Developing and Labeling *In vitro* Companion Diagnostic Devices for a Specific Group or Class of Oncology Therapeutic Products
Guidance for Industry

DRAFT GUIDANCE

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I. INTRODUCTION

This guidance describes considerations for the development and labeling of *in vitro* companion diagnostic devices (referred to as "companion diagnostics" herein) to support the indicated uses of multiple drug or biological oncology products,[1] when appropriate. This guidance expands on existing policy, surrounding broader labeling (i.e., labeling that is expanded), which notes that in some cases, if evidence is sufficient to conclude that the companion diagnostic is appropriate for use with a specific group or class of therapeutic products, the companion diagnostic's intended use/indications for use should name the specific group or class of therapeutic products, rather than specific products.[2] The specific group or class of oncology therapeutic products would be identified for this purpose based on sufficient and consistent clinical experience with the therapeutics with the same approved indications, including mutation(s) and disease, for which a companion diagnostic could potentially be labeled (as discussed in this document). To describe FDA's current thinking on this topic, the guidance discusses a specific example, companion diagnostics that identify patients with non-small cell lung cancer (NSCLC) whose tumors have the most common epidermal growth factor receptor (EGFR) mutations, exon 19 deletions or exon 21 (L858R) substitution mutations.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[1] For purposes of this guidance, drug and biological oncology products are referred to as therapeutic products or oncology therapeutic products.

[2] FDA's Guidance for Industry and FDA Staff: *In Vitro Companion Diagnostic Devices*, August 2014, page 11, available at: https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf.

II. BACKGROUND

A companion diagnostic is an *in vitro* diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product. The use of a companion diagnostic with a therapeutic product is stipulated in the instructions for use in the labeling of both the companion diagnostic and the corresponding therapeutic product, including labeling of any generic equivalents of the therapeutic product.[3]

In oncology, precision medicine (also referred to as "personalized medicine") aims to match therapeutic products to those patients (and only those patients) who will positively respond to that therapeutic product, to maximize benefits and minimize risks from the therapeutic product received. Precision oncology therefore depends on 1) understanding the molecular pathophysiology of cancer and 2) the ability of companion diagnostics to accurately and reliably detect and measure molecular biomarkers. These companion diagnostics inform both the development and the approved use of therapeutic products.

Trials designed to support approval of a specific therapeutic product and a specific companion diagnostic have led to companion diagnostic labels that reference only a specific therapeutic product(s). Such specificity in labeling can limit a potentially broader use of a companion diagnostic that may be scientifically appropriate. In some cases, there are multiple companion diagnostics approved by FDA to detect the same mutations in the same specimen type. Similarly, in some cases, there are multiple FDA-approved therapeutics within a specific group or class of oncology therapeutic products (i.e., approved for use in the same indications, including the same mutation(s) and the same disease).[4] This results in, in some cases, not all of the oncology therapeutic products in a specific group or class being included on all of the labels of approved companion diagnostics to detect mutations that define the specific group or class (see Table 1). FDA is concerned that the current situation is not optimal for patient care because a clinician may need to order a different companion diagnostic (i.e., one that includes other therapeutic products on the label), obtain an additional biopsy(ies) from a patient, or both, to have additional therapy treatment options. FDA is interested in discussing with sponsors wishing to pursue labeling a companion diagnostic to reference a specific group or class of oncology therapeutic products, when the evidence would support expanding the indication.

An example in precision oncology, which illustrates the issue regarding companion diagnostic labeling in oncology, is the identification of specific EGFR mutations in tumors of patients with

[3] FDA has previously issued guidance to define companion diagnostics, clarify the goal of contemporaneous approval of the therapeutic product and the companion diagnostic, provide guidance on premarket regulatory pathways and FDA's regulatory enforcement policy, and describe statutory and regulatory requirements for labeling; FDA's Guidance for Industry and FDA Staff: *In Vitro Companion Diagnostic Devices*, August 2014, available at: https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf.

[4] The specific group or class refers to the indication, mutation(s), and disease that the therapeutic products have in common which is captured in the therapeutic products' labeling (including sections other than the indication section). A therapeutic product could have other indications than those within the specific group or class that a companion diagnostic is labeled to identify. Likewise, a companion diagnostic could have other intended uses outside of the specific group or class of therapeutic products or for other specimen types. Broader labeling may be appropriate regarding the indications that the specific group or class of therapeutic products have in common.

NSCLC. There are five FDA-approved therapeutic products indicated for the treatment of patients with NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test: afatinib, gefitinib, erlotinib, osimertinib, and dacomitinib (see Table 1).[5,6] However, the FDA-approved companion diagnostics that identify these specific mutations in EGFR in tissue samples are only indicated for a subset of the five FDA-approved therapeutic products.

