussels (Belgium): The Commission; 2008 Dec. Report No.: ENTR/F/3/D(2008) 39582.