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December 22, 2025

U.S. Food and Drug Administration,
Center for Devices and Radiological Health
Electronic Submission to Federal Rulemaking Portal

Re: **Docket ID FDA-2025-N-4622**
Immunology and Microbiology Devices; Reclassification of Nucleic Acid-Based Test Systems for Use With a Corresponding Approved Oncology Therapeutic Product; Proposed Amendment; Proposed Order; Request for Comments

To whom it may concern:

Boudicca® DX, a precision medicine consulting firm that supports Biopharma and In Vitro Diagnostic (IVD) manufacturers developing targeted therapeutics and Companion Diagnostic (CDx) devices, fully supports the proposed order: "*Reclassification of Nucleic Acid-Based Test Systems for Use with a Corresponding Approved Oncology Therapeutic Product.*" This will significantly reduce regulatory burden and costs for Biopharma developing targeted therapeutics that require Nucleic Acid-Based CDx test systems. This will increase the market availability of Nucleic Acid-Based CDx products and reduce barriers for patient testing in the United States. The availability of CDx testing is key to identifying therapeutics for patients with life-threatening and debilitating conditions.

Overall the special controls proposed by FDA are not highly burdensome and are appropriate for Nucleic Acid-Based Test Systems being used with corresponding therapeutic products. Boudicca® DX is providing recommendations for FDA's consideration, which are reflected using strike-throughs and capitalized text along with rationale for the recommended amendments. Boudicca® DX appreciates the opportunity to provide feedback to FDA and looks forward to the finalization of this order.

Sincerely,

Kelly Gordon Digitally signed by Kelly Gordon
Date: 2025.12.22 08:03:58 -06'00'

Kelly Gordon, PhD, MB(ASCP)^{CM}, RAC-Devices
CEO and Founder, Boudicca® DX

Recommendations for FDA Consideration

Written by Kelly J. Gordon, PhD, MB(ASCP)^{CM}, RAC-Devices, CEO and Founder, Boudicca® DX, a precision medicine consulting firm.

FDA-2025-N-4622-0001 Electronic Submission on December 22, 2025

Dr. Gordon is an ASCP-certified molecular technologist, PhD-trained translational scientist, and Regulatory Affairs Professional Society (RAPS)-certified device global regulatory affairs expert (European Union, United States, and Rest of World) who has worked in the Companion Diagnostics (CDx) industry for 15 years. Dr. Gordon founded the precision medicine consulting firm Boudicca® DX to support Biopharma developing targeted therapies and In Vitro Diagnostic (IVD) manufacturers developing CDx products for these corresponding therapies. Boudicca® DX has supported 100+ CDx co-development programs, many of which have included the use of Nucleic Acid-Based CDx Test Systems. Boudicca® DX fully supports the FDA-2025-N-4622-0001 reclassification order and is providing additional recommendations in this document for FDA consideration prior to finalization.

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Recommendation: Amendment to § 866.6075

Nucleic Acid-Based Test Systems for Use with a Corresponding Approved ~~Oncology~~ Therapeutic Product.

Rationale: Do Not Restrict to Oncology Therapeutic Products

Nucleic Acid-Based Test Systems are currently being co-developed as companion diagnostics (CDx) for use with Non-Oncology therapeutic products. Boudicca® DX Biopharma clients developing targeted Non-oncology therapeutic products are also facing the same challenges of high regulatory burden and costs for Nucleic Acid-Based CDx Test Systems. Many of the proposed special controls are focused on the Nucleic Acid-based test system analytical performance to ensure that there is accurate, precise, and robust detection of genetic variant(s), gene(s), and nucleic acid biomarker(s). The proposed special controls are also appropriate for ensuring analytical performance if these Nucleic Acid-Based Test Systems are used for detecting genetic variant(s), gene(s) and/or nucleic acid biomarkers in specimens acquired from patients with Non-Oncology indications for Non-Oncology therapeutic products. This special control:

> "(C) Clinical data generated using clinical specimens representative of the intended use population demonstrating appropriate, as determined by FDA, clinical performance of the device for its intended use"

would ensure that clinical performance is demonstrated for these test systems when used for Non-oncology indications. There are no proposed special controls in this order that are specific to Oncology. All proposed special controls would provide adequate assurance of safety and effectiveness when using Nucleic Acid-Based Test Systems for corresponding Non-Oncology therapeutic products.