Table 1 – FDA approved companion diagnostics labeled for identifying patients with NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations and the associated therapeutic products listed on the companion diagnostic labels

FDA Approved Companion Diagnostics	**Therapeutic Products**				
	Afatinib	Gefitinib	Erlotinib	Osimertinib	Dacomitinib
Therascreen EGFR RGQ PCR Kit	X	X	-	-	X
Cobas EGFR Mutation Test V2	-	X	X	X	-
Oncomine Dx Target Test	-	X	-	-	-
FoundationOne CDx	X	X	X	-	-

While EGFR is just an example, it could be possible for companion diagnostics that are adequately validated to detect the biomarker(s) of interest and to identify appropriate patients for treatment to be indicated more broadly for use with a specific group or class of therapeutic products. In this example, the oncology community would be better served by a companion diagnostic that detects EGFR exon 19 deletions or exon 21 (L858R) substitution mutations indicated for "*identifying patients with NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations and are suitable for treatment with a tyrosine kinase inhibitor approved by FDA for that indication.*" This could enable greater flexibility for clinicians in choosing the most appropriate therapeutic product based on a patient's biomarker status. However, labeling for such a broader use is not as simple as just matching diagnostic targets with therapeutic targets. Different diagnostics for the same target may utilize different cut-offs, filters, or other design features that impact the patient populations they identify and, consequently, the likelihood of a biomarker positive patient to respond to a given therapy. Any potential differences must be evaluated to ensure it is clinically appropriate to take a broader labeling approach. See section IV for considerations regarding broader labeling.

[5] For purposes of this example, we are focusing on the indication described in the guidance. However, examples of products in the illustrative example with indications that are outside of the indication described in the illustrative example are 1) afatinib which, at the time of this guidance, is indicated for a broader population, i.e., those "whose tumors have non-resistant epidermal growth factor receptor (EGFR) mutations as detected by an FDA-approved test" and 2) the Cobas EGFR Mutation Test V2 which is also approved for identifying EGFR exon 19 deletions or exon 21 (L858R) substitution mutations in plasma specimens.

[6] EGFR exon 20 T790M alterations are excluded from the scope of this illustrative example.

III. DEVELOPMENT AND LABELING OF COMPANION DIAGNOSTICS IN ONCOLOGY

Some companion diagnostics in oncology could be developed in a way that results in labeling for a specific group or class of oncology therapeutic products. Similarly, for sponsors seeking to broaden the labeling of already approved or cleared companion diagnostics, sponsors may submit a marketing application supplement in support of broader labeling (see section V). These approaches will ensure the resulting evidence-based indication optimally facilitates clinical use. This approach is consistent with FDA's labeling for *in vitro* diagnostic product regulations which requires, among other things, "the intended use or uses of the product"[7] be included in the labeling. In addition, this approach aligns with FDA's guidance regarding therapeutic product labeling, which states that "the therapeutic product labeling should specify use of an FDA approved or cleared IVD companion diagnostic device, rather than a particular manufacturer's IVD companion diagnostic device. This will facilitate the development and use of more than one approved or cleared IVD companion diagnostic device of the type described in the labeling for the therapeutic product."[8]

When it is scientifically appropriate, FDA supports developers of companion diagnostics to develop their products (or pursue broader labeling for approved companion diagnostics) in a way that results in broader labeling for their products (i.e., for a specific group or class of oncology therapeutic products). FDA acknowledges that such an approach may require collaboration with therapeutic product developers and encourages this to enable the companion diagnostic labeling to provide greater flexibility for clinicians in choosing the most appropriate therapeutic product based on a patient's biomarker status.

IV. CONSIDERATIONS REGARDING BROADER LABELING

The labeling for a companion diagnostic is required to specify its intended use (21 CFR 809.10(a)(2)). Therefore, a companion diagnostic that is intended for use with a therapeutic product must specify the therapeutic product(s) for which it has been approved or cleared for use. In some cases, however, if evidence is sufficient to conclude that the companion diagnostic is appropriate for use with a class of therapeutic products, the intended use/indications for use should name the therapeutic class, rather than each specific product within the class.

FDA recommends that companion diagnostic developers consider a number of factors, including but not limited to those listed below, when determining whether their test could be developed, or the labeling for approved companion diagnostics could be revised through a supplement, to support a broader labeling claim such as use with a specific group or class of therapeutic products (rather than listing an individual therapeutic product(s)). In addition, these considerations include examples of when companion diagnostics may not be appropriate for

[7] 21 CFR part 809.10(a)(2).