Not limiting the reclassification to Oncology therapeutic products would reduce regulatory burden and costs as Non-Oncology CDx IVDs could also leverage the least expensive 510(k) regulatory pathway rather than having to submit more costly and burdensome De Novo Requests for each Non-Oncology therapeutic product. There is already one FDA-authorized Non-Oncology Nucleic Acid-based CDx Test System for adult and pediatric patients 6 years of age and older who have obesity and certain variants in POMC, PCSKJ or LEPR genes for treatment with the therapeutic product IMCIVREE® (setmelanotide):

> POMC/PCSK1/LEPR CDx Panel
> De Novo: DEN200059
> Setmelanotide eligibility gene variant detection system

Thus, there is already a precedent for a Class II regulatory approach for a Nucleic Acid-Based Test System for Use with a Corresponding Approved Non-Oncology Therapeutic Product. Boudicca® DX recommends not limiting the reclassification to Oncology to reduce unnecessary regulatory burden for Non-Oncology therapeutic developers.

The majority of FDA-approved CDx IVDs to date and those referenced in the proposed order have been developed for Oncology therapeutics. These Oncology products provide extensive valid scientific evidence supporting the analytical performance of PCR and NGS-based Nucleic Acid-Based Test Systems for the accurate, precise, and robust detection of genetic variant(s), gene(s) and nucleic acid biomarkers. The "Identified risks to health" observed from experience with CDx Premarket Approval (PMA) applications and commercial use of these FDA-approved CDx products are listed in Table 1 (below) of the proposed order. These "Identified risks to health" would also be expected when Nucleic Acid-based Test Systems are used with corresponding therapeutics for Non-Oncology indications. None of these identified risks are specific to Oncology, as highlighted below in bold capitalized font. The same proposed special controls would mitigate the risks of: (1) false positive test results or false negative test results, (2) failure of the test system to perform as intended or indicated, and (3) failure to correctly interpret test results when a Nucleic Acid-Based Test System is being used to detect genetic variant(s), gene(s) and/or nucleic acid biomarkers in patients with Non-Oncology indications. Boudicca® DX recommends removing "Oncology" throughout the reclassification order to create the least burdensome regulatory pathway for all Nucleic Acid-based Test Systems used for all corresponding therapeutic products spanning Oncology and Non-Oncology.

Table 1—Risks to Health and Mitigation Measures for Oncology Therapeutic Nucleic Acid-Based Test Systems **ARE EXPECTED TO BE THE SAME FOR NON-ONCOLOGY THERAPEUTIC NUCLEIC ACID-BASED TEST SYSTEMS**

Identified risks to health **EXPECTED TO BE THE SAME FOR NON-ONCOLOGY USE**.	Mitigation measures **APPROPRIATE FOR NON-ONCOLOGY USE.**
False positive test results or false negative test results	Certain design verification and validation activities, including certain analytical validation and clinical validation data. Certain labeling information, including certain performance information.
Failure of the test system to perform as intended or indicated	Certain design verification and validation activities, including certain analytical validation and clinical validation data. Certain labeling information, including certain performance information.
Failure to correctly interpret test results	Certain design verification and validation activities, including certain analytical validation and clinical validation data. Certain labeling information, including certain performance information.

Recommendation: Amendment to § 866.6075 (a) Identification

(a) Identification. Nucleic acid-based test systems indicated for use with a corresponding approved ~~oncology~~ therapeutic product are identified as prescription in vitro diagnostic devices intended for the detection of specific genetic variant(s), GENE(S), and/or other nucleic acid biomarkers in human clinical specimens using nucleic acid amplification (e.g., polymerase chain reaction) and/or sequencing technology (e.g., next generation sequencing) to provide information related to the use of a corresponding approved ~~oncology~~ therapeutic product OR A SPECIFIC GROUP OF THERAPEUTIC PRODUCTS. These test systems include COMPANION devices that provide information that is essential for the safe and effective use of a corresponding approved ~~oncology~~ therapeutic product OR A SPECIFIC GROUP OF THERAPEUTIC PRODUCTS and COMPLEMENTARY devices that, while not essential to the safe and effective use of the corresponding approved ~~oncology~~ therapeutic product OR A SPECIFIC GROUP OF THERAPEUTIC PRODUCTS, provide information about known benefits and/or risks related to the use of the corresponding approved ~~oncology~~ therapeutic product.

Rationale: Addition of Gene(s)

Gene and Genetic Variants are distinct terms (definitions from NCI Dictionary of Genetics Terms: https://www.cancer.gov/publications/dictionaries/genetics-dictionary/):

> GENE: The basic unit of heredity passed from parent to child. Genes are made up of sequences of DNA and are arranged, one after another, at specific locations on chromosomes in the nucleus of cells. They contain information for making specific proteins that lead to the expression of a particular physical characteristic or trait, such as hair color or eye color, or to a particular function in a cell
>
> VARIANT: An alteration in the most common DNA nucleotide sequence. The term variant can be used to describe an alteration that may be benign, pathogenic, or of unknown significance. The term variant is increasingly being used in place of the term mutation.

Boudicca® DX recommends also including “gene” throughout the regulation.

Rationale: Addition of Companion and Complementary Terminology

Integrating these terms may provide additional simplification for therapeutic developers, IVD manufacturers, and clinicians, e.g., oncologists, pathologists, etc. using the two distinct devices:

> COMPANION: These test systems provide information that is essential for the safe and effective use of a corresponding approved therapeutic product.
>
> COMPLEMENTARY: These test systems while not essential to the safe and effective use of the corresponding approved therapeutic product, provide information about known benefits and/or risks related to the use of the corresponding approved therapeutic product.

The distinction between Complementary and Companion Diagnostics was the focus of a publication in January 2017 (Scheerens, H et al. Current Status of Companion and Complementary Diagnostics Strategic Considerations for Development and Launch, Clin Transl Sci (2017) 10, 84–92). The FDA has also used Complementary terminology (even though it is not formally integrated into FDA guidance) as illustrated in these examples:

- US FDA D.I.S.C.O.: Niraparib in Ovarian Cancer Transcript. FDA medical oncologists discuss the agency's March 2017 approval of niraparib for the maintenance treatment of patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy:
  - https://www.fda.gov/drugs/resources-information-approved-drugs/fda-disco-niraparib-ovarian-cancer-transcript
  - *"SB: You know, that's a common question. Basically, a companion diagnostic device is essential for the safe and effective use of the drug, and is identified in the product label. In this case, niraparib does not require testing with a companion diagnostic, since it was found that patients negative for the marker could also potentially benefit. In contrast, we have situations where a drug may have a favorable clinical benefit in the entire population of patients, but a subset of those patients identified by a test have a greater benefit. That test would be a complementary diagnostic. It is not required for the use of the drug, but provides information about a population who may derive greater benefit. It can help inform the discussion between prescriber and patient. In this case, women with BRCA mutated ovarian cancer have the greatest benefit from treatment with niraparib, and so the complementary diagnostic can inform the risk-benefit analysis for its use, but it is not required."*
- US FDA. Durvalumab (Imfinzi) 05/01/2017
  - https://www.fda.gov/drugs/resources-information-approved-drugs/durvalumab-imfinzi
  - "*The FDA also approved the VENTANA PD-L1 (SP263) Assay (Ventana Medical Systems, Inc.) as a complementary diagnostic for the assessment of the PD-L1 protein in formalin-fixed, paraffin-embedded urothelial carcinoma tissue."*
- US FDA approves rucaparib for maintenance treatment of recurrent ovarian, fallopian tube, or primary peritoneal cancer
  - https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-rucaparib-maintenance-treatment-recurrent-ovarian-fallopian-tube-or-primary-peritoneal
  - *"The FDA also concurrently approved the complementary diagnostic test, FoundationFocusTM CDx BRCA LOH, for tumor samples to determine HRD status."*
- US FDA. How Do I Use Prescription Drug Labeling
  - https://www.fda.gov/about-fda/oncology-center-excellence/how-do-i-use-prescription-drug-labeling