[8] FDA's Guidance for Industry and FDA Staff: *In Vitro Companion Diagnostic Devices,* August 2014, page 11, available at: https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf.

broader labeling because such labeling could lead to incorrect identification of patients for therapeutic treatment. These considerations or factors do not change the relevant regulatory standards for evaluating whether broader labeling should be approved or cleared, including whether any information to support such labeling meets the standard of valid scientific evidence under 21 CFR 860.7(c)(2). When a companion diagnostic has been approved or cleared for use with a therapeutic product(s) in one disease or setting, a PMA supplement or new 510(k), as appropriate, will be needed to expand the companion diagnostic labeling to broaden the indication for use with a specific group or class of oncology therapeutic products in the same disease/setting. We encourage sponsors considering development of a companion diagnostic for broader labeling to meet with CBER, CDRH, or CDER, in coordination with the Oncology Center of Excellence (OCE), as appropriate, early in development, to discuss. Developers of approved companion diagnostics considering broader labeling should contact CDRH or CBER, as appropriate, to discuss (see section V).

1. **Whether a specific group or class of oncology therapeutic products can be defined for which a companion diagnostic will identify an appropriate patient population for potential treatment.** A key issue for such development and labeling will be identifying the specific group or class of oncology therapeutic products to be included in the labeling for the companion diagnostic. For the purposes of this guidance, a specific group or class of oncology therapeutic products are those approved for the same indications, including the same mutation(s) and the same disease[9] for which clinical evidence has been developed with at least one device for the same specimen type for each therapeutic product. Developers should discuss the specific group or class of oncology therapeutic products with CBER, CDRH, or CDER, in coordination with OCE, as appropriate, early in development.

   FDA recognizes that as science evolves, our understanding of the mechanism of action of therapeutic products and of the interaction between therapeutic products and biomarkers will evolve, which may impact how specific groups or classes of oncology therapeutic products are defined. For example, the definition of "wildtype" for RAS, which is included in the labels of drugs such as cetuximab and panitumumab, has significantly changed over time.

2. **Whether there is a detailed understanding of a) the mechanism of action of the specific group or class of oncology therapeutic products being considered for use with the companion diagnostic and b) the interaction between the therapeutic products and the biomarker(s), at the mutation level, detected by the companion diagnostic**. The mechanism of action for a therapeutic product can be influenced by a number of factors, including the mutation itself. Therapeutic products may target different areas of a protein and can therefore be differentially influenced by, for example, the resultant tertiary structure changes from various amino acid substitutions. Similarly, a therapeutic product may target a unique genetic alteration or be influenced by surrounding genetic mutations. Additionally, an understanding of the prevalence of the biomarker in the population or the relationship between the expression or level of the

[9] See footnotes 4 and 5 for additional information regarding the indication(s).

biomarker and the therapeutic response is important and can greatly influence whether it would be scientifically appropriate to consider a broader labeling approach. Having a detailed understanding of the mechanism of action for the therapeutic is critical to support broader labeling identifying the specific class of therapeutics for which a companion diagnostic could be safely and effectively used.

A detailed understanding of the interaction between the therapeutics and biomarker could be achieved through clinical studies, supported or extended by nonclinical information. The sponsor could use sources of valid scientific evidence as described in 21 CFR 860.7(c)(2), such as the therapeutic product labeling or therapeutic product study data or peer-reviewed scientific literature, or the sponsor could perform clinical studies as needed. For example, EGFR exon 19 deletions and exon 21 (L858R) substitution mutations are known to upregulate EGFR phosphorylation and respond to treatment with tyrosine kinase inhibitors of EGFR based on functional studies.[10] Special care, however, should be taken to identify aspects of biomarkers which would exclude them from being included in a group or class. For example, many mutations in EGFR exon 20 are tyrosine kinase inhibitor resistant (e.g., EGFR T790M).

3. **Whether there is sufficient clinical experience with at least two therapeutic products for the same biomarker-informed indications**. The sponsor could utilize currently available information, such as that published in peer-reviewed literature, or perform new clinical studies, if necessary, to show that there is sufficient and consistent clinical experience with the group or class of therapeutic products for the same biomarker-informed indications. There should generally be experience with at least two FDA-approved therapeutic products that would comprise the group or class that the broader companion diagnostic indication would apply to. For example, afatinib, erlotinib, gefitinib, osimertinib, and dacomitinib are all indicated for the treatment of patients with NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations, so they will all fall under one specific group or class (tyrosine kinase inhibitor indicated for the treatment of patients with NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations). Also, it would not be appropriate to include therapeutic products in this specific group or class that only target resistant mutations, such as EGFR T790M and C797S, for which there may not be sufficient or consistent clinical experience.