- Section 2: Dosage and Administration
  Provides the recommended dose, including the dosage range, dosing interval, usual duration, dosage modifications due to adverse reactions, recommended dosage in patients with renal or hepatic impairment if different from the dose from those with normal organ function, recommended dosage in patients taking other drugs with the potential for clinically important interactions, and instructions on how to safely prepare and administer the drug. For oncology drug products, this section may also provide information on tests to be performed prior to administration (e.g., companion or complementary diagnostic tests), premedications or concomitant medications required to ensure safe use, and a reference to information for special handling and disposal of cytotoxic drugs.

Boudicca® DX Biopharma clients frequently use Companion versus Complementary terminology when describing the potential intended uses of the test systems for their therapeutic products based on the design of their registrational clinical studies (e.g., biomarker-selected trial or allcomer trial) and the final therapeutic efficacy and safety clinical outcome data. Having formal definitions for distinct complementary and companion intended uses would be helpful to the precision medicine community:

Including distinct terminology to reflect the differential complementary and companion intended uses may be helpful for therapeutic developers and IVD manufacturers, as they can use this terminology for these products when they are marketed to facilitate discussions with test users, e.g., oncologists, pathologists, and primary physicians. Otherwise, it may be confusing for the user to discern what tests are required (Companion) versus not required (Complementary) for the safe and effective prescription of a therapeutic. For example, the differentiation between Complementary and Companion diagnostics has been challenging for FDA-approved PD-1 and PD-L1 targeting therapeutic products. Having clarity with additional regulatory definitions in this order would be helpful to the community. As mentioned in the Niraparib case study, complementary can help inform the discussion between prescriber and patient.

Integrating distinct terminology could also enable the creation of separate FDA databases for Companion and Complementary devices for IVD manufacturers to navigate to identify the most appropriate predicate for their 510(k) submission to demonstrate substantial equivalence. There is currently only one CDx FDA database:

List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools).

https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools

A separate database could be generated if distinct regulatory terminology was used for Complementary Diagnostics with the finalization of this classification order, e.g. the following database could be created,

> List of Cleared Complementary Diagnostic Devices (In Vitro and Imaging Tools).

Boudicca® DX utilizes the current database very often and as a power user, believes that having separate FDA databases would simplify finding regulatory information on Complementary and Companion IVD products, as this information can only be identified from deep diving into product-specific labeling, which is becoming burdensome with each new product approval. The current "*List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools)*" database is becoming quite large and challenging to navigate from a user perspective. Having products with distinct and different intended uses through differential Companion and Complementary terminology would be less burdensome also for the users, e.g., clinicians, who are navigating FDA-approved therapeutic product labels trying to locate the corresponding FDA-cleared companion and complementary diagnostic devices on FDA's website. Novel biomarkers and therapeutic products are emerging on a continual basis, and it will be important to simplify the location of information for both developers and users.

Rationale: Include Therapeutic Group Labeling

Given the April 2020 FDA Guidance "Developing and Labeling In vitro Companion Diagnostic Devices for a Specific Group of Oncology Therapeutic Products" and the existence of the following FDA-approved CDx devices indicated for a Specific Group of Oncology Therapeutic Products (https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools):

> cobas EGFR Mutation Test v2 (Roche Molecular Systems, Inc.)
>
> FoundationOne CDx (Foundation Medicine, Inc.)
>
> FoundationOne Liquid CDx (Foundation Medicine, Inc.)
>
> ONCO/Reveal Dx Lung & Colon Cancer Assay (O/RDx-LCCA) (Pillar Biosciences, Inc.)
>
> MI Cancer Seek (Caris Life Sciences);

Boudicca® DX recommends adding to the regulation that these special controls also apply to specific groups of therapeutic products. It is expected that this reclassification will result in more CDx products with group labelling entering the market due to reduced regulatory burden and costs, and because of the continual development of safe and effective therapeutics targeting the same biomarkers.

Recommendation: Amendment to § 866.6075 (b) Classification

(b) Classification: Class II (special controls).

(1) Design verification and validation must include:

(ii) Device performance data demonstrating appropriate, as determined by FDA, analytical and clinical performance of the device for the intended use. This must include:

(A) Data demonstrating the precision, analytical accuracy, analytical sensitivity, analytical specificity, and sample and reagent stability of the test system. Analytical performance data must be evaluated for each GENETIC VARIANT, GENE, AND/OR OTHER NUCLEIC ACID BIOMARKER, or alternatively, justification for an alternative approach must be provided and determined by FDA to be appropriate, such as the use of a representative set of genes and/or variants.

Rationale: Align Genetic Variants, Genes, and Nucleic Acid Biomarkers Language

Boudicca® DX recommends to include both “gene” and genetic variant given these are distinct terms as previously mentioned. “Nucleic Acid Biomarker” can also be included here to cover biomarkers being detected with these Nucleic Acid-Based test systems, such as DNA methylation, DNA acetylation, Microsatellite Instability (MSI), Tumor Mutational Burden (TMB), etc.

Recommendation: Amendment to Labeling

Based on the previous rationale provided, Boudicca® DX recommends the following labeling special control amendments:

(2) Labeling

(iii) For those COMPANION test systems intended to provide information that is essential for the safe and effective use of a corresponding approved ~~oncology~~ therapeutic product OR A SPECIFIC GROUP OF THERAPEUTIC PRODUCTS, language indicating that the test system is indicated for use with a corresponding FDA-approved ~~oncology~~ therapeutic product OR A SPECIFIC GROUP OF THERAPEUTIC PRODUCTS. Device labeling must be consistent with the information set forth in the corresponding FDA-approved ~~oncology~~ therapeutic product labeling.

(iv) For those COMPLEMENTARY test systems intended to provide information about known benefits and/or risks related to the use of a corresponding FDA-approved ~~oncology~~ therapeutic product OR A SPECIFIC GROUP OF THERAPEUTIC PRODUCTS but are not essential for the safe and effective use of the corresponding approved ~~oncology~~ therapeutic product OR SPECIFIC GROUP OF THERAPEUTIC PRODUCTS, language summarizing the benefits and/or risks related to the use of a corresponding FDA-approved ~~oncology~~ therapeutic product that must be consistent with the information set forth in the corresponding FDA-approved ~~oncology~~ therapeutic product labeling.

Summary

Boudicca® DX proposes that these recommendations will further reduce regulatory burden and costs for Biopharma developing targeted Oncology and Non-Oncology therapeutic products and IVD manufacturers developing the Nucleic Acid-Based Test Systems for these corresponding approved therapeutic products. Integrating distinct language for Companion and Complementary intended uses into the regulation could potentially simplify the use of these devices for Biopharma, IVD manufacturers, clinicians, and facilitate discussions with patients. This integration could also support further optimization of FDA device databases for power users who rely on this information to identify predicates and to understand analytical and clinical performance expectations for Companion and Complementary IVDs. Boudicca® DX appreciates the opportunity to provide feedback to FDA and looks forward to the finalization of this order as quickly as possible in 2026.

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