4. **Whether analytical validity of the companion diagnostic has been demonstrated across the range of biomarkers that inform the indication**. Analytical validity is the ability of a companion diagnostic to perform as intended in terms of its sensitivity, specificity, accuracy, precision, and other relevant performance characteristics using a specified technical protocol. Companion diagnostics that already have an approval or

[10] Lynch TJ, Bell DW, Sordella R, et. al., 2004, Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non-Small-Cell Lung Cancer to Gefitinib, *NEJM*, 350(21): 2129-39. Pao W, Miller V, Zakowski M, et. al., 2004, EGF Receptor Gene Mutations are Common in Lung Cancers from "Never Smokers" and are Associated with Sensitivity of Tumors to Gefitinib and Erlotinib, *PNAS*, 101(36): 13306-11.

clearance of a test for use with a therapeutic product in a potential group or class can generally leverage the information in their already cleared or approved submission to demonstrate analytical validity of the companion diagnostic across the range of biomarkers that inform the indication. Future sponsors of companion diagnostics that do not already have an approval or clearance of a test for use with a therapeutic product in a potential group or class should demonstrate analytical validity of the companion diagnostic across the range of biomarkers that inform the indication. The sponsor should discuss with CDRH or CBER, as appropriate, to determine the criteria for analytical validation.

It is important to ensure that the companion diagnostic can detect the specific mutation(s) of interest that would identify which patients would benefit from the therapeutic products that are included in the defined group or class. Using a test that is validated to detect the specific analyte(s) of interest is critical to ensuring that false negative or false positive results are not driving clinical decisions or therapeutic choices. Further, since technologies used to detect a biomarker can vary widely with significant performance differences between them, differences in technology should be considered as some mutations might not be detectable by every technology. For example, a non-trivial difference in discordance rate between next generation sequencing-based mutation profiling and immunohistochemistry could lead to differences in the number of patients identified as biomarker positive depending on the technology used.

5. **Whether clinical validity of the companion diagnostic has been demonstrated with the therapeutic products in the disease of interest**. Clinical validity is the ability of a companion diagnostic to identify, measure, or predict the presence or absence of a clinical condition or predisposition for which the companion diagnostic is intended. Companion diagnostics that already have an approval or clearance of a test for use with a therapeutic product in a potential group or class can generally leverage the information in their already cleared or approved submission to demonstrate clinical validity of the companion diagnostic with the therapeutic products in the disease of interest. Future sponsors for companion diagnostics that do not already have an approval or clearance of a test for a therapeutic product in a potential group or class should perform concordance studies with a previously approved companion diagnostic for that indication to demonstrate comparable performance, or the sponsor could choose to do a clinical study establishing the link between the result of the companion diagnostic and patient outcomes for that indication.

   In an evaluation of clinical validity, the defined cut-off for a specific companion diagnostic is important to consider when assessing whether broader labeling is appropriate. For example, a challenge with gene expression tests is that they may have differing thresholds by which a tumor sample is called positive or negative in a specimen. These assays may also have their own scoring algorithm and method of measuring cells which may impact what is needed regarding clinical validation. For companion diagnostics that detect the same marker of interest and have similar analytical performance, different cut-offs may identify different groups of patients. A cut-point that

is set too high could mean that patients will be determined to not be candidates for a therapeutic or the cut-point may be too low and a patient be put on a therapeutic course that confers limited or no benefit.

We encourage the sponsor to discuss with CDRH or CBER, as appropriate, to determine the criteria for clinical validation to support broader labeling.

V. PROCESS FOR BROADENING LABELING FOR APPROVED OR CLEARED COMPANION DIAGNOSTICS

For companion diagnostics that may be appropriate for broader labeling that describes use with a specific group or class of oncology therapeutic products (rather than listing individual therapeutic product names), the companion diagnostic developer should contact CDRH or CBER, as appropriate, to discuss, using the appropriate pathway.[11] Such submissions should generally include justification for use with a specific group or class of therapeutic products and valid scientific evidence under 21 CFR 860.7(c)(2) to support the broader labeling claim.

[11] Companion diagnostic developers should submit a PMA supplement or a new 510(k), as appropriate. If developers have specific questions, they can also submit a pre-submission request through which developers may obtain information concerning the appropriate submission. See FDA's Guidance for Industry and FDA Staff: *Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff*, September 2017, available at: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm311176.pdf.